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Formulation and Evaluation of Candesartan Cilexetil 4mg Transdermal Patch

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Abstract

Transdermal patches containing antihypertensive drugs are preferable to conventional-dose forms because they minimize administration frequency, are less intrusive, and cause no gastrointestinal upset. Candesartan is an angiotensin-converting enzyme inhibitor that can be used alone or in combination with other drugs to treat hypertension. It may also be used as an alternative agent for the treatment of heart failure, myocardial infarction, and coronary artery disease. A transdermal patch is superior to oral administration as it avoids first past metabolism and delivers the drug for a prolonged duration. It might be the best option for the treatment and management of hypertension. The objective of this study is to develop a well-designed, stable, effective, and safe dosage form for the delivery of antihypertensive drugs.

Keywords*:* Candesartan Cilexetil, TDDS, Transdermal Patches, Hypertension, First-pass metabolism

1. Introduction

Drug administration by skin permeation has grown in popularity over the last decade due to its several benefits over alternative dosage options. Its benefits include regulated medication distribution, bypassing first-pass metabolism, and reducing gastrointestinal adverse effects. The TDDS has become an essential aspect of the pharmaceutical business.

Hypertension is characterized by excessive blood pressure. The cases of hypertension are becoming more prevalent day by day and are a leading cause of mortality in people. Hypertension is responsible for 57 % of stroke fatalities and 24 % of coronary heart disease.

Candesartan works on the mechanism of angiotensin II receptor blocking. It prevents angiotensin II from binding to AT1, inhibiting angiotensin II vasoconstriction and aldosterone secreting actions through AT1 and lowering blood pressure. As a result, Candesartan Cilexetil transdermal patches can be utilized to treat hypertension.

1.1 Basic Components:

Polymer

The backbone of TDDS is polymer, which regulates the drug release. Drug dispersion in a liquid or a solid-state synthetic polymer base can be used to make a polymer matrix. The polymer used in TDDS should be biocompatible and chemically compatible with other drug components (Patnaik et al. 2009).

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Permeation Enhancer
These are the chemical compounds that increase stratum corneum permeability to achieve higher therapeutic levels of the drug candidates. (Nicoli et al., 2010).

Plasticizer
Plasticizers give transdermal patch plasticity, flexibility, and dispersibility. E.g. dibutyl phthalate, triethyl citrate, polyethylene glycol, and propylene glycol.

2. Material and Method of preparation

2.1 List of Ingredients:

- ***Candesartan Cilexetil (Drug):***

Candesartan is an angiotensin II receptor blocker used alone or in combination with other drugs to treat hypertension. It's given orally as a prodrug. By inhibiting the renin-angiotensin-aldosterone pathway(RAAS), candesartan reduces blood pressure. Hypertension, isolated systolic hypertension, left ventricular hypertrophy, and diabetic nephropathy is among some conditions that can be treated with candesartan. It may also be used as an alternative agent for the treatment of heart failure, systolic dysfunction, myocardial infarction, and coronary artery disease **(National Centre for Biotechnology Information, 2022)**.

- ***Ethylcellulose (Polymer):***

The polymer is obtained from etherification. Ethylcellulose is characterized as a non-ionic material, having the advantage of being non-reactive. EC is a semi-synthetic polymer material that has good thermal stability, biocompatibility, biodegradability, and good film-forming properties. EC has been widely used in the pharmaceutical industry for decades, being utilized in oral and topical pharmaceutical formulations for various purposes **(National Centre for Biotechnology Information, 2022)**.

- ***Polyethylene Glycol 400 (Plasticizer):***

Polyethylene Glycol 400 has a low-molecular-weight. It is a colourless viscous liquid. PEG 400 is a common ingredient in pharmaceutical formulations. It can be used as a plasticizer in various products. **(National Centre for Biotechnology Information, 2022)**.

- ***Dibutyl phthalate:***

Dibutyl phthalate is an organic compound that is commonly used as a plasticizer because of its low toxicity. It's used to make plastic. It appears to have a lower acute (short-term) and chronic toxicity profile. It is water-insoluble. **(National Centre for Biotechnology Information, 2022)**

- ***Methanol:***

It has the appearance of a colourless, volatile liquid with a mildly sweet pungent odour similar to ethyl alcohol. It completely dissolves in water. It is an excellent alternative to water and is utilized as a solvent in the Transdermal drug delivery system. Because candesartan is water-insoluble, methanol can be used as a solvent.

