Research Article CODEN: IJPRNK ISSN: 2277-8713
M Sunitha Reddy, IJPRBS, 2015; Volume 4(6): 28-41 IJPRBS

INTERNATIONAL JOURNAL OF
PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

FORMULATION OF MATRX TRANSDERMAL PATCHES OF OMEPRAZOLE BY USING DIFFERENT PERMEATION ENHANCERS AND THEIR INVITRO EXVIVO EVALUATION STUDY

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Accepted Date: 13/10/2015; Published Date: 27/12/2015

Abstract: Transdermal drug delivery system of Omeprazole has been formulated by using solvent casting method. Monolithic system was prepared by using ethyl cellulose polymer by incorporating glycerin as plasticizer. Olive oil, Caster oil, poly ethylene glycol 400, capryol90 is used as permeation enhancers. All patches are uniform with respect to physicochemical properties. The prepared system releases the drug in following order polyethylene glycol 400 > olive oil > castor oil > capryol90. Flux was determined for all batches and maximum flux for poly ethylene glycol 119.56mg/cm²/h. was observed. The order of flux was polyethylene glycol> olive oil > castor oil > capryol90. In-vitro release studies reveled that release was sustained up to 24 hrs and it follows zero order kinetics all time. All patches are found to be stable at 37℃-45℃ with physicochemical parameters and drug content etc.

Keywords: Omeprazole, Olive oil, Caster oil, Capryol90, poly ethylene glycol400.

PAPER-QR CODE

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How to Cite This Article:

M Sunitha Reddy, IJPRBS, 2015; Volume 4(6): 28-41

INTRODUCTION

Transdermal drug delivery systems are topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate.[1]

A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication. These devices allow for pharmaceuticals to be delivered across the skin barrier. A drug is applied in a relatively high dosage to the inside of a patch, which is worn on the skin for an extended period of time. Through a diffusion process, the drug enters the blood stream directly through the skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow[2]. The present study was designed to develop suitable matrix type transdermal drug delivery systems of Omeprazole using polymers ethyl cellulose with different permeation enhancers in different ratios, which have been used to make drug-polymer matrix patches for transdermal delivery systems which are reported to be compatible with many drugs.

MATERIALS & METHODS

Omeprazole was obtained as a gift sample from Dr. Reddy's laboratories Hyderabad. Ethyl Cellulose, Poly Ethylene Glycol 400 from Merck Ltd., Mumbai, Olive oil, Castor oil from Degussa, Germany Capryol 90 was kindly gifted from Gatteofos.

METHODOLOGY

Preformulation Studies

Preformulation was the first step in the rational development of dosage forms of a drug substance.

Organoleptic properties

The Organoleptic character of the drug like color, odor and appearance play an important role in the identification of the sample.

Solubility Studies[3]

Solubility was carried out in methanol, ethanol, dichloromethane, dimethyl sulfoxide and other solvents to know about solubility characteristics of a drug in lipophilic systems.

Melting point

Melting point of omeprazole drug was determined by melting point apparatus.

Linearity Plot of Omeprazole[4]

Linearity Plot of Omeprazole was determined in P^H 7.4 buffer at the concentrations of 0.2, 0.4, 0.6, 0.8 and1.0µg/ml (2,4,6,8,10ppm respectively) and were analysed in UV- double beam spectrophotometer absorbance at 270nm.

Compatibility Studies

IR spectroscopy can be used to investigate and predict any physicochemical interactions between different components in a formulation. Drug and excipients were scanned from 4000cm^{-1} to 400cm^{-1} in Bruker IR spectrophotometer.

Formulation of Omeprazole Transdermal Patches[5,6]

Accurately weighed 100mg of ETHYL CELLULOSE was dissolved in 20 ml of ETHANOL. After complete dissolution of Ethyl cellulose in Ethanol add 2-3 drops of glycerin to this solution and mix the solution. Take 200mg of omeprazole and dissolved in 10ml of ethanol and mix the omeprazole containing solution and the ethyl cellulose containing solution. Mix the solution by using magnetic stirrer till get a uniform solution. Then pour this solution into a Petri dish of area 69.75cm^2 and allowed to stand for 24 hrs in open air. After 24 hrs of time a clean dried transdermal patch was obtained. From each batch 10 patches of 6.97cm^2 was carved.

Table 1. Composition of Omeprazole transdermal patches

Formulation code	Drug (mg)	Ethyl cellulose (mg)	Ethanol (ml)	Permeation enhancer
F1	200	100	20	Olive oil
F2	200	100	20	Capryol90
F3	200	100	20	Castor oil
F4	200	100	20	P.E.G. 400

Characterization of Omeprazole Transdermal Patches

Physicochemical properties [7,8]

The Patches prepared by general procedure were evaluated for the following properties

Thickness

The thickness of the film was measured at ten different points on one film using vernier calipers. For each formulation three selected Patches were used and average thickness was recorded.

