WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 12, 2004-2016. Research Article ISSN 2277– 7105

DEVELOPMENT AND INVITRO CHARACTERIZATION OF TRANSDERMAL PATCHES OF IMIDAPRIL

Pamu Sandhya[*1,2] and Syeda Shadan Samreen[2]

[1]University College of Technology, Department of Pharmacy, Osmania University, Hyderabad 500 007, Telangana State, India.

[2]Shadan Women's College of Pharmacy, Department of Pharmaceutics, Khairatabad, Hyderabad, 500 004, Telangana State, India.

Article Received on
23 Oct 2015,

Revised on 13 Nov 2015,
Accepted on 03 Dec 2015

***Correspondence for Author**
Pamu Sandhya
University College of Technology, Department of Pharmacy, Osmania University, Hyderabad 500 007, Telangana State, India.

ABSTRACT

Transdermal drug delivery systems are polymeric patches containing dissolved or dispersed drugs that deliver therapeutic agents at a constant rate to the human body. Matrix type transdermal patches containing imidapril were prepared by solvent casting method employing a mercury substrate by using the combinations of HPMC, PEG-400 in different proportions. The transdermal patches were evaluated for their physicochemical properties like thickness, weight variation, tensile strength, folding endurance, drug content, swellability, in -vitro permeation studies. FTIR and UV studies indicated no interaction between drug and polymers. The permeability of imidapril was increased with increase in PEG-400 content. The burst effect due to the incorporation of PEG-400 was because of the rapid dissolution of the surface hydrophilic drug which results in the formation of pores and thus leads to the decrease of mean diffusional path length of the drug molecules to permeate into dissolution medium and higher permeation rates. The in vitro drug permeation followed higuchi kinetics as its coefficient of correlation values predominates over zero order, which indicated fickian transport diffusion. Among all the prepared patches F8 would be better formulation based on the in vitro permeation studies. Based on the above observations, it can be reasonably concluded that HPMC, PEG-400 polymers are better suited for the development of transdermal patches of imidapril.

KEYWORDS: Transdermal patches, imidapril, *in vitro* permeation, HPMC, PEG-400.

INTRODUCTION

The goal of any drug delivery system is to provide therapeutic amount of drug to the proper site in the body to promptly achieve and then maintain the desired drug concentrations. Controlled release drug administration means not only prolonged duration of drug delivery, as in sustained release, but also implies predictability and reproducibility of drug release kinetics. Major benefits of drug delivery system include prolong, efficient and effective delivery of therapeutic dosages, patient compliance and localization of therapy.[2]

Transdermal drug delivery systems are a new class of novel drug delivery systems. A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a time released dose of medication through the skin for treating systemic illness.[3,4]

The systemic treatment of disease via transdermal route is not a recent innovation. But, in the last two decades, transdermal drug delivery has gained increasing interest. The delivery of drugs using skin as the port of entry is known as transdermal administration and the drug delivery systems are known as transdermal therapeutic systems or transdermal drug delivery system or popularly known as transdermal patches[5]

The success of this approach is evidenced by the fact that there are currently more than 35 approved transdermal drug delivery products for the treatment of a wide variety of conditions including hypertension, angina, motion sicknesses and recently contraception and urinary incontinence.[6]

Sufficient aqueous and lipid solubility, a Log P (octanol/water) between 1-3 is required for the permeate to successfully traverse the stratum corneum and its underlying aqueous layers for systemic delivery to occur.

MATERIALS AND METHODS

Materials

Imidapril was obtained as a gift from Natco pharma ltd. Hyderabad. Hydroxy propyl methyl cellulose was obtained from S.D. Fine Chem. Ltd. India. Polyethylene glycol, Di-chloro methane, Di- methyl sulfoxide from S.D.fine chemicals, Mumbai, India. Methanol was obtained from Merck. Ltd. India. All other chemicals used were of analytical grade.

Method

Drug polymer interaction studies

This was carried out to check the compatibility between drugs and various polymers. It is therefore necessary to confirm that drug is not interacting with polymers under experimental conditions and shelf life.

UV analysis

The aqueous solutions of the pure drug and the patches containing Imidapril are scanned for UV absorption between 200-400nm.

