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Research Article

Formulation and Characterization of Transdermal Patch of Candesartan Celexetil

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ABSTRACT

The aim of the present study is to formulate and characterized the transdermal patch of Candesartan celexetil. The objective is study was to increase the bioavailability of drug. In the present study, transdermal patch of Candesartan celexetil were prepared by solvent casting technique employing HPMC cps 50 polymer and glycerin as plasticizer using mercury as substrate. Total thirteen formulation (F1-F13) were prepared having drug and polymer ratio (1:2, 1:4, 1:6, 1:8, and 1:10). From the selected batch F2 containing drug polymer ratio (1:4), four formulations each were prepared and evaluated containing drug urea (1-4%) and oleic acid (1-4%) as permeation enhancer. The prepared transdermal patches were evaluated on the basis of different parameters like weigh, thickness, folding endurance, percent moisture absorption, percent moisture loss, drug content uniformity, in vitro skin permeation study. The fabricated final transdermal patches were further subjected to in vitro permeation study. In order to confirm the exact mechanism of drug release from all the patches, the data were computed and graphed according to Korsmeyer equation. Diffusion exponent of release process controlled by Super case II transport Non-Fickian diffusion, n values of Korsmeyer-Peppas model shows a combination of diffusion and dissolution mechanism indicating the drug release from the formulation was controlled by more than one process. It was concluded that the prepared formulation F13 (4% w/v of oleic acid) showed highest cumulative percent drug release and increase the bioavailability of the drug.

Keywords: Novel drug delivery system, Transdermal drug delivery, Transdermal drug delivery system, Differential scanning calorimetry.

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INTRODUCTION

Novel drug delivery is development friendly dosage form of various formulations with the ultimate aim of increasing their dosing convenience to the patient. The NDDS may involve a new dosage form eg. From thrice a day dosage to once a day dosage form or developing a transdermal patch in place of other drug formulation¹. Today about 74% of drug are taken orally and are found not to be as effective as desired Transdermal drug delivery offers an attractive alternative to the oral administration and injection. With the creation of current time pharmaceutical dosage form, transdermal drug delivery system is recognized itself as an important part of NDDS². Transdermal dosage forms, still a costly alternative to conventional formulation, are becoming popular because of their exclusive advantages improved bioavailability, extra uniform plasma level, controlled absorption, painless and reduced side effects easy application and flexibility of terminating drug administration by simple removing the patch to the skin are the some of the

potential advantages of TDD³. Oral dosage form like tablets and capsules are most widely used drug delivery system but dosage forms face problem of destruction of drug by gastric acid and digestive juices, irritation to gastric mucosa (nausea and vomiting), effect too slow for emergency, and unable to use in unconscious patient. Oral route has many further problems like unpleasant taste of some drugs, odor and color. TDDS patches drug are used by continuous release so they show their effect for exact duration and Transdermal patch is non-irritating and noninvasive technique⁴.

Present study was aimed to increase the bioavailability of drug. Candesartan celexetil was chosen as a model drug for study since it posses near ideal characteristics that a drug must have in formulating a transdermal drug delivery such as high lipid solubility, low molecular weight, effective in low concentration.

Candesartan Celexetil is antihypertensive drug used in treatment of high blood pressure (hypertension), heart attacks, Lowering high blood pressure helps prevent strokes

and kidney problems. Candesartan belongs to angiotensin receptor blockers (ARBs) class of drugs. It works by selectively blocks the binding of angiotensin II to AT1 in many tissues including vascular smooth muscle and the adrenal glands. This inhibits the AT1-mediated vasoconstrictive and aldosterone-secreting effects of angiotensin II and results in an overall decrease in blood pressure ⁵.

MATERIAL

Candesartan celexetil was obtained as gift sample from Aurobindo Pharma Ltd., Hyderabad. Other material such HPMC cps50, Alcohol, Glycerine, Dichloromethane, Chloroform, Sodium hydroxide, Sodium chloride, n-octanol, Methanol, Potassium dihydrogen phosphate was provide by institute.