Weight variation

Six Patches from each batch of an area of 6.97 cm^2 were weighed individually and the average weight was calculated.

Folding endurance

Folding endurance of the patch was determined manually by repeatedly folding a small strip of the medicated patch at the same place until broke. The number of times the strip could be folded at the same place without breaking gave the folding endurance number.

Estimation of drug content in polymeric Patches

The formulated polymeric patches were assayed for drug content in each case. Three polymeric patches from each formulation were assayed for content of drug.

Procedure

Patches from each formulation were taken, cut into small pieces and was allowed to dissolve in a 100 ml solution containing 50 ml of methanol and 50 ml of dichloromethane. The solution was diluted suitably and the absorbance of the solution was measured using UV-Vis spectrophotometer at a wavelength of 242 nm against methanol dichloromethane mixture (1:1) as blank.

Moisture Content Determination[9,10]

The patches were weighed accurately and placed in a desicator containing calcium chloride at 40^oC for 24hr. Then the final weight was noted when there was no further change in the weight of individual patch. The percentage of moisture loss was calculated as difference between initial and final weight with respect to final weight.

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

In vitro Release Studies[11]

The drug release studies from Omeprazole transdermal patches were performed using Franz diffusion cell. The drug containing patches was kept between donor and receptor compartments, separated from these compartments by Cellophane membrane. The receptor compartment containing diffusion medium was stirred with magnetic bead operated by magnetic stirrer, to prevent the formation of concentrated drug solution layer below the Cellophane membrane. 5ml of sample was collected from the receptor compartment at appropriate time intervals and replaced with phosphate buffer pH 7.4 Analysis was carried out using UV-Visible spectrophotometer at 242 nm against phosphate buffer pH 7.4 as reference.

Data Analysis[12,13]

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order, Higuchi matrix, Peppas model. Based on the r-value, the best-fit model was selected.

Zero Order Kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation,

$$Q\,t = Q\,o + K\,o\,t$$

$$Where\ Q\,t = amount\ of\ drug\ dissolved\ in\ time\ t.$$

$$Q\,o = initial\ amount\ of\ the\ drug\ in\ the\ solution\ an$$

$$K\,o = zero\ order\ release\ constant.$$

First Order Kinetics

To study the first order release rate kinetics, the release rate data were fitted to the following equation,

$$Log\ Qt = log\ Qo + K1t/2.303$$

Where Qt is the amount of drug released in time t, Qo is the initial amount of drug in the solution and K1 is the first order release constant.

Higuchi Model

Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semisolids and/or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. And the equation is,

$$Qt = KH \cdot t1/2$$

$$Where\ Qt = amount\ of\ drug\ released\ in\ time\ t,$$

$$KH = Higuchi\ dissolution\ constant.$$

Korsmeyer and Peppas Release Model

To study this model the release rate data are fitted to the following equation,

$$Mt / M\infty = K \cdot t\,n$$

Where Mt / M is the fraction of drug release, K is the release constant, t is the release time and n is the diffusional coefficient for the drug release that is dependent on the shape of the matrix dosage form.

Stability Studies [14,15]

The best formulation was sealed in aluminium foil and kept in humidity chamber maintained at 35±2°c/ 60±5% RH or 40 ±2°c/ 75±5% RH for a period of one month.

RESULTS AND DISCUSSIONS

Preformulation Studies

Table No 2- Omeprazole Preformulation studies

S.NO	PARAMETERS	REPORT
1	Physical appearance	Off white fine crystalline power.
2	Solubility	Freely soluble in dimethyl sulphoxide, dichloromethane and methanol.

		Slightly soluble in ethanol and isopropanol.
3	Melting point	114-115^{o}C

In Preformulation studies drug characteristics was performed and results were complies with pharmacopoeial values.

Linearity Plot of Omeprazole

The solutions of Omeprazole were prepared and the absorbance of resulting solutions was measured in UV spectrophotometer at 270 nm.

