Research Article CODEN: IJPRNK ISSN: 2277-8713
P. Prem Kumar, IJPRBS, 2015; Volume 4(2): 503-518 IJPRBS

INTERNATIONAL JOURNAL OF
PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

DESIGN AND EVALUATION OF CONTROLLED RELEASE TRANSDERMAL DOSAGES FORM OF SELECTED CARDIOVASCULAR DRUG LOSARTAN

P. PREM KUMAR, K. BALAMURUGAN, SYED ABDUL AZEEZ

Department of Pharmacy, Annamali University, Annamalai Nagar, Chidambaram, Tamilnadu, India.

Accepted Date: 19/04/2015; Published Date: 27/04/2015

Abstract: The aim of the present research work is to design and evaluate controlled release transdermal patches of selected cardiovascular drug losartan. Under with aim, the following major or broad objectives have been set to design and formulate matrix and membrane moderated based transdermal patch of losartan by solvent evaporation method using a few selected polymers as permeation enhancers such as HPMC, PVA, PVP, DMSO, DMF, Oleic acid, and Eudragit as release retardant for controlled release. To optimize the prepared formulations by different trial approaches. Losartan was chosen as a model drug for study since it possess near ideal characteristic that a drug must have in formulating a drug delivery system such as low molecular weight, high lipid solubility, effective in low plasma concentration as well as high degree of first-pass effect and short oral half-life of 1.5-2h has made the drug a suitable candidate for transdermal delivery. It also means multiple administrations with subsequent lack of patient compliance. The aim of the study was to prevent its first-pass metabolism and achieve control release by designing transdermal drug delivery system.

Keywords:, FT-IR, Transdermal patches, Losartan, HPMC, PVA, PVP, DMSO, DMF, Oleic acid and Eudragit.

PAPER-QR CODE

Corresponding Author: MR. P. PREM KUMAR

Access Online On:

www.ijprbs.com

How to Cite This Article:

P. Prem Kumar, IJPRBS, 2015; Volume 4(2): 503-518

INTRODUCTION

From cardiovascular diseases, 5.2 million people death in world wide and 9.1 million people death in economically developed countries. Worldwide prevalence estimates for hypertension may be as much as 1 billion individuals and approximately 7.1 million people deaths per year may be attributable to hypertension (Selvam R.P., et al, 2010). Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths in India (Ghosh V.G et al, 2006**)**. From Indian epidemiological studies show that hypertension is attacks 25% urban and 10% rural subjects. Therefore, cost effective treatment to optimally control blood pressure among Indians are very much needed. So, transdermal drug delivery systems (TDDS) are ideally suited and demanded for chronic treatment diseases like hypertension and cardiovascular diseases and many more (Selvam R.P., et al, 2010).. Despite the suitability of TDDS in the treatment of chronic diseases like hypertension and other cardiovascular diseases required high cost of antihypertensive patches than conventional products made the target patients to think twice. In spite of the high cost of trans dermal patches for hypertension treatment, antihypertensive patches with the established dosage forms reduced the occurrence of hospitalization and diagnostic costs is the major advantages to develop such delivery systems (swain S.K.,et.al, 2011,).

Trans dermal therapeutic systems (TTS) are defined as a self-contained and discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at a control rate to the systemic circulation by maintaining drug concentration within the therapeutic window (Gannu R., et al, 2007). It is an alternative route for systemic delivery of drug which minimizes the drug absorption and increases bioavailability of the drugs (Jain, N.K., et al, 1997). Transdermal patches are delivered the drug through the skin in controlled and predetermined manner in order to increase the therapeutic efficacy of drug and reduced side effects of drug **()**. Controlled drug release can be achieved by transdermal drug delivery systems (TDDS) which can deliver medicines via the skin portal to systemic circulation at a predetermined rate over a prolonged period of time. Matrix type transdermal system remains most popular, among various transdermal systems including membrane moderated, matrix, adhesive matrix, micro reservoir and membrane-matrix hybrid the most popular, because of its easy manufacturing (Mukherjee B., et al, 2005). HPMC is a partially o-methylated and o-(2-hydroxy propylated) cellulose, hydrophilic, nontoxic and biocompatible polymer used in most of the topical pharmaceutical formulations like TDDS (Pawde S., et al, 2008). PVA is an excellent film forming property used to develop films in combination with other polymers containing number of drugs such as nitro furazone (Kim, J.O., et al, 2008a), clindamycin (Kim, J.O., et al, 2008), minocycline (Sung, J.H., et al, 2010), and gentamycin (Hwang, M.R., et al, 2010). In recent years, Eudragit (EG), EG-RL and EG-RS are the zwitterionic copolymers of acrylic and methacrylic esters with pH

independent properties and these copolymers of acrylic and methacrylic acid esters with a low content (2.5-5%) of quaternary ammonium groups widely used to prepare transdermal system because; (i) its ability to retain high percentage of active ingredients, (ii) well tolerated by the skin (Acartfirk, F., et al, 1996), and (iii) controlled release properties (Bagchi, S., et al., 2012). Thus, a number of drugs such as bromhexidine, diclofenac and isosorbit dinitrate, felodipine (Lin, S.Y., et al, 2000), pinacidil monohydrate (Aqil, M., et al, 2002) were formulated with EG as matrix layers of transdermal delivery systems.