METHOD

In the present study matrix type patch of Candesartan Celexetil was prepared by solvent casting method using mercury substrate and evaluated for various parameters. Monolithic transdermal systems of candesartan celexetil were prepared as per formulae given in table 1. Selected polymer ration of HPMC cps50 was dissolved completely in casting solvent Dichloromethane, chloroform & alcohol in ratio 2:2:1. The solutions were stirred for 20 min using magnetic stirrer. Glycerin (50% w/w of polymer) as plasticizer and urea and oleic acid used as permeation enhancer in different concentration was added to beaker's solution. Specific quantity of drug was respective polymer solution. The solution were stirred and poured within a glass bangle placed on mercury surface in a petridish. The rate of evaporation of the solvent was controlled by inverting funnel over the petridish. After 24hrs, the dried film was taken out and stored in a desiccator for further study.

Table 1: The detail formulae of different monolithic transdermal system containing candesartan celexetil

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Plasticizer glycerine (%w/w)	50	50	50	50	50	50	50	50	50	50	50	50	50
Drug: Polymer	1:2	1:4	1:6	1:8	1:10	1:4	1:4	1:4	1:4	1:4	1:4	1:4	1:4
Urea	-	-	-	-	-	1%	2%	3%	4%	1%	2%	3%	4%
Oleic acid	-	-	-	-	-	1%	2%	3%	4%	1%	2%	3%	4%
Casting Solvent	2:2:1	2:2:1	2:2:1	2:2:1	2:2:1	2:2:1	2:2:1	2:2:1	2:2:1	2:2:1	2:2:1	2:2:1	2:2:1

Optimization:

• Preformulation studies

Preformulation study is defined as the process of optimizing the delivery of drug through determination of physicochemical properties of the active compound that could affect drug performance and development of an efficacious, stable and safe dosage form. It describes the process of optimizing the delivery of drug through determination of physical, chemical properties of drug ⁶.

• Physical Appearance

Physical appearance of drug was noted by visual observation.

• Fourier Transform Infra-Red Spectroscopy (IR)

IR study was performed for identification and structural analysis of the procured drug using Perkin Elmer Fourier transformed infrared spectroscopy ⁷. The potassium bromide (KBr) disk technique was employed using 100mg of spectroscopy grade dried KBr. KBr was ground into fine powder using a mortar/ pestle and compressed into disc under a hydraulic pressure at 10,000psi. Candesartan was placed on the KBr disc with the help of capillary tube. Each KBr disc was scanned 32 times in the region of 4000-400cm⁻¹ and characteristic bands were recorded.

• Absorption maxima (λ max)

A UV absorption maxima of drug was determined by scanning (10 μ g/ml) solution of drug in 7.4 phosphate buffer between 200-400nm.

• Standard curve of Candesartan Celexetil

Candesartan Celexetil (50mg) was dissolved in 10 ml of 7.4 phosphate buffer in a 50 ml volumetric flask and the volume was making up to 50ml with the same to obtain a stock solution of 1000 μ g/ml. 25ml of this solution was diluted to

100ml with 7.4 phosphate buffer in 100ml volumetric flask to obtain stock solution of 250 μ g/ml. From this stock solution, aliquots of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ml were taken and transferred to 10ml volumetric flasks and volume was made up to 10ml with 7.4 phosphate buffer. The absorbance of this solution was measured at 254nm using 7.4 phosphate buffer as blank. The calibration curve was plotted between concentration and absorbance.

• Partition coefficient

Partition coefficient is an indicator of lipophilic or hydrophobic nature of drug molecule. The partition coefficient of a substance between n-octanol and water is referred to as $P_{o/w}$, which corresponds to the negative logarithm of the ration of the concentration of the substance ninth aqueous and hydrophobic phase. Log P is the ratio of drug dissolved into immiscible solvent s, most commonly water and n-octanol that are in equilibrium. Log P is applicable to unionized compound ⁸.

• Differential scanning calorimetry (DSC)

DSC thermograms of pure drug (candesartan celexetil) and its physical mixture with additives (HPMC and PVP K-30) were carried out to investigate any possible interaction between the drug and the utilized additives. The selected heating rate was from 50°C to 300°C at an increase of 5°C per minute using Perkin Elmer 6 DSC ⁹.

Evaluation of Prepared Transdermal Patch

• Physical appearance

All the transdermal films were visually inspected for color, clarity, flexibility and smoothness ¹⁰.

• Weight uniformity

The dried film was weighed on Afcoset digital balance. The average of five observation was taken I each batch ¹¹.