FTIR analysis

Infra red spectroscopy was carried out on pure drug and physical mixtures of drug and polymer between 400 cm^{-1}-4000cm^{-1}.

Formulation of transdermal patches

Matrix type transdermal patches containing Imidapril were prepared by solvent casting technique.[7] The composition of transdermal patches is shown in Table 1.

Table 1: Formulation of transdermal patches using various polymers.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Imidapril	5	5	5	5	5	5	5	5
HPMC K15 M	40	30	50	40	40	40	30	50
PEG 400	5.6	4.5	7.5	4.8	6.4	5.6	4.5	7.5
DCM & Methanol (20:20)	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1
DMSO (%)	1	1	1	1	1	1	0.75	1.25

Evaluation of transdermal patches

Post formulation evaluation parameters

The prepared transdermal patches were evaluated for Thickness, Weight variation Folding Endurance, Swelling Index, Percentage of Moisture Content, Tensile Strength Test, *In-vitro* Permeation Study, *In-Vitro Dissolution study*, Kinetics of drug release.

Thickness

The thickness of film is measured using micrometer screw gauge. The thickness was measured at five different points on the film and average of five readings was taken and standard deviation and from also calculated.[8]

Weight variation

Weight variation was determined by cutting the transdermal patch into 1cm^2 using mold, weighing three patches individually, from each batch and then average weight was calculated.[9]

Folding endurance

A modified USP tablet disintegration tester was used to determine the folding endurance of the membrane. It consisted of fixed and movable jaws that could be moved up and down at the rate of 30 stokes per minute. The distance between 2 jaws at their farthest and closest were 6 centimeter and 0.5 centimeter respectively. The membrane (6cm length) was clamped between the jaws in such a way that the jaws were at their closest, the membrane beats across its middle and when at their farthest, the membrane was in a stretched condition Thus for every stock of the movable jaw the membrane went through one cycle of bending and stretching. The folding endurance is expressed as the number of strokes required to either break or develop visible cracks on the membrane. The test was conducted for 20min equating 600 strokes**.** The locally fabricated folding endurance tester.[14]

Bursting strength

The bursting strength of all the films were evaluated by using standard burst strength tester the result obtained in terms of Kg/ cm^2.[10]

Swelling index

The polymer membrane cut into 3cm^2 was weighed accurately and kept immersed in 50 ml of phosphate buffer. The films were taken out carefully at 5,10,30,60 minute intervals blotted with filter paper to remove the water present on their surface and weighed accurately swelling index calculated using formula.[15]

$$\text{Swelling Index} = \frac{\text{Wet weight - Initial weight}}{\text{Wet weight}} \text{X}\,100$$

Percentage of moisture content

The membrane of size 3cm^2 were weighed individually and stored in desiccator consists of fused calcium chloride at room temperature for 24 h. Individual membranes were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated until they showed a constant weight. The percentage of moisture content was calculated as difference between initial and final weight with respect to final weight.

$$\%\text{Moisture Content} = \frac{\text{Initial weight - final weight}}{\text{final weight}} X\,100$$

Tensile strength and extension

Tensile strength[11] of the films was determined by using house field universal testing machine. The sensitivity of the machine was 1mg-500mg. It consists of two load cell jaws. The upper one is movable and lower one is fixed. The films of specific size (4x1cms) was fixed between these grips and upper jaw was moved at speed of 100 mm/min. (ISI STD speed) applying force gradually till the films break. The tensile strength of the films was taken directly from the dialed reading in kilograms and extension of film in mm.

Films were fixed over the brim with the help of an adhesive tape. These pre weighed vials were placed in a closed desiccators containing saturated solution of potassium chloride. The cells were removed and weighed every day for seven days of storage.

WVT= WL/S

Where, W= Weight of water vapour transmitted in g,

L= Thickness of film in cm^2

S= Exposed surface area in cm^2

Drug content

A film of $1cm^2$ area cut into small pieces and dissolved in 10ml of methanol and volume was adjusted with phosphate buffer pH to 100ml of above solution was taken in a 100ml volumetric flask. The solution was filtered and the drug was determined spectroscopically.[15]

***In vitro* permeation study**

The in vitro skin permeation experiments were conducted in a modified diffusion cell (receptor compartment capacity: 16ml surface area: 1.5 cm^2). The temperature of whole assembly was maintained at 37 ± 0.5^oC by circulating hot water inside the water jacket. The samples were withdrawn at different time intervals up to 24 h and replenished with an equal volume buffer at each tie interval.[21] The absorbance of withdrawn samples was measured at 247 nm using U.V spectrophotometer.