Losartan is a competitive antagonist of angiotensin-II which shows higher affinity for angiotensin type I receptor by blocking the action of angiotensin II and it dilates blood vessels and reduces mean systolic blood pressure **(**Radha G.V., et al, 2013**)**. It is used for the management of high blood pressure (BP), congestive heart failure and post-myocardial infarction . It is a BCS class II drug, exhibits low aqueous solubility <0.1 mg/mL with high log P value of 5.8 and low oral bioavailability (25-35%) due to first pass metabolism in liver (cytochrome 450 enzymes) **(**Choi J.K., et al, 2005**)**. Due to its slow dissolution rate in the gastro-intestinal tract coupled with extensive first-pass metabolism, about 38±11% of an oral dose is excreted in urinary excretion **(**Mukherjee, B., et al, 2005**)**. In addition, the ideal properties of losartan such as molecular weight of 422.911, log P value of 4.7 **(**Jain N.K., et al, 1997**)**, melting point of 184°C **(**Srikanth Reddy P ., et al, 2014**)**, and short oral half-life of 1.5-2h has made the drug a suitable candidate for transdermal delivery **(**Rajesh Asija J., et al, 2015**)**.

2. MATERIALS USED

Losartan, Hydroxy Propyl methyl cellulose (HPMC), Poly vinyl Acrylate (PVA), Poly vinyl pyrrolidine (PVP), Dimethyl Sulphaoxide (DMSO), Dimethyl Formamide (DMF), Oleic acid and Eudragit.

3. EXPERIMENTAL METHODS

3.1. Preparation of Transdermal patches of Losartan

Transdermal patches of Losartan were prepared by solvent evaporation technique for the formulations. Solutions of HPMC E-15 and eudragit RS 100 were prepared separately in dichloromethane: methanol (1:1) mixture. The two polymeric solutions were mixed to which weighed amount of Losartan was added slowly. To the mixture, 4 drops of glycerin (0.25 ml), and permeation enhancer (oleic acid/DMSO/DMF) were added and mixed (Ujjawal Nautiyal,. Et al, 1992) The drug-polymer solution was casted in aluminum mould of 25cm2which is wrapped by aluminum foil. The mould was kept aside for drying at room temperature for 24 hrs. Inverted funnel was placed over the mould to prevent the current of air. After drying, the patches were peeled from mould, wrapped in aluminum foil, and preserved in desicator for further studies.

3.2. Evaluation of Losartan patches

3.2.1. *In - vitro* diffusion study of Losartan

An in vitro diffusion study of Losartan from various polymeric matrices was studied using modified Keshary-Chien diffusion cell. The effective permeation area of the diffusion cell and receptor cell volume was 3.14cm2 and 40 ml, respectively. The temperature was maintained at 37 ±0.5oC. The receptor compartment contained 40 ml of P^H 7.4 Phosphate Buffer stirred by magnetic stirrer. Samples (2 ml) were withdrawn and replaced with the same volume of fresh receptor solution, through the sampling port of the diffusion cell at different time intervals. The absorbance of the withdrawn samples were measured using UV -VIS spectrophotometer at 254 nm using P^H 7.4 Phosphate Buffer as a blank. The experiments were done in triplicate. Amount of drug released per square centimeter of patch were plotted against function of square root of time for different formulations. The release rate Q/√T was determined by simple regression analysis of steady state data.

3.2.2. Skin irritation studies

A primary skin irritation test was performed since skin is a vital organ through which drug is transported (Sarkar K., et al, 2014). Skin irritation studies were performed on healthy rabbits (average weight: 1.5 to 2.25 kg). The dorsal surface (50 cm^2) of the rabbits was cleaned, and the hair was removed by shaving. The skin was cleansed with rectified spirit. The best formulation (F4) was placed over the skin with the use of adhesive tape and was removed after 24 hrs. The resulting skin reaction was evaluated.

3.2.3. Physical appearance

The prepared patches were physically examined for colour, clarity and surface texture.

3.2.4. Thickness

The thickness of patches was measured by using electronic caliper, with a least count of 0.01mm (Ramkanth S., et al, 2004*)*. Thickness was measured at three different points on the film and average readings were taken. The order of the thickness of patches is F3 < F4 < F6 < F5 < F2 < F1.

3.2.5. Uniformity of weight

The patch of size 1X1 cm^2 was cut and weight of each patch was taken individually, the average weight of the patch was calculated (Pawde S, et al, 2008).

3.2.6. Tensile strength

Tensile strength of the patches was determined with Universal Strength Testing Machine. The sensitivity of the machine was 1 gram. It consisted of two load cell grips. The lower one was fixed and upper one was movable. The test film of size (4 × 1 cm^2) was fixed between these cell grips and force was gradually applied till the film broke. The tensile strength of the film was taken directly from the dial reading in kg. Tensile strength is expressed as follows (Surya N., et al, 2010)

The order of the tensile strength of patches is F3<F5<F4<F6<F2<F1.

Tensile strength= Tensile load at break cross sectional area.

3.2.7. Folding endurance

The folding endurance was measured manually for the prepared patches. A strip of patch (2x2 cm^2) was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance (Sarkar K., et al, 2014). The order of the folding endurance of patches is F5<F3<F6<F4<F2<F1.