- **Thickness uniformity**

Film thickness was measured by screw gauge (Mitutoyo Japan) at five different random points on the film. The average of five observations was taken ¹².

- **Folding Endurance**

The folding endurance was expressed as the number of folds or number of times the film was folded at the same place either to develop visible cracks or to develop visible cracks. This was important to check the ability of sample to withstand folding. This also gives an indication of brittleness ¹³.

- **Drug content uniformity**

Candesartan Celextil film of 1 sq.cm was cut into small pieces and transferred into 100ml volumetric flask. 25ml of methanol was added and shaken for 4 hrs to extract the drug. Finally, suitable dilution was made using phosphate buffer of pH 7.4 and the absorbance was measured at 254 nm using UV spectrophotometer ¹⁴.

- **Percentage moisture content**

Individually weighed patches are kept in the desiccator having fused calcium chloride at room temperature for 24 hrs. After 24 hrs the patches are to be reweighed and percentage moisture content is calculated by the formula:

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

In vitro permeation through the goat skin:

- **Preparation of the goat skin**

The experiment was carried out by using goat abdominal skin obtained from the local slaughter house and stored at -20°C. The hair of test animal were carefully trimmed short with the pair of scissors and to remove any skin content skin was shaved using a hard razor to removed subcutaneous tissue. The epidermis was washed with water and used ^{15, 16}.

- **Permeation studies**

In vitro release studies were performed in a modified Franz diffusion cell over a period of time 24hrs. The above skin was mounted on the diffusion cell and receiver compartment was filled with 20 ml phosphate buffer of ph 7.4 and the temperature was maintained 37°C with the help of circulating water bath. The samples were withdrawn at appropriate time interval (replaced with 2 ml of fresh buffer to maintain sink condition) and their concentration were measured at 254 nm using UV-spectrophotometer ¹⁷.

Kinetics Modeling of Drug Dissolution Profiles

To analysis the in vitro release data various kinetic models were used to describe the release kinetic. The dissolution profile of the all formulations was fitted to higuchi and Korsmeyer – Peppas's model to ascertain the kinetic modeling of the drug release and mechanism of drug release ¹⁸.

- **Zero Order kinetics (Constant rate process)**

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly can be represented by following equation.

$$F_t = K_0 t$$

Where f_t is the fraction of drug dissolved in time t and K_0 is zero order release constant.

Pharmaceutical dosage form following this profile release the same amount of drug by unit of time and this is ideal method of drug release in order to achieve a pharmacological prolonged action. The following relation can in a simple way express this model.

$$Q_t = Q_0 + K_0 t$$

Where, Q_t is the amount o drug dissolved in time t , Q_0 is initial amount of drug in solution and K_0 is zero order release rate constant. Most of the time $Q_0 = 0$.

- **First order kinetics (Linear kinetics)**

Rate is directly proportional to the concentration, of drug undergoing reaction i.e. greater the concentration, faster the reaction. The drug dissolution study was first proposed by Gibaldi and Feldman in 1967. The following relation in a simple way can be expressed as

$$\ln(Q_t/Q_0) = K_1 t$$

or in decimal logarithm.

$$\log Q_t = \log Q_0 - K_1 t / 2.303$$

Where, Q_t is amount of drug dissolved in the time t , Q_0 is initial amount of drug in solution and K_1 is first order release rate constant. In this way a graphic of decimal logarithm of the release amount of drug versus time will be linear.

- **Higuchi model**

Higuchi described the release of drug insoluble matrix as a square root of time dependent processes based on Fickian diffusion. A large number of modified release dosage form contain some sort of matrix system. In such instance, the drug dissolved from the matrix. The dissolution pattern of the drug is dictated by water penetration rate (diffusion controlled). In higuchi model, a plot of % drug release versus square root of time is linear.

$$Q = K_h t^{1/2}$$

Where, K_h is constant, t is time.

- **Korsmeyer- Peppas model**

To find the mechanism of drug release, drug release data was fitted in Korsmeyer –Peppas model, log of % cumulative drug release versus log of time.

$$Mt/M_\infty = K t^n$$

Where, Mt/M_∞ is fraction of drug released at time t and K is rate constant, n is release exponent.