2.2 Preformulation Studies-

Preformulation is a group of studies that determines the physicochemical properties of any drug moiety that could influence the formulation development. The objective of this study is to develop a well-designed, stable, effective, and safe dosage form by establishing the kinetic rate profile and compatibility with the other ingredients.

These studies included-

1) **Organoleptic Properties:**
   Organoleptic properties include colour, odour, and taste

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a) **Colour**- A small quantity of the drug, Candesartan Cilexetil was taken on butter paper and viewed in a well-lighted place and colour was observed.

b) **Odour and Taste** - Very less quantity of Candesartan Cilexetil should be taken for the taste and odour testing. **(Vinay C H et al, 2015)**

2) Determination of melting point:
A crystalline substance is a powder. Take the capillary tube and heat one end of it to seal it. Push the capillary tube's open end into the heap. Fill the tube with 2-3 mm of the sample. Connect the capillary tube to the thermometer, which is in a liquid paraffin bath. The bath liquid's surface tension is sufficient to keep the capillary tube in place. The flame is lowered when the temperature reaches 15°C of the pure substance's melting point. When the substance begins to melt, the temperature is recorded. When it is completely melted, the temperature is recorded once more. **(https://www.learncbse.in/determination-melting-point/)**

3) FTIR Spectrophotometer:
This technique is mainly used to identify organic compounds. The IR absorption spectrum of Candesartan Cilexetil was taken in the range of 400-4000 cm^{-1} by the KBr disc method. To check the compatibility between the Candesartan Cilexetil and its excipients this study was carried out. To obtain the FTIR spectrum combination of Candesartan Cilexetil and excipients was weighted accurately and kept under an IR lamp for 30 minutes. Candesartan Cilexetil and KBr were mixed together in 1:100 proportion and grinded to form a homogenous mixture. This blend was then subjected to FTIR studies. **(Olivier et al., 2003)**

4) Drug and excipients compatibility studies:
The FTIR spectra of the drug and excipients were compared to check the compatibility.

5) Calibration curve using UV spectrophotometer
Linearity range solutions containing 2,4,6,8,10 µg/ml of Candesartan Cilexetil were prepared. After setting the instrument for its spectral properties the solutions were scanned at 258 nm wavelength. The calibration curve was prepared by plotting the concentration of Candesartan Cilexetil on the X-axis and their respective absorbances on the Y-axis. From the graph, we derive the r^2 value. **(Panchumarthy Ravishankar, et al 2016)**

2.3 Formulation of transdermal patch
Candesartan drug-loaded matrix type transdermal patches were made by using a combination of polymer and plasticizers. The patch was made using the solvent casting method. The polymer Ethyl Cellulose was weighed and dissolved in 20 ml Methanol. Then plasticizer and the drug were added to the above solution. This solution was mixed using a magnetic stirrer. Then the solution was transferred on a petri-plate and placed on the film-forming apparatus for 2-3 hours at 65℃. After drying, it was cut into $2 \times 2\ cm$ patch size.
The formulation table is given in table 1.

2.4 Evaluation of transdermal patch
The developed patches were evaluated by performing the following tests:

Thickness:
Screw Gauge or Digital Micrometre was used to determine the thickness of the selected patches. Thickness was measured at 5 different locations and an average was taken.

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Uniformity of weight:
Uniformity of weight was calculated by weighing the patches on a digital balance. The test was performed on five patches and the average weight was calculated by using the formula given below. (Equation 5.3.1)

Moisture content:
For moisture content, a desiccator filled with $CaCl_2$ was used. Patches to be evaluated were initially weighed and put in the desiccator for 24 hrs. After 24 hrs patches were reweighed and moisture content was calculated by using the following formula given below (Equation 5.3.2)

Folding endurance:
A strip of a specific area was cut and repeatedly folded at one place till it breaks. The point or fold number at which the patch breaks is the folding endurance.

Drug content Determination:
A patch of the area $2\ cm \times\ 2cm$ was dissolved in 10ml methanol. Then the whole solution was ultrasonicated for 15 minutes. After filtration, the drug was estimated spectrophotometrically at a wavelength of 258nm. Then the drug content was calculated.

Percentage elongation Break Test:
The percentage elongation break was determined by noting the initial and final length after the stretching of the patch.