3.2.8. Percentage moisture loss

The patches were weighed individually and kept in a desicator containing calcium chloride. The final weight was noted when there was no change in the weight of individual patch. The percentage of moisture content was calculated as a difference between initial and final weight with respect to final weight. The order of the percentage moisture loss of patches is F2<F1<F3<F5<F6<F4.

3.2.9. Percentage moisture uptake

The patches were weighed accurately and placed in a desicator where a humidity condition of 80-90% RH was maintained by using saturated solution of potassium chloride. The patches were kept until uniform weight is obtained, then taken out and weighed. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight (Ujjawal Nautiyal,. Et al, 1992). The order of the percentage moisture uptake of patches is F4<F2<F3<F5<F6<F1.

3.2.10. Water vapour transmission (WVT) rate

Water vapour transmission (WVT) rate

$$= \frac{\text{Final weight} - \text{Initial weight}}{\text{Time} * \text{Area}}$$

For this study vials of equal diameter were used as transmission cells. These cells were washed thoroughly and dried in an oven. About 1 g of fused calcium chloride was taken in cells and the polymeric patches measuring 1 cm2 area were fixed over the brim with the help of an adhesive (Sarkar k., et al 2014) . The cells were weighed accurately and initial weight was recorded, and then kept in a closed desicator containing saturated solution of potassium chloride to maintain 80-90% RH. The cells were taken out and weighed after 24 hrs. The amount and rate of water vapour transmitted was calculated by the difference in weight using the formula. Water vapour transmission rate is usually expressed as the number of grams of moisture gained/hr/cm2.

The order of Water vapour transmission (WVT) rate of patches is F3<F1<F6<F5<F4<F2.

3.2.11. Drug content uniformity

The patches were tested for the content uniformity. The patches of size 1 cm2 was cut and placed in a 100 ml volumetric flask. The contents were stirred using a magnetic bead for 24 hrs to dissolve the patches. Subsequent dilutions were made with phosphate buffer (pH 7.4). The absorbance of the solution was measured against the corresponding blank solution at 254 nm using UV-visible spectrophotometer. The experiment was repeated three more time to validate the result.

3.2.12. Release kinetics

The analysis of the drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of Transdermal controlled release systems. As a model dependent approach, the dissolution data was fitted to four popular release models such as zero-order, first-order, diffusion and Korsemeyer-Peppas equations, which have been described in the literature. The order of drug release From Transdermal controlled release systems were described by using zero order kinetics or first orders kinetics. The mechanism of drug release from the Transdermal controlled systems was studied by using the Higuchi equation and the Korsemeyer - Peppas equation.

3.12.1. Zero order release

It defines a linear relationship between the fractions of drug released versus time

$Q = kot$

Where, Q is the fraction of drug released at time t and ko is the zero order release rate constant. A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

3.12.2. First order release

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that drug release from most of the slow release tablets could be described adequately by apparent first-order kinetics. The equation that describes first order kinetics is

In (1-Q) = - K1t

Where, Q is the fraction of drug released at time t and k1 is the first order release rate constant. Thus, a plot of the logarithm of the fraction of drug undissolved against the time will be linear if the release obeys the first order release kinetics.

3.12.3. Higuchi equation

It defines a linear dependence of the active fraction released per unit of surface (Q) and the square root of time.

Q=K2t½

Where, K2 is the release rate constant. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependant.

3.12.4. Power law

In order to define a model, which would represent a better fit for the formulation, dissolution data was further analyzed by Peppa's and Korsemeyer equation (Power law).

Mt/Mα = K.tn

The drug release, the value of n can be used. A plot between logs of Mt/Mα against log of time will be linear if the release obeys Peppa's and Korsemeyer equation and the slope of this plot represents "n" value.

3.2.13. Compatibility study by FT-IR analysis

The infrared (IR) spectra were recorded using an FTIR by the KBr pellet method and spectra were recorded in the wavelength region between 4000 and 400 cm^{-1}. The spectra obtained for Losartan, polymers, and physical mixtures of Losartan with polymers were compared (Tangri Pranshu.,et al, 2012) .

4. RESULTS

Table-1: Composition of Different Formulations Containing Losartan Transdermal Patches

Formulations	F1	F2	F3	F4	F5	F6
Losartan (mg)	50	50	50	50	50	50
HPMCE-15 (15CPS)(mgs)	300	200	150	150	150	150
Eudragit RS 100 (mgs)	-	100	150	150	150	150
Glycerine (ml)	0.25	0.25	0.25	0.25	0.25	0.25
Dichloromethane: Methanol(1:1) ml	7	7	7	7	7	7
Oleic acid (ml)	-	-	-	0.25	-	-
DMSO (ml)	-	-	-	-	0.25	-
DMF (ml)	-	-	-	-	-	0.25