Table 2: Interpretation of diffusion release mechanism from polymeric film

Release Exponent(n)	Drug Release Mechanism	Rate as a function of Time
0.5	Fickian Diffusion	$t^{-0.5}$
$0.5 < n < 1.0$	Anomalous Transport	T^{n-1}
1.0	Case II Transport	Zero order release
Higher than 1.0	Super case II Transport	T^{n-1}

RESULT AND DISCUSSION

Physical Appearance and Melting point

Sample of Candesartan Cilexetil was white to off white to off white powder with a melting point of 170°C± 0.5°C which

was accordance with the literature value and this was also confirmed by DSC (shown in figure 1,2) also. This confirm the authentically and purity of drug.

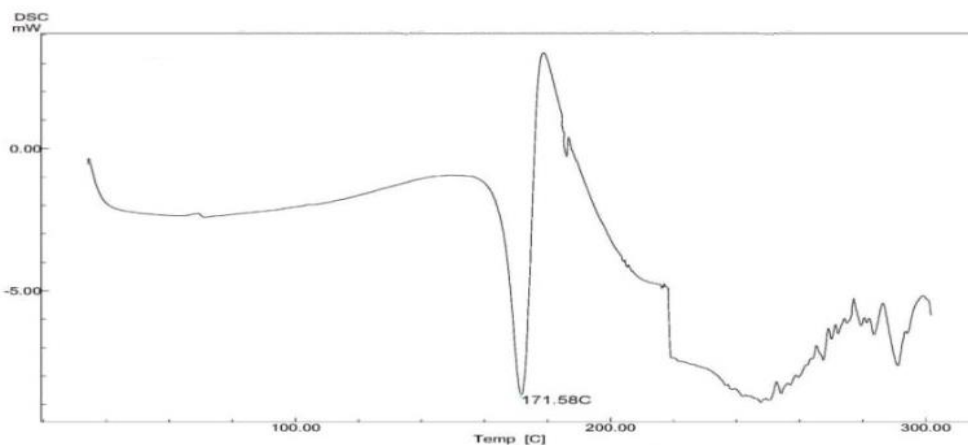


Fig1: DSC of pure drug (Candesartan Cilexetil)

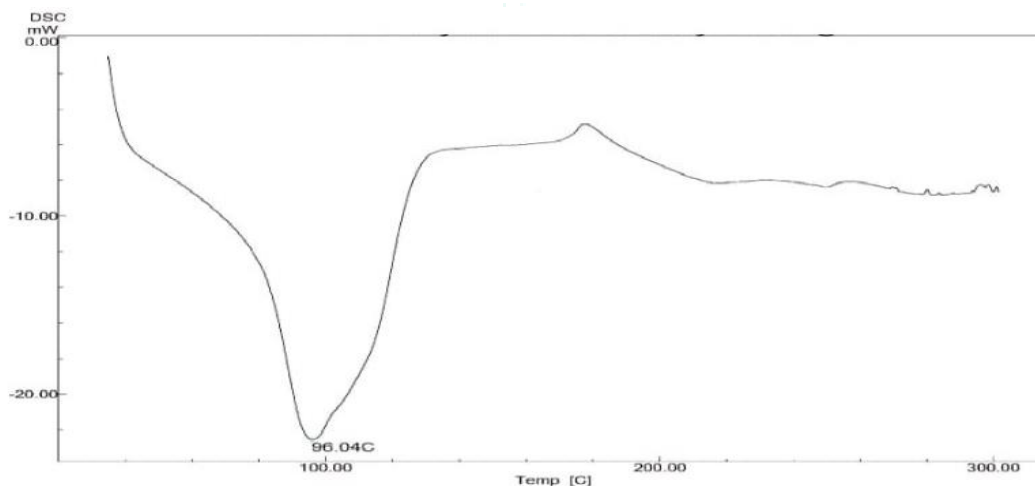


Fig 2: DSC of drug with excipient

Fourier Transform Infra-Red Spectroscopy

The FT-IR spectrum of drug and drug with excipient was showed in Figure- 3, Figure- 4.

