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FORMULATION AND STUDIES ON CANDESARTAN TRANSDERMAL PATCHES

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ABSTRACT

In the present work, Transdermal drug delivery of candesartan were formulated by using polyethylene glycol 300 as plasticizer in different concentration (8%, 16% and 24%) along with PVA with PVPK30, and Eudragit RS 100 with HPMC as a blend of two in different concentrations of polymers were formulated by solvent casting method. Candesartan is an Angiotensin II Receptor Antagonists Antihypertensive Agents. Drug polymer interaction study was carried out using FTIR. The formulated products characterized by DSC, XRD and SEM studies. Phosphate buffer pH 7.4 is used for In-vitro diffusion studies at λ max 208nm, by using an artificial Keshary chein diffusion cell (cellophane membrane (0.45µ)). All the physico chemical parameters were evaluated. The products exhibited good physicochemical characteristics. Phosphate buffer pH 7.4 is used for In-vitro diffusion studies at λ max 208nm, by using an artificial Keshary chein diffusion cell (cellophane membrane (0.45µ)). Also the kinetic study and mechanism for the diffusion of candesartan transdermal patches were carried out. The results indicate, an increase in the concentration of plasticizers increases the diffusion rate of candesartan patches. The diffusion data were fitted in various models to aces the kinetics and mechanism of diffusion. Candesartan patches formulated by using 24% PEG 300 shows enhanced rate of diffusion than the patches prepared with 16% and 8% PEG. Among polymers, combination of Eudragit and HPMC had enhanced diffusion rate than the combination of PVA and PVPK30 in all formulations.

Keywords *Transdermal Drug delivery, Diffusion rate, Patches, Candesartan, Plasticizer.*

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INTRODUCTION

Transdermal drug delivery systems (TDDS) are defined as discrete dosage forms containing drugs, which when coming intact with skin delivers the drug into the adjacent tissues & systemic circulation [1, 2]. The motto of pharmaceutical research is to overcome the hurdles coming in fixing the effective therapeutic level and inhibiting the undesired side effects[3]. To deliver the right amount of medicine at the right target site becomes complicated if each medication were to be delivered in an optimal and preferred manner to the individual patient [4]. The Transdermal products are to avail the maximum amount of dose via the skin to the systemic circulation and simultaneously avoiding the retention and metabolism of drug in the dermis[5].

In present days TDDS is one of the prominent methods in drug applications. A large number of drugs are being formulated by this route. Transdermal drug delivery systems are also known as patches.

Advantages of Transdermal Drug Delivery Systems[7] are as follows, Avoidance of first pass metabolism, avoidance of gastro intestinal incompatibility, predictable and extended duration of activity, minimizing undesirable side effects, provides utilization of drugs with short biological half lives and narrow therapeutic window.

Disadvantages of Transdermal Drug Delivery System[6, 7, 8] are, skin irritation or contact dermatitis at the site of application also causes local edema, itching etc. The aim of the study is to achieve the objective of systemic medication through topical application and release of drug via skin by developing transdermal drug delivery system.

Candesartan is an angiotensin II receptor antagonist and is widely used in the management of hypertension to reduce cardiovascular mortality in patients with left ventricular dysfunction following myocardial infarction, and in the management of heart failure. It acts selectively at the AT_1 receptor subtype. By blocking the rennin-angiotensin system at this point, it prevents angiotensin II mediated effects including vasoconstriction. Sodium and water retention enhanced sympathetic activity and cardiovascular cellular growth [10]. Candesartan is a potent and highly selective angiotensin II receptor type I antagonist that lowers blood pressure in hypertensive patients[6]. The drug is rapidly absorbed following oral administration[9].