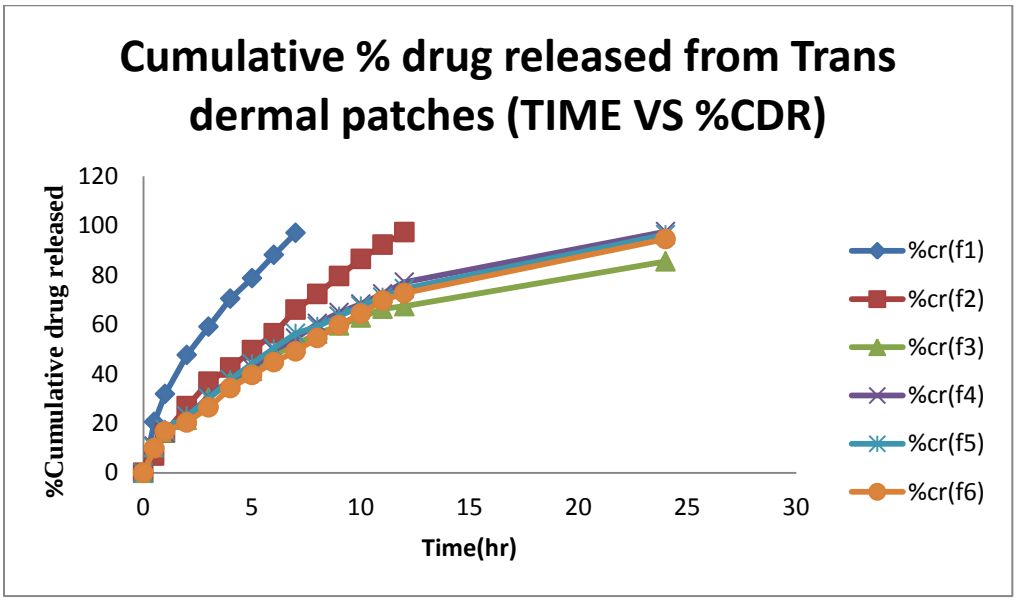

Fig-1- Cumulative percentage of Drug release from Losartan Transdermal Patches

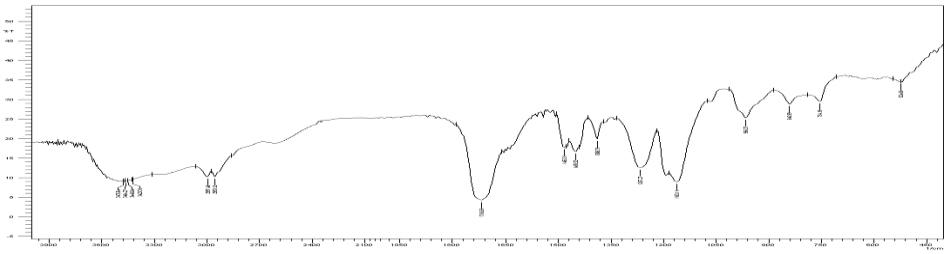

Fig-2- FT-IR Spectrum of Pure Eudragit RS100

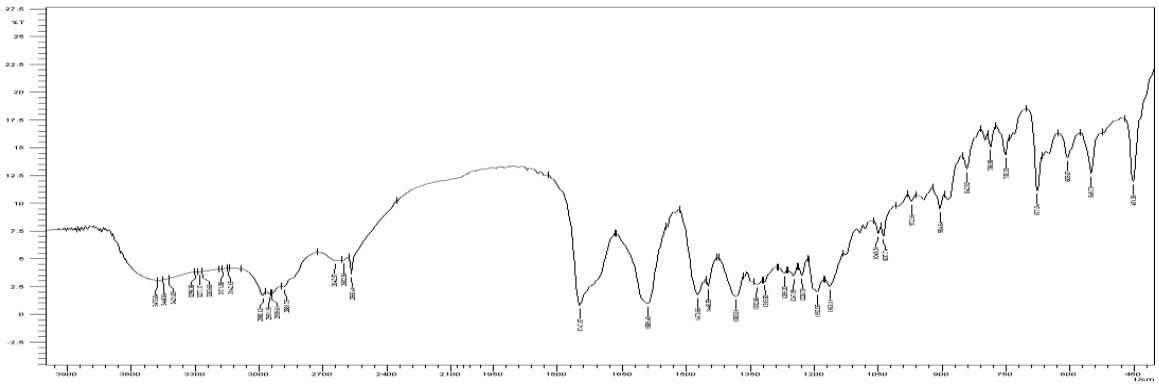

Fig-3-FT- IR Spectrum of Losartan, HPMC-15 and Eudragit Mixture

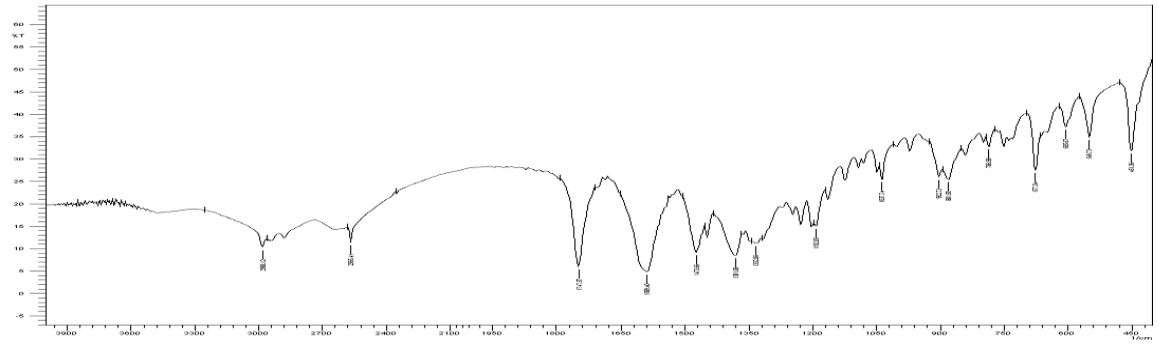

Fig-4-FT- IR Spectrum of pure Losartan

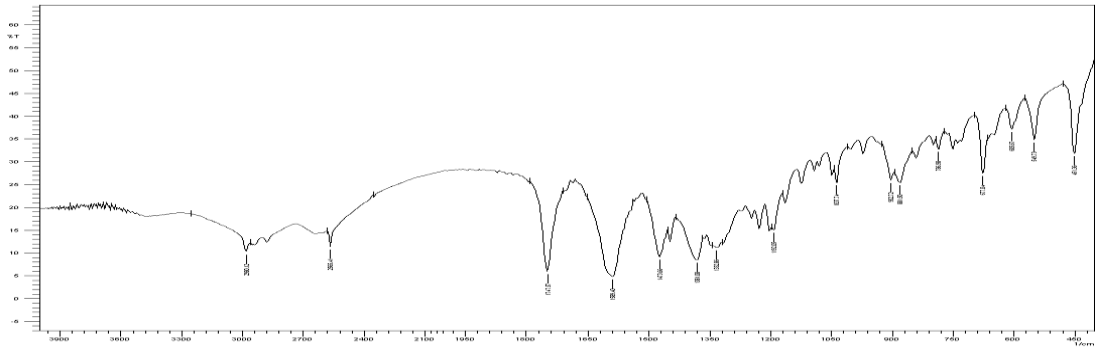

Fig-5-FT- IR Spectrum of (F4) Formulation

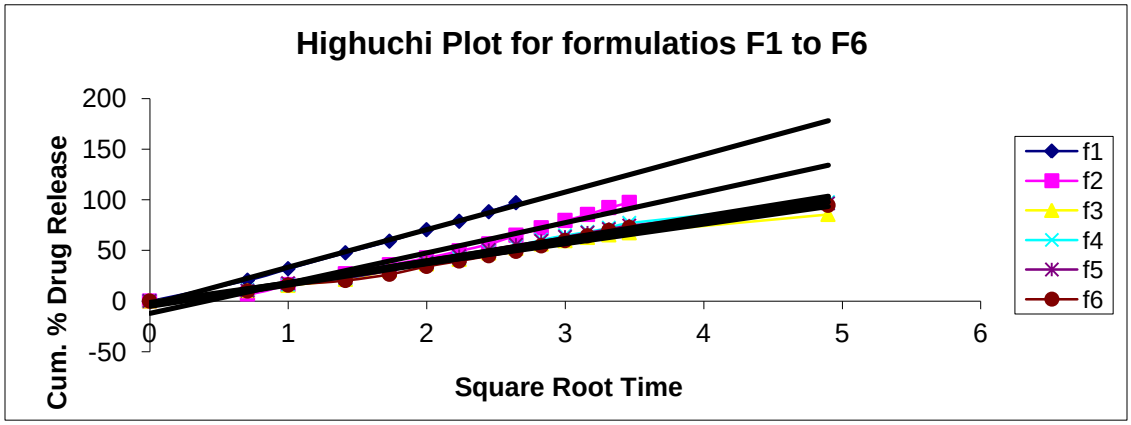

Fig-6- Highuchi Plot for formulations F1 to F6