***In-vitro* drug release profile**

A Paddle over disc assembly was used for the assessment of release of drug. The TDDS patch was mounted on the glass slide and placed at the bottom of dissolution vessel. The

dissolution medium was 900 ml phosphate buffer of pH 6.8. The apparatus was equilibrated at 37±0.50C and operated at 50rpm. The samples (5ml aliquots) were withdrawn at appropriate time intervals upto 10 hrs and analyzed on UV spectrophotometer at 247 nm.

RESULTS AND DISCUSSION

Matrix type transdermal patches of Imidapril were prepared by using hydroxyl propyl methyl cellulose, peg-400, DMSO as film formers by solvent casting method.

Table 2: Spectrophotometric data for the estimation of Imidapril; mean(n=3).

Conc (µg/ml)	Area
0	0
10	0.184
20	0.353
30	0.532
40	0.697
50	0.865

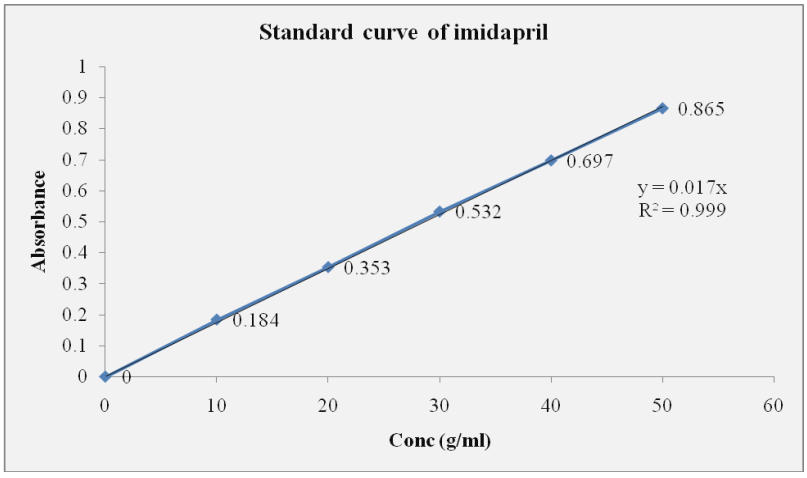

Figure 1: Standard curve of Imidapril in pH 6.8.

FTIR spectroscopy

The results revealed no considerable changes in the IR peaks of imidapril when mixed with excipients compared to pure Imidapril these observations indicated the compatibility of HPMC with Imidapril. The FTIR studies revealed that there is no interaction between drug and polymers. The major peak was observed at 3748.68.