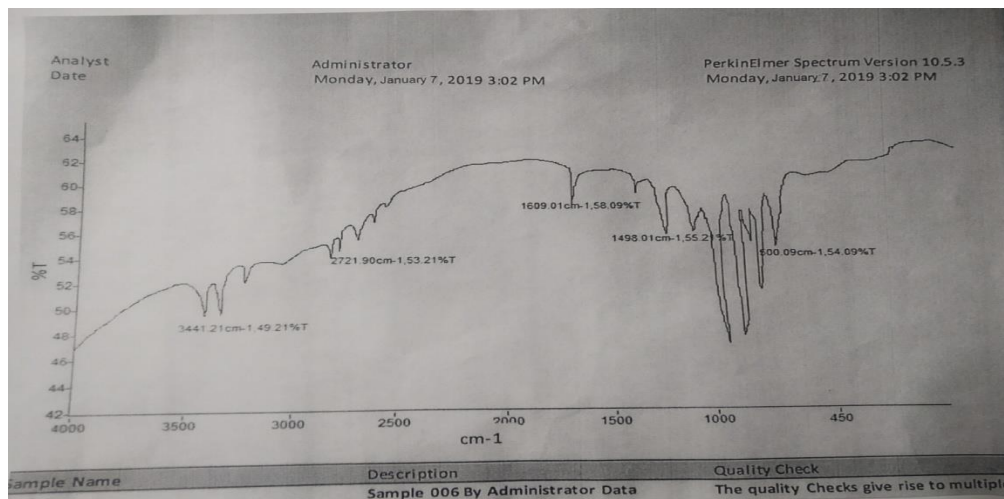


Figure 3: FT-IR spectrum of drug

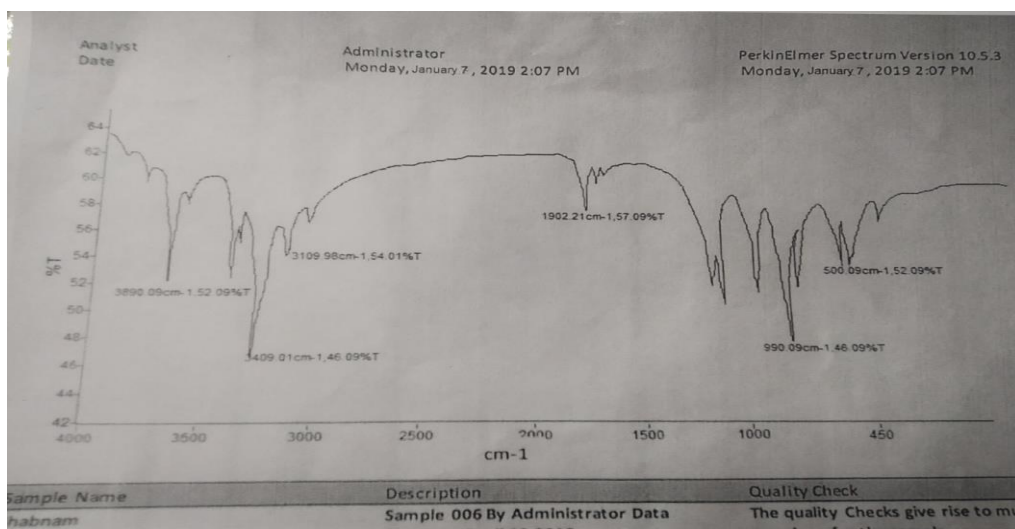


Figure 4: FT-IR spectrum of drug with excipient.

Absorption maxima (λ_{max})

The absorption maximum (λ_{max}) Candesartan Cilexetil was found to be 272nm (fig. 5) and the spectrum has been found shown in fig.6. In the UV analysis, we considered the broad peak with maximum absorbance.