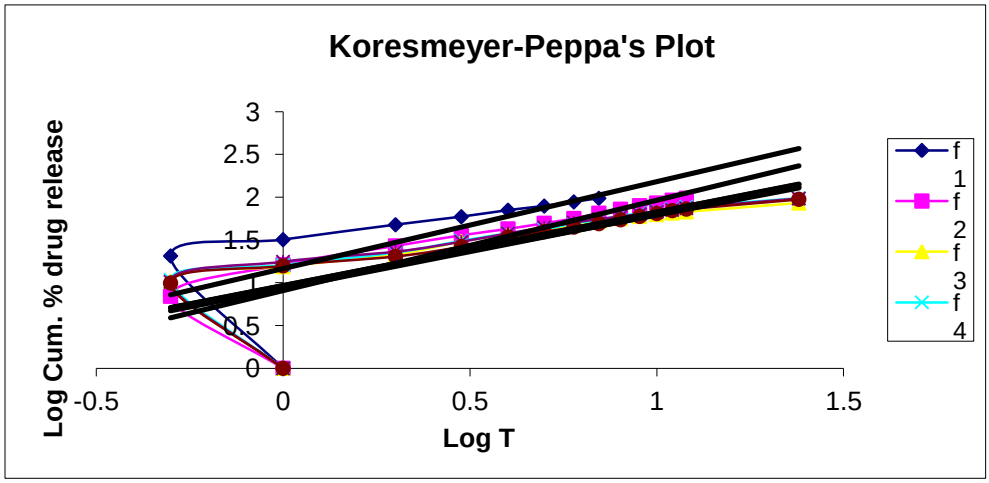

Fig-7- Koresmeyer-Peppa's Plot for formulations F1 to F6

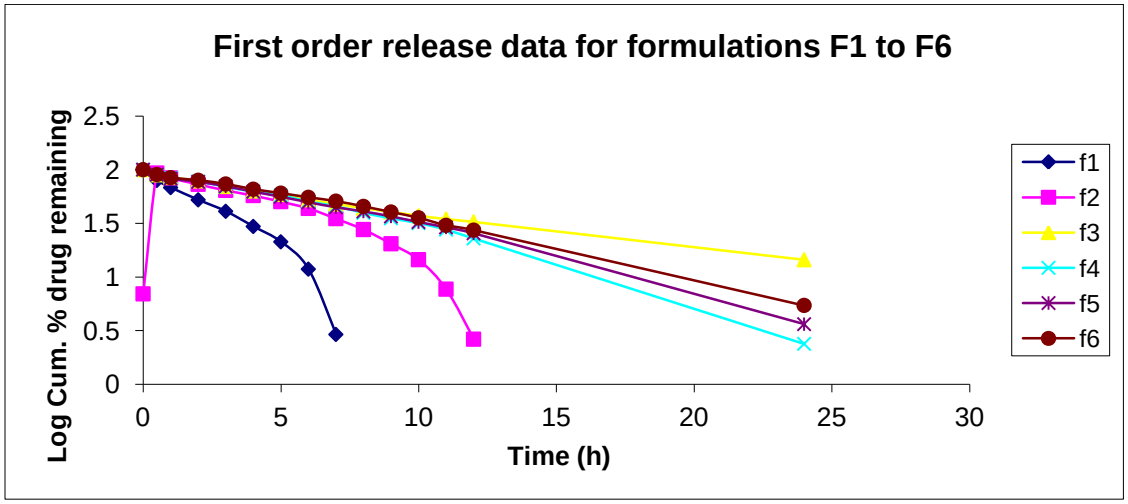

Fig-8- First order release data for formulations F1 to F6

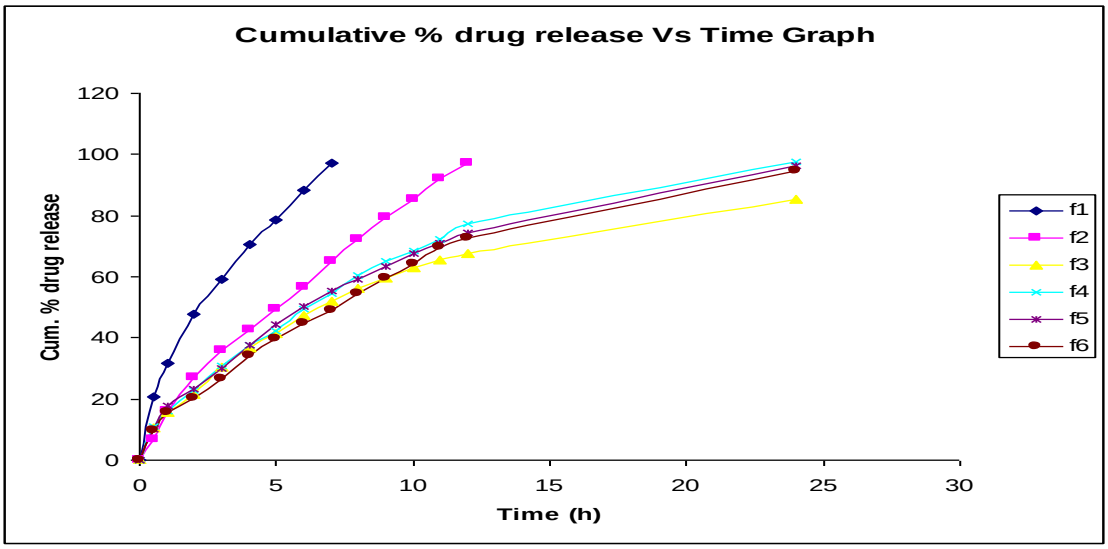

Fig-9- Zero order release data for formulations F1 to F6

Table-2: Cumulative percentage drug release data of transdermal patches of formulations F1 to F6

Time(h)	Cum. % drug release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
0.5	20.57	6.96	10.37	10.81	10.23	9.92
1	31.9	16.23	15.43	16.12	17.58	15.75
2	47.66	26.94	21.41	22.61	23.04	20.35
3	59.1	35.84	30.31	30.87	30.13	26.48
4	70.45	42.59	36.74	37.79	37.73	34.26
5	78.74	49.6	41.21	42.43	44.19	39.58
6	88.17	56.42	47.52	49.5	50.39	44.77
7	97.09	65.01	52.15	54.46	55.46	49.12
8		72.33	56.3	60.44	59.28	54.54
9		79.6	59.6	64.87	63.39	59.7
10		85.51	62.82	68.3	67.55	64.42
11		92.3	65.37	72.41	71.06	69.71
12		97.37	67.41	77.17	74.52	72.69
24			85.53	97.62	96.37	94.57

Table-3: Standard plot for Losartan pH 7.4 phosphate buffer

Concentration µg/ ml	Absorbance at 254 nm
4	0.180
8	0.295
12	0.460
16	0.584
20	0.746
24	0.855
28	1.005