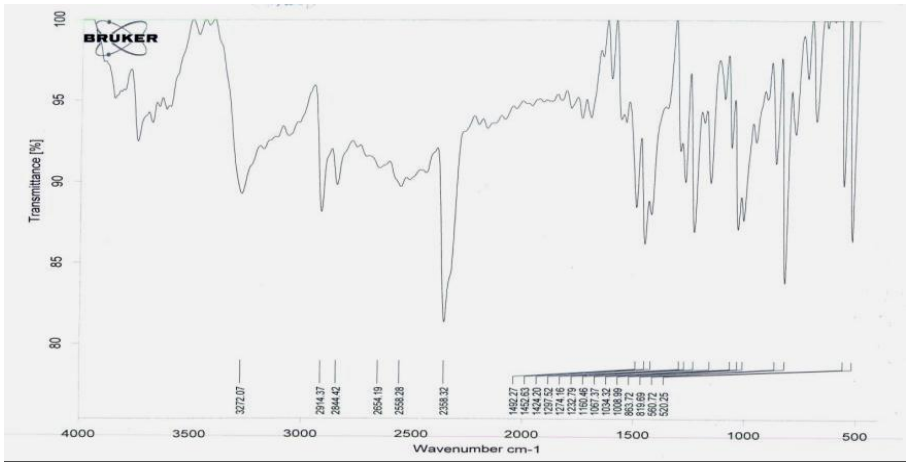

Figure 2: **FTIR spectra of Imidapril.**

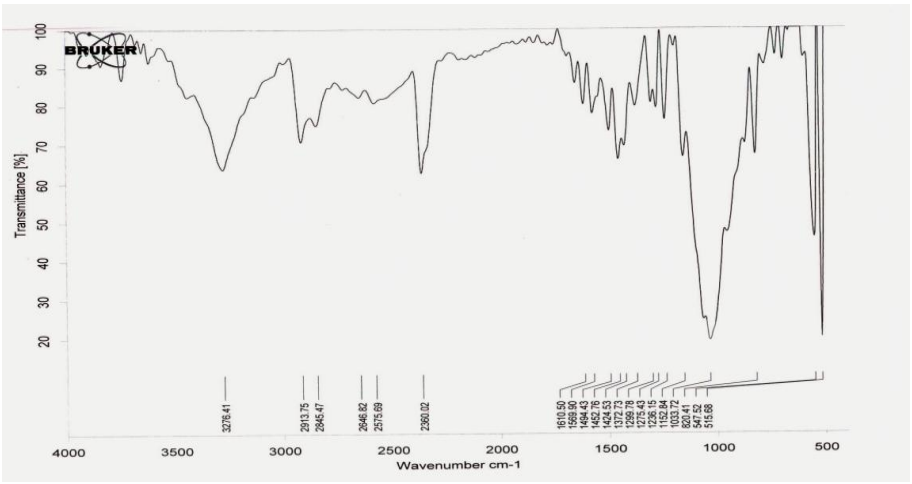

Figure 3: FT-IR spectra of HPMC + Drug.

Evaluation of transdermal patches

A) Pre-formulation evaluation

The bulk density of value is used for determination of compressibility index and hausner ratio.

Compressibility index of formulations indicate the excellent flow property.

Hausner ratio of all formulations are showed indicate the good flow property in >1.25.

Table 3: Pre-Compression Parameters.

Formula Code	Angle of repose (°)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's ratio
API	22.5	0.607	0.647	6.18	1.066

B) Post formulation evaluation

Table 4: Thickness, weight variation and folding endurance of different formulations.

Formulation code	Thickness(mm)* ± SD	Weight variation* (mg) ± SD	Folding endurance*
F1	0.222±0.008	25.66±1.363	No visible cracks
F2	0.234±0.009	29.10±0.967	No visible cracks
F3	0.198±0.016	17.33 ±4.526	No visible cracks
F4	0.206±0.010	27.66±2.778	No visible cracks
F5	0.238±0.012	18.33±3.819	No visible cracks
F6	0.214±0.004	22.11±1.146	No visible cracks
F7	0.226±0.003	29.33±3.958	No visible cracks
F8	0.228±0.005	24.33 ± 0.423	No visible cracks

***mean (n = 5) *mean (n = 3) *mean (n = 3).**

a) Thickness and Weight uniformity

All films were found to be quite uniform in thickness and weight. The results are shown in Table 4.

b) Folding endurance

Results indicated that the membrane would not break and would maintain their integrity with general skin folding when applied.

c) Swelling index

All the films show increase in weight with time. Formulation F1 show highest swelling index of 64.88% where as F6 shows lowest swelling index of 31.42%. The films with show low swelling index as compared to that of films with HPMC.

d) Moisture content

Formulation F6 shows highest moisture content 34.090 ± 2.35 and F2 shows low 9.275 ± 2.733.

e) Bursting strength

Formulation F2 with 30% was found to be highest 4.4±0.2kg/cm^2 where as bursting strength of membrane F5 with 20% glycerin Show lowest 2.23±0.15.

f) Tensile strength and extension

Formulation F8 shows highest tensile strength of 0.815 ± 0.055 and (HPMC blend 30% with plasticizer). Formulation F2, F8 show highest extension where as F3 show low extension (Table 6).

g) Drug content

The membranes were analyzed for drug content. The content of imidapril ranged between (94.59 to 101.78%).

Table 5: Swelling index of different formulations; *mean (n=3).