OBJECTIVES

To formulate and evaluate candesartan patches using 8%, 16% & 24% PEG 300 as plasticizer. Formulations contain suitable blend of (two polymers) PVA with PVPK30 and Eudragit RS100 with HPMC as polymers in different concentrations by solvent casting method. To carry out compatibility studies by using IR spectroscopy and to characterize the prepared candesartan patches by DSC, XRD & SEM studies. To evaluate diffusion rate of the prepared patches in phosphate buffers pH 7.4 and to study physical parameter of the prepared patches like weight variation, thickness and folding endurance etc. To evaluate drug content, percentage moisture content, percentage water vapors permeability and flatness of the prepared patches. To evaluate kinetic mechanism of the prepared patches. To evaluate stability studies of prepared candesartan patches as per ICH guidelines.

MATERIALS

Candesartan pure drug gift sample from Biocon life sciences, Bangalore. Eudragit rs100, Gangwal chemicals Pvt Ltd, Navi Mumbai. Polyvinylpyrrolidine, Indechemie health specialties Pvt. Ltd. Sikkim. Methanol SD Fine chemicals, Mumbai and all other materials used were of Pharmacopoeial grade.

METHODS

The Candesartan patches were prepared by solvent casting method. The pure candesartan drug was solubilized in methanol and kept it aside. The polymer with highest concentration was dissolved in warm distilled water at a temperature of 45-50^{o}c initially low RPM with and the speed is increased. The above prepared drug mixture is poured in the polymer solution and mixed

thoroughly the specified amount of plasticizer was added drop wise to the beaker with continous stirring till whole dispersion is done. The solution is poured in anumbra petridish covered with funnel and air dried at 40-50^{o}c air circulating dryer for 12 hrs. the patches obtained were cut with the help of borer of 2cm in diameter and packed in aluminium foils and stored in dessicators of stability of patches.

EVALUATION OF TRANSDERMAL PATCHES

Weight Uniformity of patches:

Three patches of the size 2cm diameter were weighed individually using digital balance and the average weights were calculated.

Folding endurance

The folding endurance was determined by repeatedly folding the film at the same place until it broke. The number of times the film could be folded at the same place without breaking was consider as folding endurance value[12, 13, 14].

Drug content

Specified area of the patches were taken into 100 ml volumetric flask and dissolved in methanol and volume was made up to with phosphate buffer pH 7.4. Subsequent dilutions were made with phosphate buffer pH 7.4 and analyzed by UV spectrometer at 208 nm[11, 15].

Flatness

Longitudinal strips were cut out from the prepared medicated patches, the length of each strip was measured, and then the variation in the lengths due to the non-uniformity in flatness was measured. Flatness was calculated by measuring constriction of strips and a zero percent constriction was considered to be equal to a hundred percent flatness.

Constriction (%) = $(L_1 – L_2)/L_2$ x 100

Where, L_1 is initial length of each strip; L_2 is final length[11, 12].

Patch thickness

The thicknesses of patches were determined by selecting randomly patches and using digital vernier calliper, the film was measured at three different places and mean value was calculated[13, 14].

***In vitro* drug diffusion studies**

The diffusion study was carried out by using keshary- chein diffusion cell. In this method cellophane membrane is used as the model membrane. The membrane was placed between the donor compartment and the reservoir compartment (phosphate buffer pH 7.4). The patch was placed on the membrane and the compartments clamped together. The receptor compartment (100ml capacity) was filled with phosphate buffer pH 7.4 and hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 100 rpm. 1 ml of sample is withdrawn and replaced with receptor medium. 1 ml sample was diluted up to 10ml with phosphate buffer pH 7.4 to get concentration in between 2-12µg/ml and assayed spectrophotometrically at 208nm and amount of drug release at various time intervals was calculated.