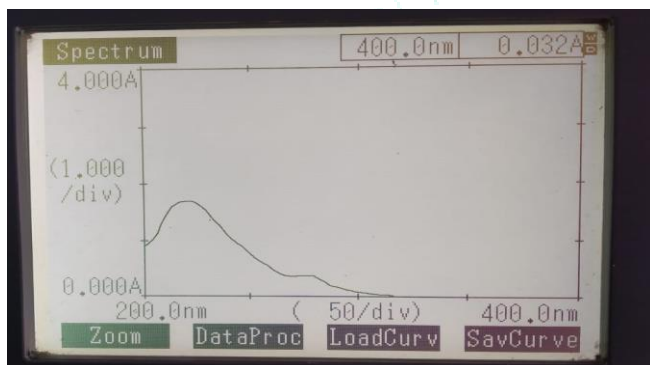


Figure 5: UV Spectrum of Candesartan Cilexetil

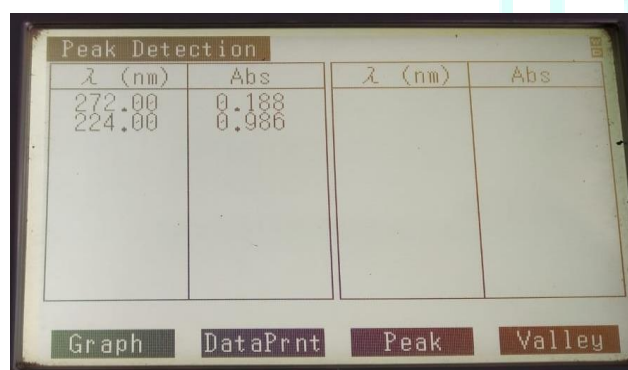


Figure 6: Representative λ_{max} of Candesartan Cilexetil

Standard curve of Candesartan Cilexetil in Phosphate buffer

Figure 7 shows the calibration curve of Candesartan Cilexetil in 7.4 phosphate buffer at 254nm (λ_{max}). Linearity was obtained in a range from 1-10 $\mu\text{g/ml}$ with R^2 value of 0.982.

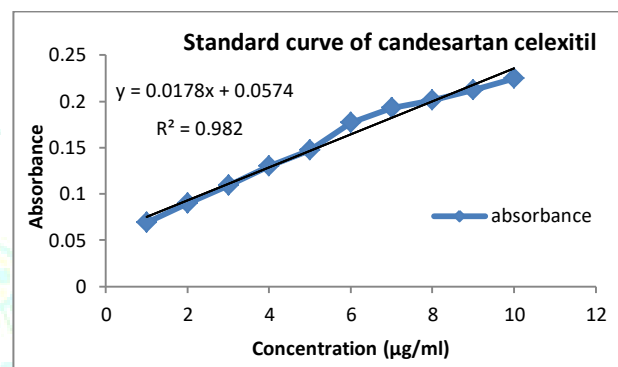


Figure 7: UV Spectrum of Candesartan Cilexetil

Partition coefficient

A drug solution of 1mg/ml was prepared in n-octanol. It was in a separating funnel and shaken with an equal volume of water (aqueous phase) for 10 min and allowed to stand for two hrs. Then aqueous phase and organic phase were collected separately and centrifuged at 2000rpm. Both the phase was analyzed for the drug concentration using U.V. spectrophotometer. Partition coefficient was calculated by taking the ration of the drug concentration in n-octanol to the drug concentration I aqueous phase. Average of triplicate reading was taken. The partition coefficient of CC was found to be 3.96.

Physical appearance

The prepared patches were found to be uniform flexible, smooth and homogenous.

Weight uniformity

The mean weight of all the prepared batches in the ranges of 0.234- 0.917.

Thickness uniformity

The thickness of the prepared batch are in the range of 0.12- 0.29.

Folding Endurance

The folding endurance of CC patches are 276- 301.

Drug content uniformity

All the patches were found to have the drug content in the range of 66%- 96%.

Table 3: Evaluation of Prepared Transdermal Patch

Formulation Code	Weight (gm)	Thickness (mm)	Percentage moisture content	Folding endurance	Drug Content (%)
F1	0.234	0.25	1.47	282	72%
F2	0.255	0.22	1.92	291	79%
F3	0.294	0.20	2.01	276	64%
F4	0.335	0.29	2.51	295	68%
F5	0.338	0.29	2.73	301	66%
F6	0.905	0.21	0.29	292	87%
F7	0.911	0.19	0.43	304	82%
F8	0.902	0.17	0.58	290	85%
F9	0.907	0.18	0.82	285	88%
F10	0.915	0.12	0.32	298	83%
F11	0.899	0.19	0.52	287	89%
F12	0.914	0.20	0.38	292	92%
F13	0.917	0.15	0.24	289	96%

Zero Order kinetics (Constant rate process)

Zero order plot of Formulation F10- F13 shown in figure -8.