Formulation	5min	10min	30min	60min
F1	51.315±9.577	53.147±8.967	57.295±9.760	64.885±12.80
F2	47.706±7.025	49.157±6.146	50.392±4.878	57.459±7.553
F3	39.494±1.218	41.819±0.957	43.514±0.015	45.529±0.882
F4	31.402±4.503	33.916±4.630	35.804±5.436	37.554±6.521
F5	24.135±9.641	27.642±9.066	31.530±8.458	34.172±8.912
F6	22.491±10.80	26.034±10.20	29.422±9.949	31.242±10.98
F7	41.438±2.593	43.775±2.340	46.428±2.075	47.998±0.863
F8	44.183±4.534	48.227±5.488	53.553±7.114	55.374±6.079

Table 6: Bursting strength, Tensile strength and drug content of F1-F8.

Formulation code	Bursting strength (Kg/cm^2) * ± SD	Tensile strength (Kg/cm^2) * ± SD	Extension* (cms)± SD	Drug content (mg/cm^2) * ±SD
F1	4.36 ± 0.701	0.755 ± 0.041	0.206 ± 0.01	98.67±0.285
F2	4.4 ± 0.730	0.796 ± 0.070	0.232 ± 0.01	97.36±0.640
F3	2.66 ± 0.500	0.583 ±0.080	0.169 ± 0.02	98.32±0.038
F4	3.2 ± 0.118	0.654 ± 0.030	0.178 ± 0.01	100.78±1.77
F5	2.23 ± 0.804	0.553 ±0.101	0.191 ±0.009	97.77±0.350
F6	2.4 ± 0.684	0.632 ± 0.045	0.197± 0.005	97.66±0.428
F7	3.66 ± 0.206	0.786 ± 0.063	0.229 ±0.017	96.59±1.185
F8	4.03 ± 0.468	0.815 ± 0.083	0.231 ±0.019	98.98±0.504

*mean (n = 3) *mean (n = 3) *mean (n = 3).

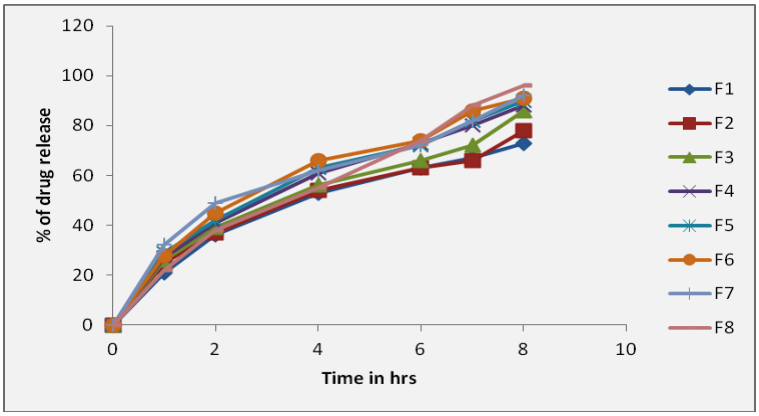

Figure 4: Cumulative In-vitro Drug release of formulations F1 to F8.

Table 7: Cumulative In-vitro Drug release of formulations F1 to F8.

Time in hrs	F1	F2	F3	F4	F5	F6	F7	F8
0	0±31.61	0±32.62	0±34.85	0±37.37	0±38.18	0±39.39	0±39.29	0±37.67
1	21±16.76	25±14.95	26±16.46	27±18.28	29±17.67	28±19.59	32±16.66	22±22.12
2	36±6.161	37±6.464	39±7.273	41±8.384	42±8.485	45±7.576	49±4.646	38±10.80
4	53±5.858	54±5.555	56±4.747	61±5.757	63±6.363	66±7.273	62±4.545	55±1.212
6	63±12.92	63±11.91	66±11.81	73±14.24	72±12.72	74±12.92	72±11.61	74±14.64
7	67±15.75	66±14.04	72±16.06	80±19.19	82±19.79	86±21.41	82±18.68	88±24.54
8	73±20.01	78±22.52	86±25.96	88±24.84	90±25.45	91±2495	92±25.78	96±30.20

Kinetics of drug release studies

The highest % cumulative drug & Enhancement also permeated was found in formulation F8 containing HPMC. The cumulative amount of drug permeated per square centimeter of membrane through dialysis membrane was plotted against time, the permeation profiles of the drug followed first order kinetics. Further to find out whether diffusion is involved in the drug release, the data was subjected to Higuchi's equation. The obtained were comparatively linear (R^2=0.823-0.926) suggesting the diffusion may be mechanism of drug release.