RESULT & DISCUSSION:

The physicochemical evaluation study of the formulated patches, reveals that the average weights of the patches are 134.45mg and the percentage (%) deviation is $\pm$ 4.5% which is in the acceptable range. The results of thickness of the patches formulated are in between 0.342 mm to 0.379 mm and the folding endurance is in between 225 to 264. The flatness study showed the formulation had no much difference in the stripe lengths before and after longitudinal cut indicates in between 99.3% to 100%. The enhancements of water vapour transmission increases as concentration of plasticizer increases and due to effect of polymers, here water vapour transmission lies in 2.39 to 4.05 gmcm/ cm^{-2} /24hrs. The drug content for the candesartan transdermal patches formulated with PEG300 indicates in between 95.8% to 99.4%. The values of co-efficient variation were found to be less than 1.5 % in all the formulation.

The results of *in vitro* diffusion study shows that, an increase in plasticizer concentration increases the diffusion rate and also the combination of Eudragit RS100 and HPMC polymers shows increase in diffusion rate which are formulated with 24 % PEG.

The data is enlisted successively between 79.134 ± 0.157 – 90.661 ± 0.130, 81.589 ± 0.142 – 93.598 ± 0.125, 84.464 ± 0.156 – 95.473 ± 0.158, in 8%, 16% & 24% respectively.

The diffusion data values were fitted in different models like Zero order, First order, higuchi and peppas to study the diffusion pattern of drug along with its kinetics. The regression co-efficient values of the compounds are enlisted in table No1, 2, and figure 1 and 2.

T_{50} (time taken for 50% diffusion), T_{90} (time taken for 90% diffusion), K1 cm^{-1} values were recorded from diffusion data profile. There was an increase in the K1 cm^{-1} values indicating enhancement in diffusion rate. These parameters were shown in table No 3.

The SEM photographs of the candesartan loaded patches and candesartan with 8% PEG 300. The SEM films indicating uniform distribution of the drug with polymers and plasticizers were shown in figure no 3.

The DSC curve of candesartan showed a single sharp endothermic peak at126.7^{0}c corresponding to its melting point. In the thermograms of candesartan–PVA and PVPK30, the intensity (or height) of the endothermic peak at 58.2^{0}c was reduced indicating interaction of candesartan with PVA and PVPK30 and absence of crystalline drug. The intensity (or height) of the endothermic peak of candesartan-Eudragit RS 100 and HPMC at 197.5^{o}c and indicating interaction of candesartan with Eudragit RS 100 and HPMC were shown in figure no 4.

XRD of candesartan exhibited diffraction peak indicating its nature. In combination with polymers with drug exhibited little changes in the diffraction peak of the candesartan observed conformity were shown in figure no 5.

Table No.1 Correlation Coefficients (R^2) Values in the analysis of Candesartan Patches (PEG 300) diffusion data Profile as per Zero order, First Order, Higuchi and Peppas.

Formulations	CORRELATION COEFFECIENT			
	Zero order Equation	First order Equation	Higuchi's Equation	Peppas Equation
	Regression coefficient (R^2)	Regression coefficient (R^2)	Regression coefficient (R^2)	Regression coefficient (R^2)
CP1	0.993	0.940	0.913	0.826
CP2	0.987	0.938	0.895	0.836
CP3	0.988	0.938	0.889	0.809
CP4	0.997	0.931	0.928	0.789
CP5	0.993	0.934	0.911	0.777
CP6	0.993	0.939	0.993	0.793
CP7	0.996	0.904	0.930	0.776
CP8	0.995	0.992	0.923	0.789
CP9	0.995	0.929	0.918	0.774

Table No. 2 Correlation Coefficients (R^2) Values in the analysis of Candesartan Patches (PEG 300) diffusion data Profile as per Zero order, First Order, Higuchi and Peppas.