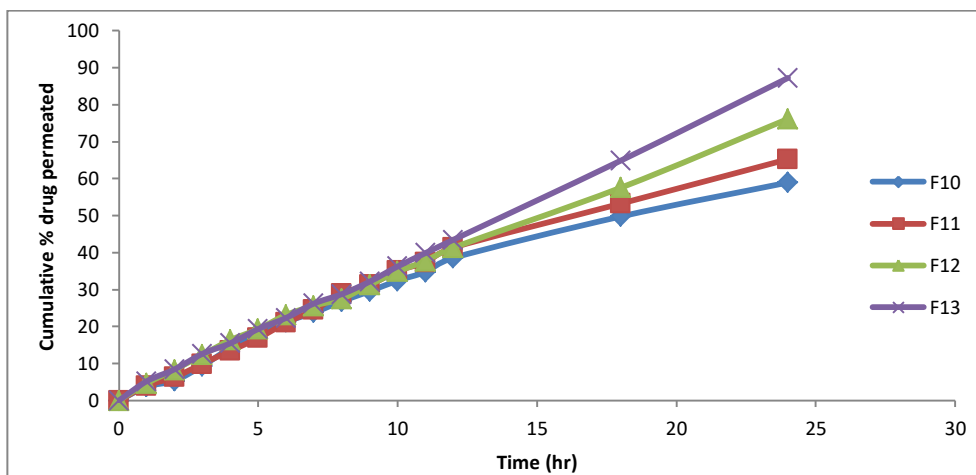


Figure 8: Plot of Cumulative Percent Drug Permeated versus Time for formulation F10-F13

First order kinetics (Linear kinetics)

First order plot of Formulation F10- F13 shown in figure -9.

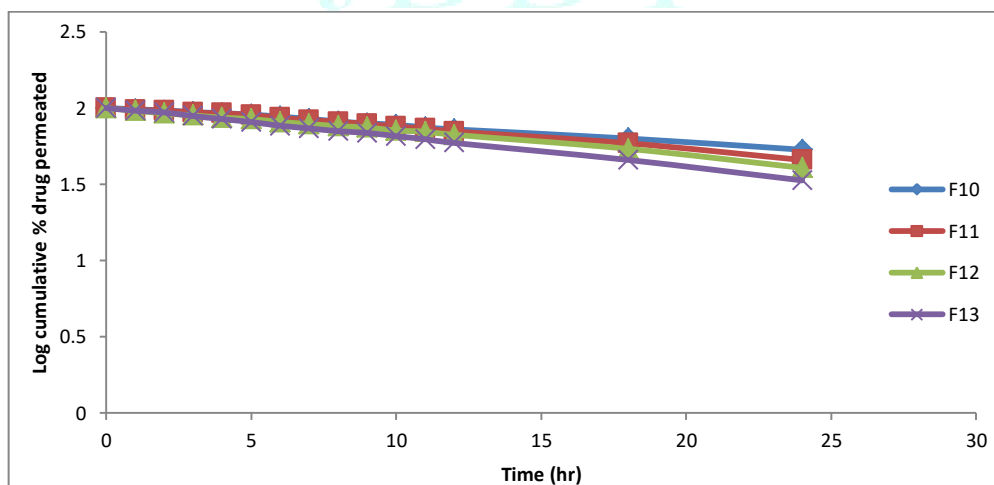


Figure 9: Plot of Log Cumulative Percent Drug Permeated versus Time for formulation F10-F13

Higuchi model

Higuchi model plot of Formulation F10- F13 shown in figure- 10.