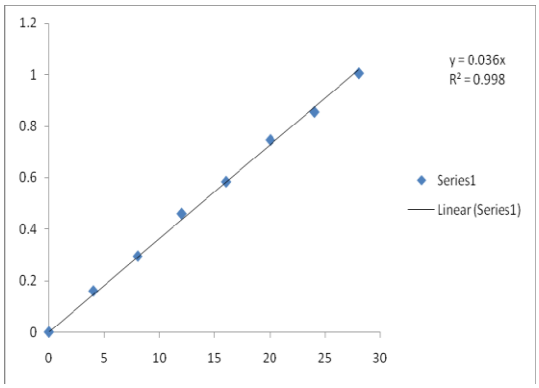

Fig-10: Calibration graph of Losartan in pH 7.4 phosphate buffer

Table-4: Release Kinetics data for transdermal patches of formulations F1 to F6

FORMULA	ZERO ORDER (R2)	FIRST ORDER	HIGUICHI	koresmeyer R^2	Peppas plot n
F1	0.9519	0.90063	0.9463	0.4345	1.0173
F2	0.987	0.4112	0.9747	0.7284	1.0573
F3	0.8349	0.9843	0.9826	0.6528	0.8358
F4	0.8682	0.9694	0.9850	0.6633	0.8625
F5	0.8651	0.9817	0.9878	0.6581	0.856
F6	0.8905	0.9874	0.9837	0.6771	0.8616

Table-5 : Evaluation Parameters of transdermal patches of Formulations F1-F6

Formulation code	Thickness (mm)	Weight uniformity	Tensile strength (kg)	Folding endurance	Percentage moisture absorption (%)	Percentage moisture loss (%)	Water vapour transmission rate	Drug content uniformity (mg)
F1	0.21	0.0426	2.841	157.66	7.751	41.666	0.0065	1.97
F2	0.19	0.0336	2.225	122.33	6.666	12.345	0.0072	1.94
F3	0.1733	0.0313	1.697	82	7.842	12.643	0.006	1.8
F4	0.18	0.0333	1.845	98	12.12	8.6016	0.0071	1.91
F5	0.1866	0.0336	1.823	72.66	9.09	13.541	0.007	1.88
F6	0.1833	0.033	1.867	89.33	10.416	14.583	0.0069	1.9

5. DISCUSSION AND CONCLUSION

Losartan, an antihypertensive agent which selected for the preparation of transdermal delivery system as it complies with physicochemical properties required to permeate through skin. The pre formulation studies involving description, solubility, melting point, partition coefficient of the drug were found to be comparable with the standard. The patches were prepared by solvent evaporation method. The patches were subjected for following evaluation parameters such as physical appearance, weight variation, thickness, folding endurance, drug content, percentage moisture absorption, percentage moisture loss, water vapour transmission rate, tensile strength, diffusion studies and skin irritation studies. All the parameters shows were within the limits. Based on all these results, the transdermal drug delivery system F1 which is containing HPMC E-15 alone showed better drug release, but lasts for only 7 hrs. Formulation F2 containing HPMC E-15: Eudragit RS 100 (2:1) shows comparable release with F1 but it lasts for 12 hrs. The formulation F3 containing HPMC E-15: Eudragit RS 100 (1:1) shows extended release up to 24 hrs when compared to formulations F1 and F2 but the drug is not completely released at the end of 24 hrs. The patches F4 to F6 were prepared by incorporating permeation enhancers, which showed promising result.

The patches containing oleic acid shows near complete release followed by DMSO and DMF, From the above studies, it is revealed that the present work was a satisfactory preliminary study of improving bioavailability of Losartan by transdermal patches using HPMC E-15 and Eudragit RS 100. Further detailed investigations and elaborate *in-vivo* studies need to be carried out and an *in vitro-in vivo* correlation need to be established to guarantee the efficiency and bioavailability of the formulation. Further studies on improving bioavailability have to be carried out with different polymers. The release kinetics was evaluated by making use of zero order, first order, Higuchi's diffusion and Korsemeyer - Peppas equation. Calculated regression co-efficient values for different formulations. These values are compared with each other for model and drug equation. Based on the higher regression values (r2), the best fit model was zero order for F1 and F2 formulations. Whereas first order release for F3, F4, F5 and F6

formulations and the release kinetics following diffusion controlled mechanism. The Peppas model is widely used when the release mechanism is not well known or when more than one type of release phenomenon could be involved. 'n' value could be used to characterize different release mechanism. As the values obtained were more than 0.5, this indicates that the release approximates non fickian diffusion.