Formulations	CORRELATION COEFFECIENT			
	Zero order Equation	First order Equation	Higuchi's Equation	Peppas Equation
	Regression coefficient (R^2)	Regression coefficient (R^2)	Regression coefficient (R^2)	Regression coefficient (R^2)
CP10	0.994	0.886	0.903	0.864
CP11	0.992	0.886	0.892	0.850
CP12	0.989	0.884	0.884	0.867
CP13	0.993	0.879	0.903	0.803
CP14	0.992	0.882	0.897	0.822
CP15	0.992	0.882	0.895	0.825
CP16	0.998	0.902	0.932	0.772
CP17	0.999	0.898	0.931	0.785
CP18	0.998	0.907	0.926	0.829

Table No.3 Diffusion Parameter Profile of Candesartan Formulation contains PEG 300 (8%, 16% &24%)

Formulations	PD_{60} (1 Hr) %	T_{50} % (hr)	T_{90} % (hr)	K_1 (Hrs^{-1})
CP 1	9.91%	6.52	--	0.1492
CP 2	8.64%	7.08	--	0.1363
CP 3	7.31%	7.34	--	0.11264
CP 4	11.11%	6.32	--	0.1603
CP 5	10.19%	6.58	--	0.1492
CP 6	8.12%	7.06	--	0.1359
CP 7	12.46%	6.24	11.52	0.1799
CP 8	11.65%	6.42		0.1635
CP 9	10.18%	6.56	--	0.1451
CP 10	8.97%	7.24	11.50	0.1522
CP 11	8.17%	7.44	--	0.1474
CP 12	7.90%	8.17	--	0.1426
CP 13	10.31%	7.21	11.24	0.1573
CP 14	9.37%	7.29		0.1522
CP 15	8.71%	7.55	--	0.1455
CP 16	12.46%	6.30	11.10	0.1796
CP 17	11.78%	7.10	11.48	0.1713
CP 18	10.38%	7.42	--	0.1633

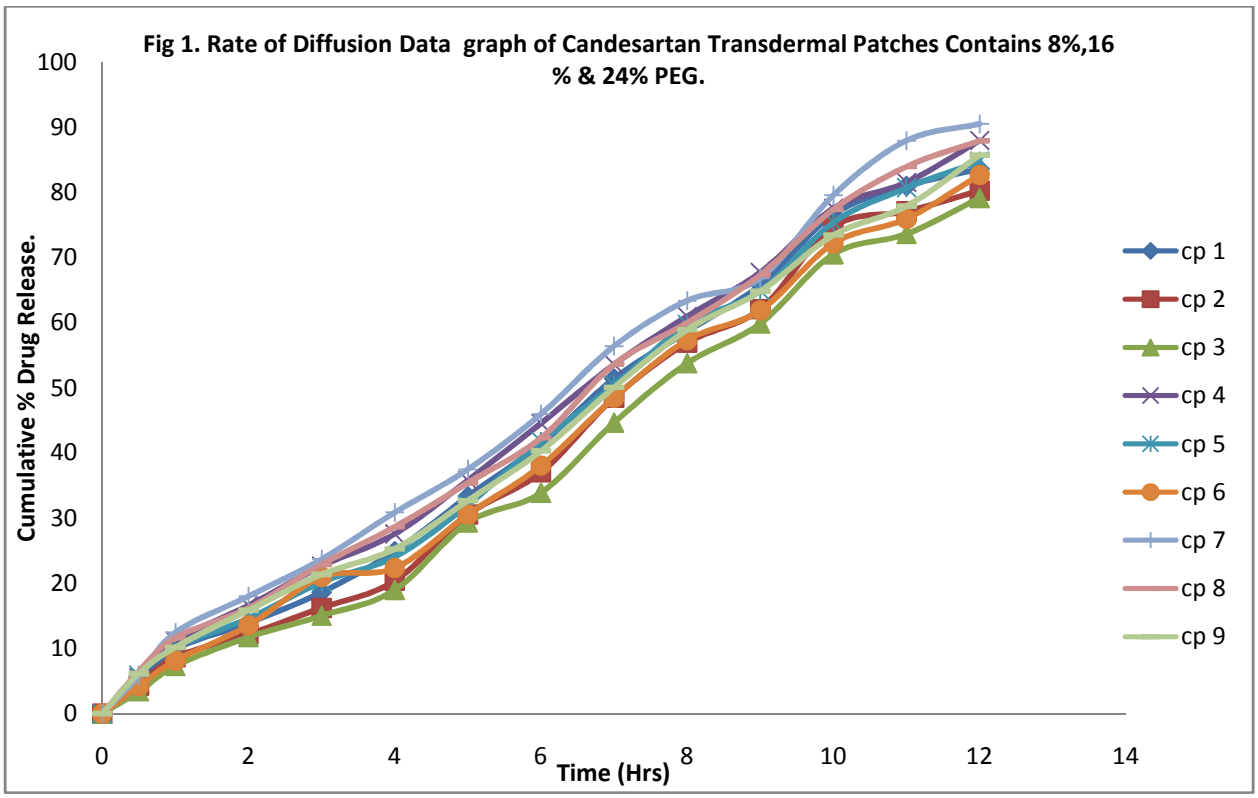
Fig 1. Rate of Diffusion Data graph of Candesartan Transdermal Patches Contains 8%,16 % & 24% PEG.
Cumulative % Drug Release.
Time (Hrs)
0
10
20
30
40
50
60
70
80
90
100
0
2
4
6
8
10
12
14
cp 1
cp 2
cp 3
cp 4
cp 5
cp 6
cp 7
cp 8
cp 9