3. Result and Discussion

3.1 Preformulation studies-

3.1.1 Organoleptic properties

a) **Colour:** The colour of candesartan cilexetil was found to be white.
b) **Taste and odour:** The taste of candesartan cilexetil is sweet according to literature. It was found to be odourless.

3.1.2 Determination of melting point:

The observed melting point is given in table 2

3.1.3 FTIR spectrophotometry and drug compatibility studies:

The FTIR spectra are given in fig.2 and fig.3 and it shows no difference between the functional group peaks of drug and drug in physical mixture. They were observed to be unaltered indicating that they were chemically compatible.

3.1.4 Calibration curve:

The calibration curve is given in fig.1 and r^2=0.9994

3.2.1 Moisture content:

Moisture content of transdermal patches of formulation F1 to F5 ranges from 2.35% to 4.19%.

3.2.2 Folding endurance:

This test was done and the results indicated that patches would not break and would maintain their integrity with general skin folding when applied. The folding endurance of batches F1 to F5 ranges from 76 to 251.

3.2.3 Elongation percentage:

The elongation percentage of the transdermal patches of formulation F1 to F5 ranges from 5.8% to 25%.

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3.2.4 FTIR Spectrophotometer:

The spectra obtained after performing the FTIR are shown in Fig no 2 and 3.

3.2.5 Drug Content:

Drug content was calculated using the formula y = mx + c. The values of m and c were obtained from the calibration curve and the value of y was the absorbance of the patch which was dissolved in methanol and diluted. Therefore, the observed drug content of the 4 cm^2 Patch was found to be 100%. The calibration curve is given in fig. 1.

The observed results show that the Candesartan Cilexetil can be introduced into the Transdermal Drug Delivery System.

4. Conclusion:

This research was done for the formulation and development of the candesartan transdermal patch and to introduce the new route of candesartan cilexetil drug for the treatment of hypertension. The preformulation of the drug was performed and a drug excipient compatibility test was carried out. This patch was prepared by solvent casting technique. Two different concentrations of the plasticizers were used with one polymer. Evaluations consisted of Thickness, elongation, folding endurance, moisture content, and drug content uniformity of weight, and observed results were found to be 0.0 mm, 24%, 251folds, 2.22 %, 100%, and 0.03gm respectively. This report provides valuable information regarding the transdermal drug delivery systems and their evaluation process in detail.

5. Tables, Figures and Equations:

5.1 Tables

Table no.1 Formulation table

Formulation code	Ethyl cellulose	PVP	PVA	HPMC	ERL	Dibutyl phthalate	PEG 400
F1	-	-	-	240mg	160mg	60mg	60mg
F2	200mg	-	200mg	-	-	60mg	60mg
F3	200mg	200mg	-	-	-	70mg	70mg
F4	-	-	-	400mg	-	80mg	80mg
F5	400mg	-	-	-	-	90mg	90mg

Table no.2 Melting point

Standard melting point	Observed melting point
163℃	162℃

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Table no.3 Evaluation parameters:

Formulation code	Thickness (mm)	% Elongation	Folding Endurance	Moisture content(%)
F1	0.15	12.9	89	3.23
F2	0.27	5.8	76	4.19
F3	0.22	25.0	182	2.35
F4	0.25	21.2	194	3.49
F5	0.05	24.0	251	2.22