Kinetics of imidapril drug

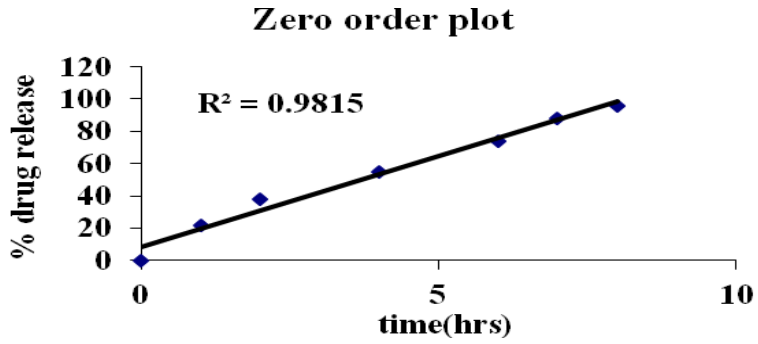

Figure 5: % Drug release Zero order plot.

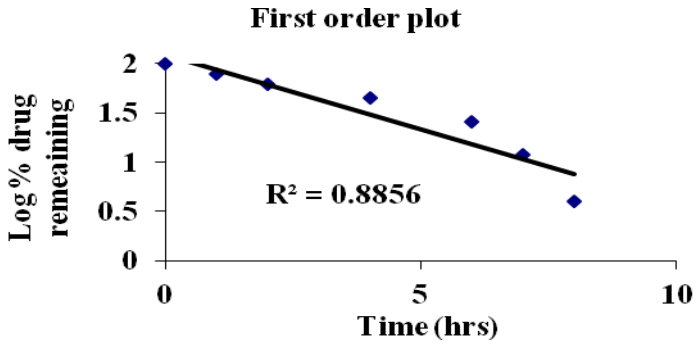

Figure 6: % Drug release First order plot.

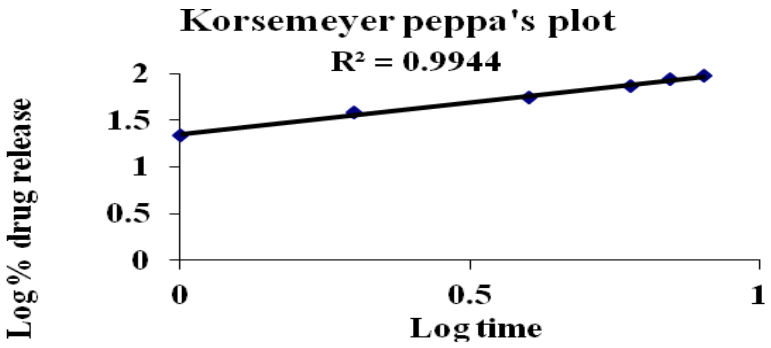

Figure 7: % Drug release Korsemeyer peppa's plot.

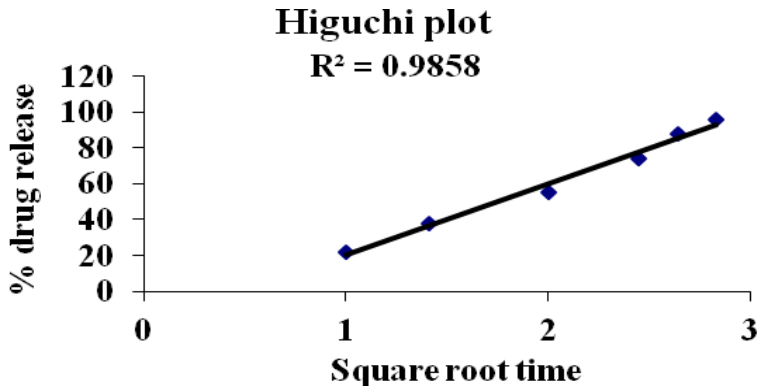

Figure 8: % Drug release Higuchi plot.

Table 8: Various Kinetic models for F1-F8 of Imidapril.