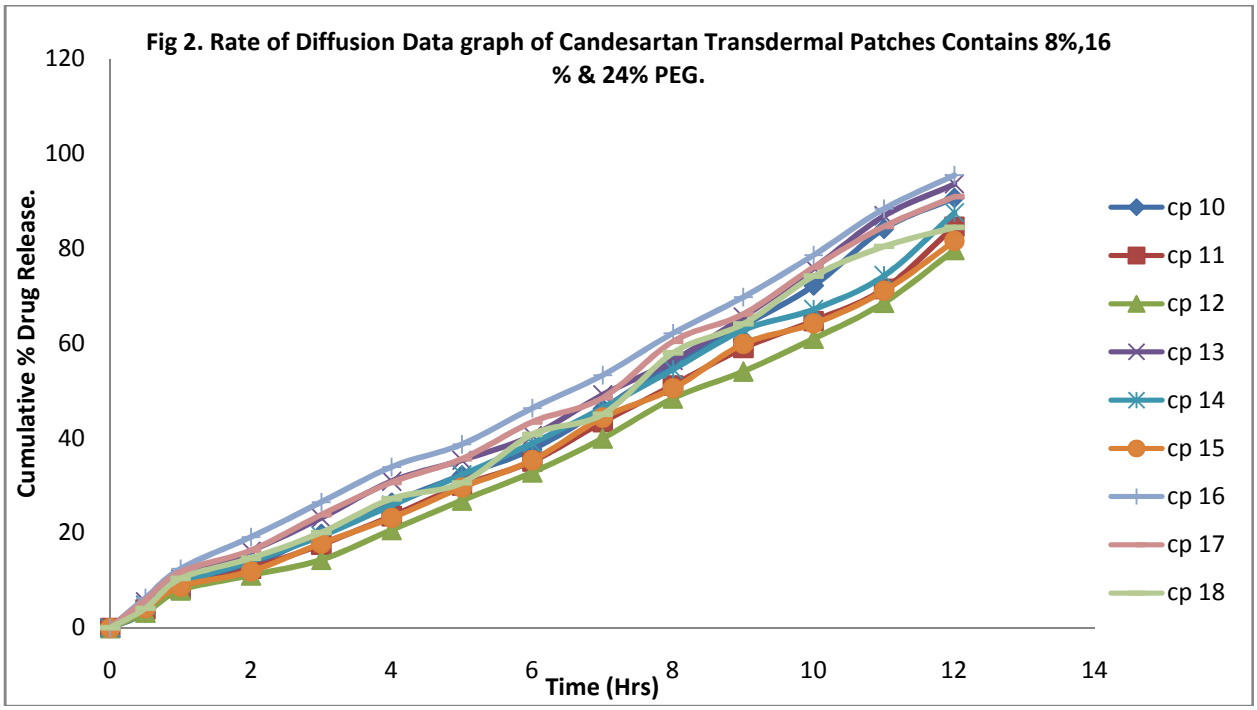
Fig 2. Rate of Diffusion Data graph of Candesartan Transdermal Patches Contains 8%,16 % & 24% PEG.
Cumulative % Drug Release.
Time (Hrs)
0
20
40
60
80
100
120
0
2
4
6
8
10
12
14
cp 10
cp 11
cp 12
cp 13
cp 14
cp 15
cp 16
cp 17
cp 18