5.2 Figures

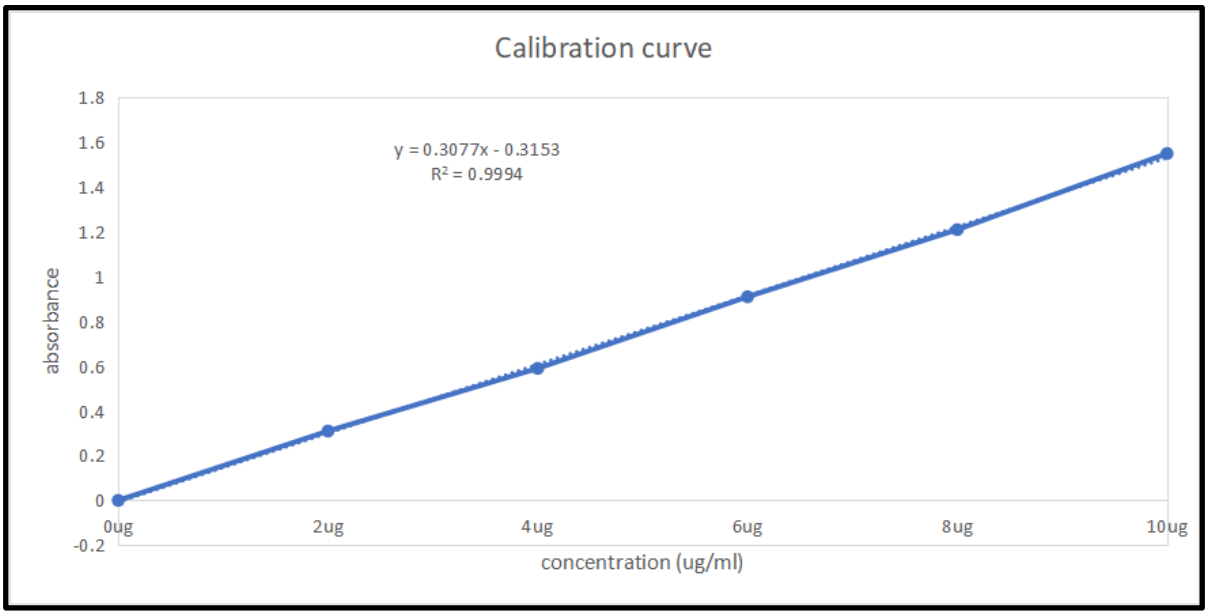

Figure no 1: Drug Content (Calibration Curve)

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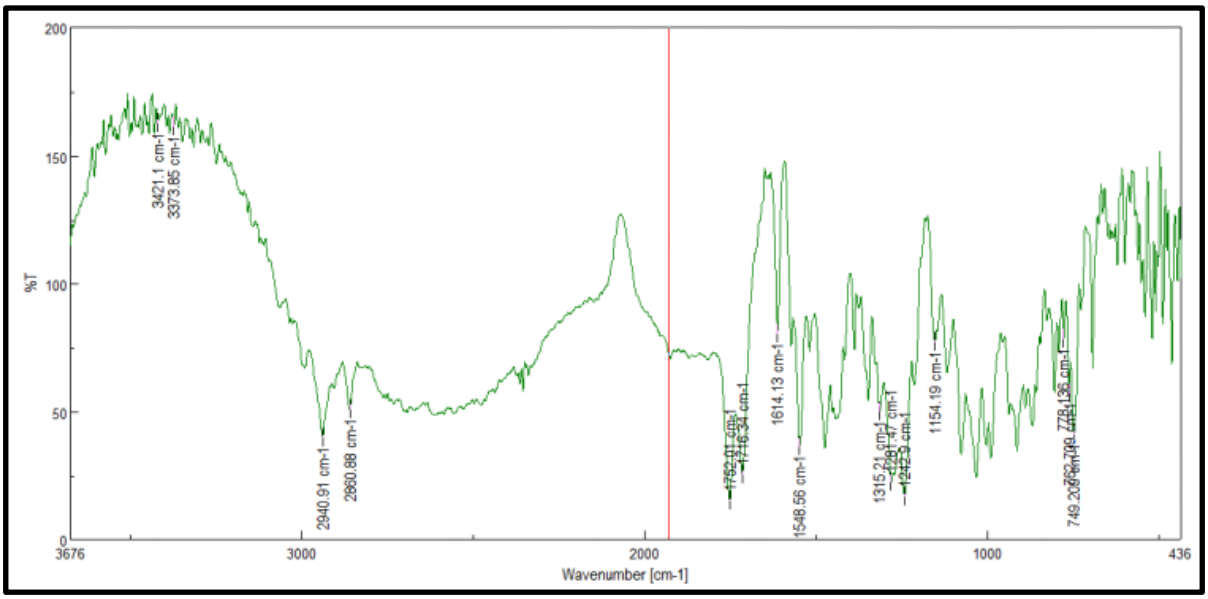