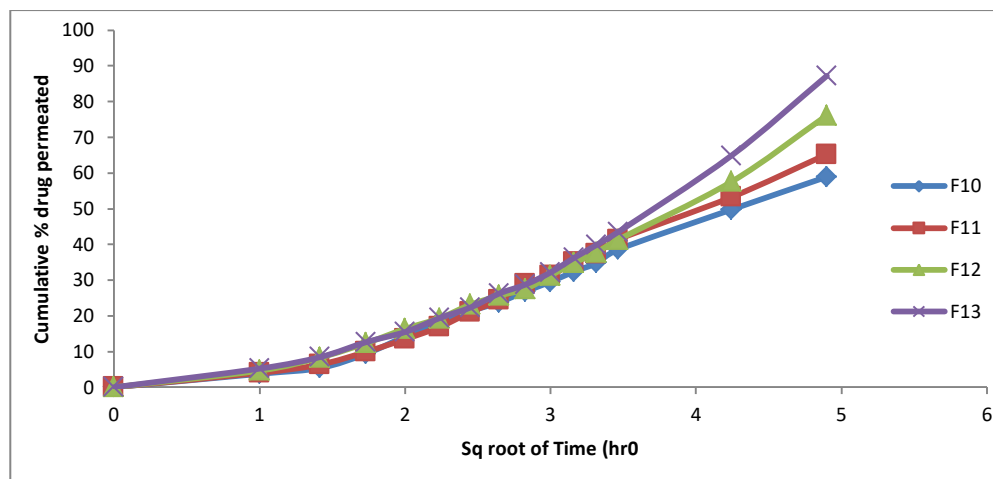


Figure 10: Plot of Cumulative Percent Drug Permeated versus Square root time for Formulation F10-F13

Korsmeyer- Peppas model

Korsmeyer – Peppas model plot of Formulation F10- F13 shown in figure- 11.

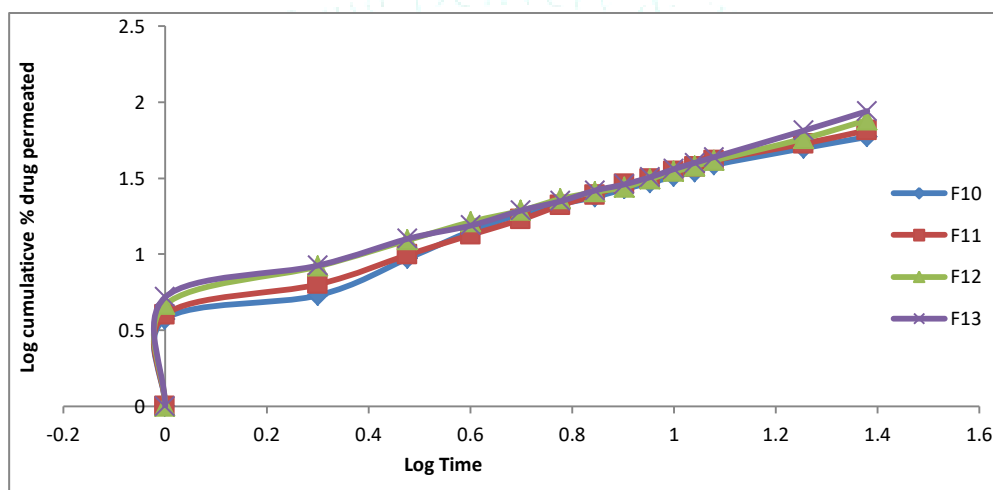


Figure 11: Plot of Log Cumulative Percent Drug Permeated versus Log time for Formulation F10-F13

CONCLUSION

From the study it was concluded that the formulation F13 which contained Oleic acid as permeation enhancer showed best result as compared to urea as permeation enhancer as there was an increase in the drug release to maximum extent in the final formulation (F13) containing Oleic acid. Physicochemical parameters of all the 13 formulation remained uniform with low SD values. High folding endurance revealed that the prepared patch have good flexibility. All the formulation were analyzed quantitatively to describe kinetics of drug release from patches using zero order, First order, Higuchi, Korsmeyer- Peppas model to determine the release profile and release mechanism. It was observed from the R^2 values for the release of drug from this formulation was governed by diffusion controlled process. Further, it was ascertained that the drug release from formulation could follow zero order kinetics. In order to confirm the exact mechanism of drug release from the patches, the data were computed and graphed according to Korsmeyer equation. Diffusion exponents of release process controlled by Non- Fickian diffusion, n values of Korsmeyer-

Peppas model shows a combination of diffusion and dissolution mechanism indicated the drug release from the formulation was controlled by more than one process. All the R^2 values of Peppas model confirmed that the drug transport mechanism was Non- Fickian Super case II transport. Stability studies on optimized batch i.e. F13 were performed at Accelerated (40°C/75% RH) conditions. The physical stability of Candesartan Celexetil patches proved to be unchanged after storage up to 2 months under accelerated condition at 40°C/75% RH. This dosage form also shows improved patient compliance due to simplified therapeutic regimen and comfort via non- invasive, painless and simple application.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

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