Formulation code	Zero order Plot (R^2)	First order plot (R^2)	Higuchi' s plot	Koresmeyer- peppas plot	
				R^2	N
F1	0.682±0.046	0.995±0.022	0.926±0.039	0.964±0.015	0.855±0.048
F2	0.603±0.009	0.978±0.009	0.911±0.028	0.957±0.010	0.792±0.093
F3	0.584±0.022	0.974±0.007	0.839±0.022	0.933±0.006	0.860±0.045
F4	0.595±0.014	0.987±0.016	0.846±0.017	0.921±0.015	0.866±0.041
F5	0.562±0.038	0.969±0.003	0.823±0.033	0.905±0.026	0.901±0.016
F6	0.627±0.007	0.989±0.017	0.871±0.002	0.940±0.001	0.775±0.105
F7	0.663±0.033	0.992±0.019	0.890±0.013	0.965±0.016	1.163±0.168
F8	0.612±0.002	0.827±0.096	0.859±0.008	0.953±0.007	1.180±0.181

CONCLUSIONS

Among all the prepared patches F8 would be better formulation based on the in vitro permeation studies. The drug release kinetics of all the formulations followed Non- Fickian diffusion mechanism and first order release kinetics. Thus it could be concluded that membranes were stable and further in vivo studies have to be performed to correlate with in vitro release data for the development of suitable patches of Imidapril.

REFERENCES

1. Shaji J, Jain V, and Lodha S. Chitosan: A novel pharmaceutical excipient: Int. J. Pharm. Applied Sci., 2010; 1(1): 11-28.
2. Langer MA, Robinson RJ, sustained release drug delivery systems: Remingtosis Pharmaceutical sciences, Gennaro A.R (ed), 17th Edition Mark publishing company, 1985; 1644-61.
3. Delgadillo JC, Fernandez CB, Pascual AC, Rondero AG, Guerrero DQ, Castellano AC, Merino V, Kalia YN: Transdermal iontophoresis of dexamethasone sodium phosphate in vitro and in vivo: effect of experimental parameters and skin type on drug stability and transport kinetics. Eur. J. Pharm. Biopharm, 2010; 75: 173-78.
4. Sanap GS, Dama GY, Hande AS, Karpe SP, Nalawade SV, Kakade RS, Jadhav UY. Preparation of transdermal monolithic systems of indepamide by solvent casting method and the use of vegetable oils as permeation enhancer. Int. J. Green Pharm, 2008; 129-33.
5. Chein YW, Novel drug delivery systems. 2nd ed. New York: Marcel Dekker Inc., 1992; 50: 338-44
6. Manish K Abheshek KR, Chauhan, Sachin K, Arun K, Sachin M. Design and evalution of pectin based metrics for transdermal patches of meloxicam. JPRHS, 2(3): 244-47.
7. Debjit B, Chiranjib, Margret C, Jayakar B, Sampath KP: Recent advances in transdermal drug delivery sytem: Int. J. Pharm. Tech Res., 2010; 1(2): 68-77.
8. Kaza R, Pitchaimani R. Formulation of transdermal drug delivery system: Matrix type, and selection of polymer, their evaluation. Current drug discovery technologies, 2006; 3: 279-85.
9. Tanu Bhargava, Ramchandini U, Shrivastava SK, Dubey PK. Current trends in NDDS with the special references to NSAIDS: Int. J. Pharm. Biosci., 2011; 2(1): 92-114.
10. Geeta A, Dr. Sanju D. Development, Fabrication and evaluation of transdermal drug delivery system - A Review. Pharmainfo. net., 2009; 7.
11. www.methodisthe health.com/…/ci_0390.gif.
12. Vyas SP, Roop KK. Controlled drug delivery concepts and advances. 1st ed., Delhi: Vallabh prakashan, 2002.
13. Franz TJ. Transdermal Delivery. In: Kydonieus A, ed. Treatise on controlled drug delivery: Fundamentals, optimization, applications. New York, Marcel Dekker Inc., 1991; 341-421.

14. Baker RW, Heller J. Material selection for transdermal delivery systems; cited in: Hadgraft J, Guys RH, editors. Transdermal drug delivery: development issues and research initiatives. New York, Marcel Dekker Inc., 1989; 293-311.
15. Walters KA. Transdermal drug delivery systems In: Swarbick K, Boylan JC, Encyclopedia of pharmaceutical technology. New York, Marcel Dekker Inc., 1997; 253-293.