Figure no 2: FTIR Spectra EC and Candesartan Cilexetil

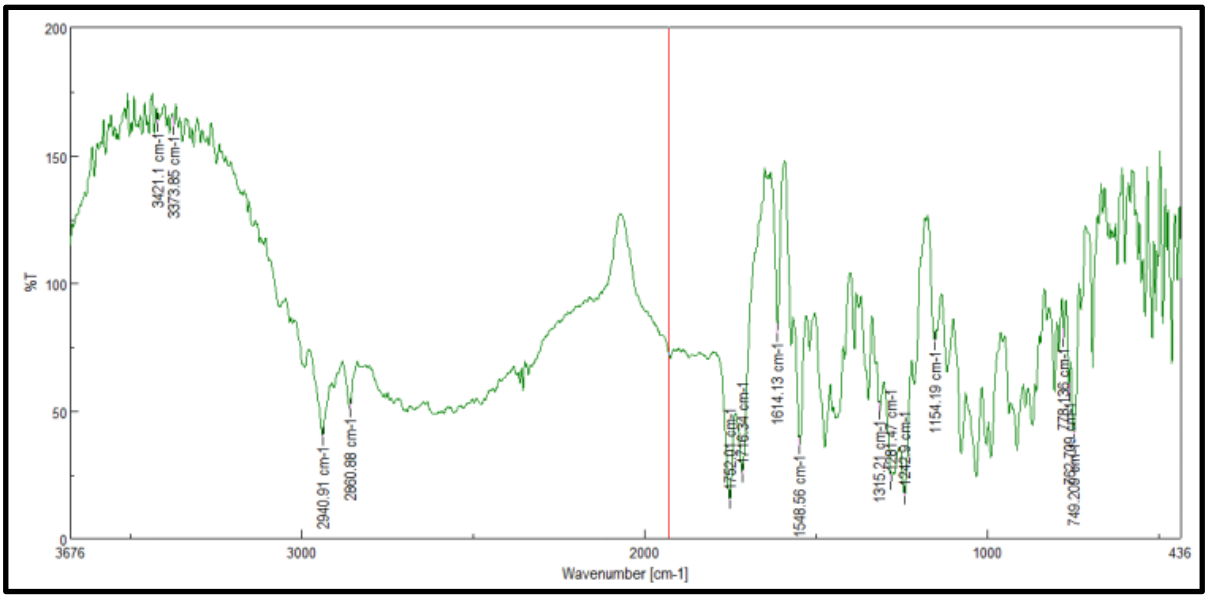

Figure no 3 FTIR Spectra of Candesartan Cilexetil

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Figure no 4: Patch Prepared from the F5 batch

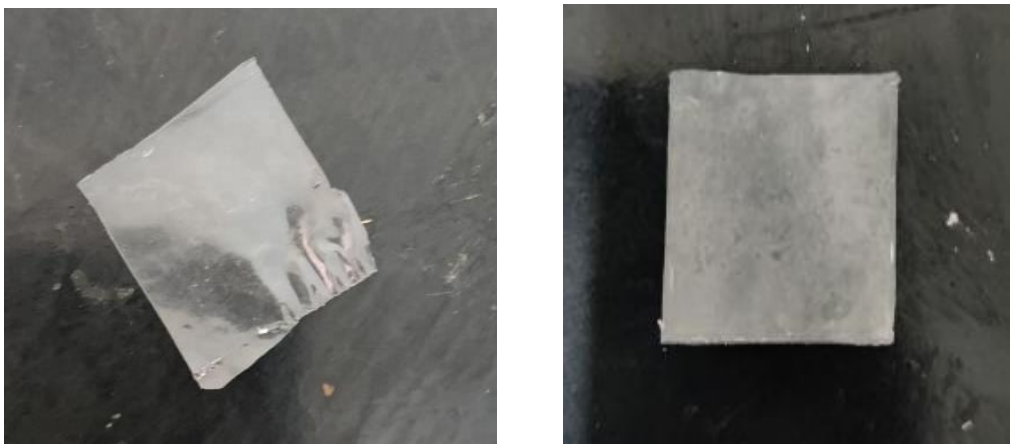

Figure no 5: Patches cut in 2cm * 2cm size

5.3 Equations:

$$Uniformity\ of\ Weight\ = \frac{Sum\ of\ the\ weight\ of\ the\ patches}{Number\ of\ the\ patches} \quad (1)$$

$$Moisture\ Content\ = \frac{Initial\ weight - Final\ Weight}{Final\ Weight} \times 100 \quad (2)$$

$$Elongation\ \% = \frac{L1 - L2}{L2} \times 100 \quad (3)$$

$$Drug\ content\ y = mx + c \quad (4)$$

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