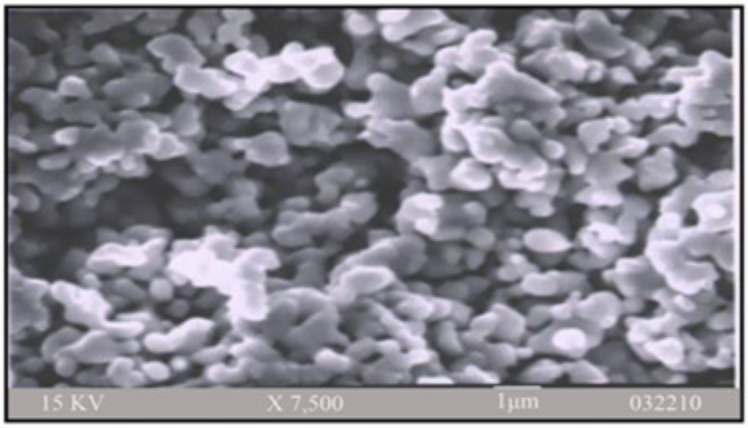

Fig 3. SEM Photograph depicting Candesartan and PEG 300 loaded

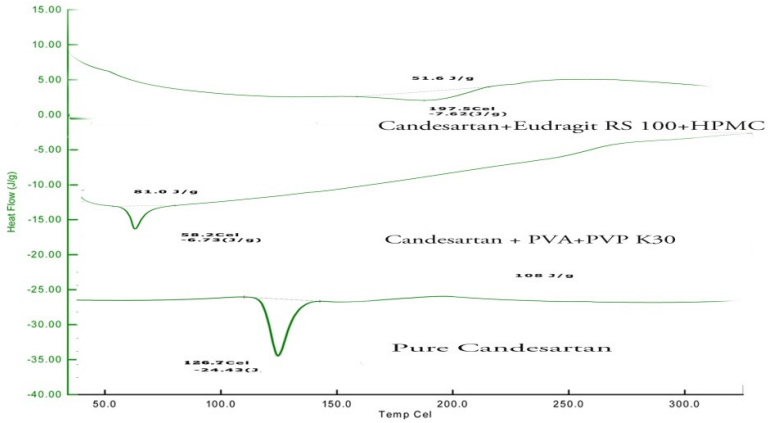

Fig 4. DSC graphs of Candesartan and Candesartan with polymers.

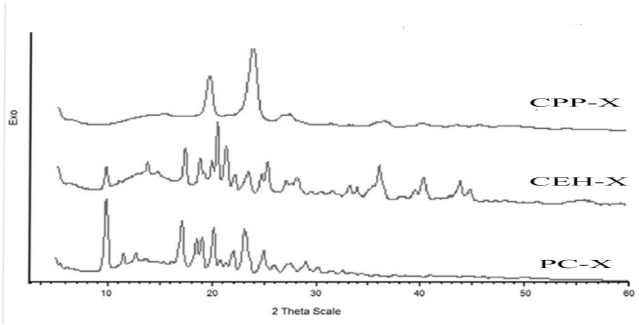

Fig 5. XRD of Cand (PC-X) & Cand+Eud+Hpmc(CEH-X), Cand+pva+pvp(CPP-X).

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