6. REFERENCES

1. Bangale, B. Stephen Rathinaraj, Rajesh K. S1, Gajanan V. **Shin** *J. Chem. Pharm. Res., 2010, 2(3):593-604*

2. Brito Raj S. *International Journal of Pharmacy & Therapeutics*, 4(2), 2013, 127-133.

3. F. Acartfirk, Sencan, A. Int. J. Pharm. 131 (1996) 183-189.

4. G.V Radha, N. swetha, P. bharathi, P.s.s.rk Aruna Gowri and K. Neeraja, Journal pharmaceutical and scientific innovation 2(1) 2013, 57-60

5. Heba S. Elsewedy, Mahmoud M. Ibrahim, Mahmoud A PHARMA SCIENCE MONITOR Vol - 4, Issue - 4, Jul-Sept 2013

6. J.H. Sung, M.-R. Hwang, J.O. Kim, J.H. Lee, Y.I. Kim, J.H. Kim, S.W. Chang, S.G. Jin, J.A. Kim, W.S. Lyoo, S.S. Han, S.K. Ku, C.S. Yong, H.-G. Choi, Int. J. Pharm. 392 (2010) 232-240.

7. J.O. Kim, J.K. Park, J.H. Kim, S.G. Jin, C.S. Yong, D.X. Li, J.Y. Choi, J.S. Woo, B.K. Yoo, W.S. Lyoo, J.A. Kim, H.G. Choi, Int. J. Pharm. 359 (2008a) 79-86.

8. J.O. Kim, J.Y. Choi, J.K. Park, J.H. Kim, S.G. Jin, S.W. Chang, D.X. Li, M.R. Hwang, J.S. Woo, J.A. Kim, W.S. Lyoo, C.S. Yong, H.G. Choi. Biol. Pharm. Bull 31 (2008) , 2277-2282.

9. Jeevanandham Somasundaram., American *Journal of Biological and Pharmaceutical Research. 2014;1(1):37-42*

10. K. Kavitha and Mangesh rajendra., International Journal of Pharma and Bio Sciences 2(2), 2011 54-62,

11. Kumboji.Shruthi, V.Uma maheshwara rao, K.Mahalaskhmi, b.shalini krishna *Int.J.Inv.Pharm.Sci.,1(6)2013;515-525*

12. M. Aqil, Asgar Ali, Eur. J. Pharm. Biopharm. 54 (2002) 161-164.

13. M. Bharkatiya, R. K. Nema, M. Bhatnagar International Journal of Pharmaceutical Sciences and Drug Research 2010; 2(1): 35-39

14. M.-R. Hwang, J.O. Kim, J.H. Lee, Y.I. Kim, J.H. Kim, S.W. Chang, S.G. Jin, J.A. Kim, W.S. Lyoo, S.S. Han, S.K. Ku, C.S. Yong, H.-G. Choi, AAPS PharmSciTech 11 (2010) 1092-1103

15. Manzoor Ahmed., Acta chimica & Pharmaceutical indica., 2(3), 2012, 134-142, Simultaneous estimation of Atenolol and hydrochlorothiazide in combined dosage form by UV-spectrophotometric method

16. Mukherjee, B., Mahapatra, S., Gupta, R., Patra, B., Tiwari, A., Arora, P. Eur. J. Pharm. Biopharm. 59 (2005) 475-483.

17. N. K. Jain. Controlled and Novel Drug Delivery, CBS Publishers & Distributors Pvt. Ltd, ed. I 1997, reprint 2011, pp. 118- 127.

18. P Srikanth Reddy, D Saritha, M Ravi Kumar and K N Jayaveera Indian Journal of Mednodent and Allied Sciences Vol. 2, No. 1, February 2014, pp- 34-40

19. Rajesh Asija, Avinash Gupta and Bhagwan Swaroop Maheshwari *International Journal of Advances in Scientific Research* 2015; 1(1): 38-44.

20. Rajesh Asija, Avinash Gupta, Bhagwan Swaroop Maheshwari Journal of Drug Discovery and Therapeutics 2014 2 (21) 2014, 13-18

21. S. Bagchi, W. Li, F. Plakogiannis, Pharm. Dev. Technol. 17 (2012) 398-406.

22. S. P. Vyas, R. K. Khar. Controlled Drug Delivery concepts and advances, Vallabh Prakashan, ed. I 2002. Reprint 2005, pp. 440-446

23. S. Pawde, K. Deshmukh, J. Appl. Polym. Sci. 109 (2008) 3431-3437.

24. S. Ramkanth *et al.,* Int. J. Res. Pharm. Sci., 2(4), 2012, 692-697

25. S.-Y. Lin, K.-S. Chen, L. Run-Chu, J. Control. Release 68 (2000) 343-350.

26. Tangri Pranshu., IRJP, 2012 3 (5)., Development and validation of UV spectrophotometric method for the estimation of Losartan bulk drugs and pharmaceutical formulation.

27. Tripathi, K.D., Essentials of Medical Pharmacology, Jaypee Brothers Medical Publications (P) Ltd, New Delhi 2008. Dekker, New York 2004.

28. Ujjawal Nautiyal, Devendra INDIAN JOURNAL OF PHARMACEUTICAL & BIOLOGICAL RESEARCH (IJPBR), Vol. 1(1); March, 2013.

29. V Sarkar, KC Yadav, Formulation and evaluation of prolonged release transdermal drugdelivery system of atenolol for the treatment of hypertension, 2014, 2(2), 134-140.

30. Jamakandi V.G.,Ghosh,B.,Desai., Indian J Pharm sci 2006,556-561.

31. Surya N. Ratha Adhikari, Formulation and Evaluation of Buccal Patches for Delivery of Atenolol AAPS Pharm Sci Tech, Vol. 11, No. 3, September 2010.