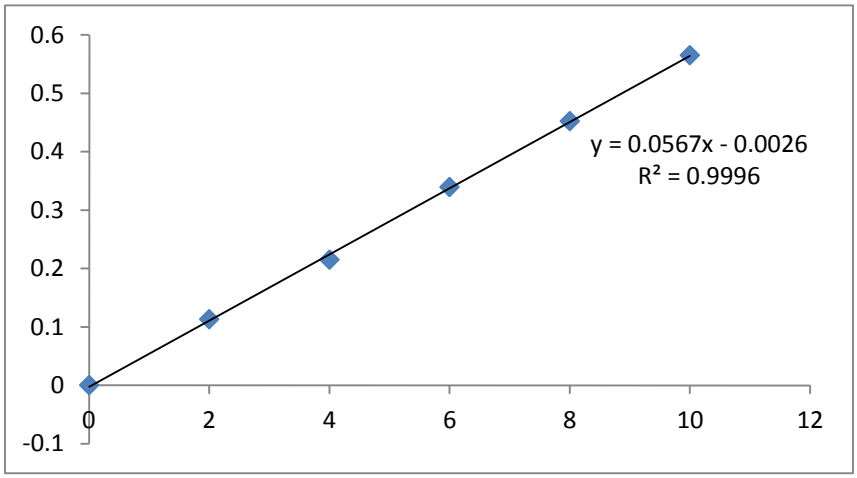

Fig No.1 -: Linearity plot of Omeprazole

DRUG EXCIPIENT COMPATIBILITY STUDIES

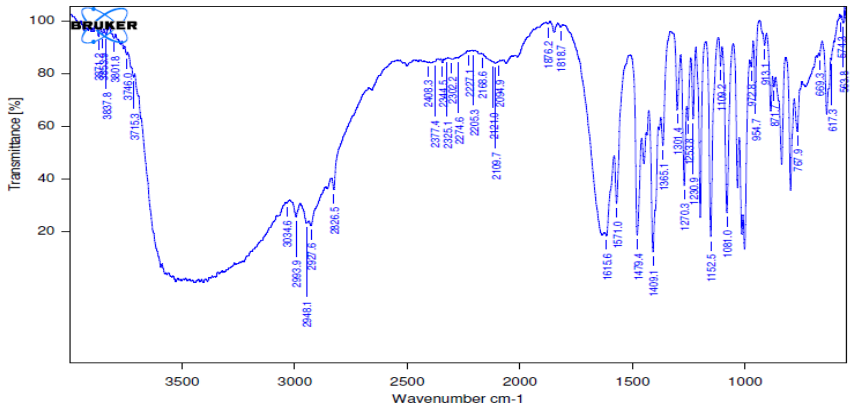

Fig No.2 FT-IR Study of Pure Omeprazole Drug

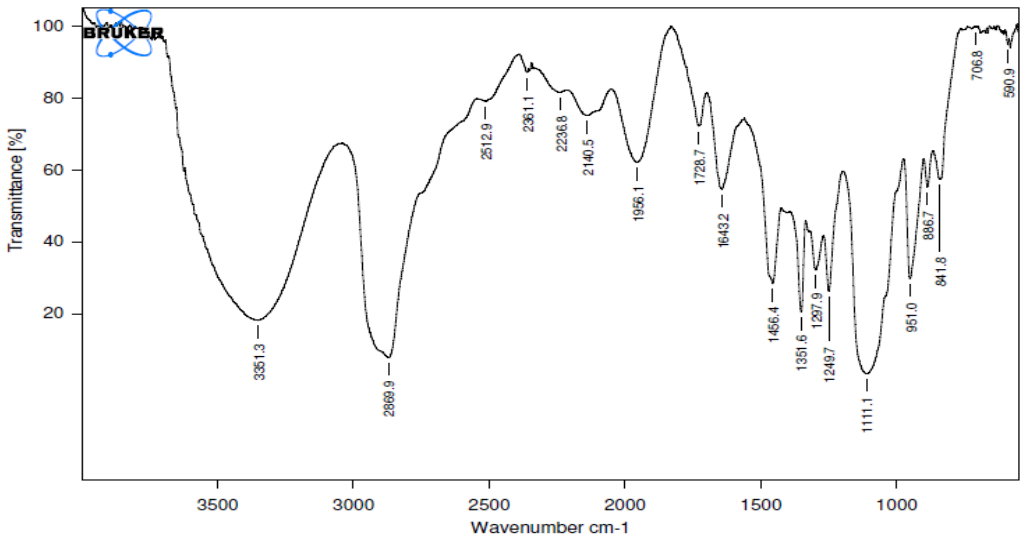

Fig No.3 FT-IR Of Optimized [Omeprazole + Poly Ethylene Glycol 400]

Table No 3: FT-IR Spectra data of Omeprazole and polymers

S.NO.	Functional group	Characteristic peak cm^{-1}	Observed peak for drug cm^{-1}	Peaks for transdermal patch formulation
1	C-H	2850-2970	2948.1	2874.08
2	CH_3	1430-1470	1470	1457.2
3	C-H ALKANE	1340-1470	1365.1	1352.1
4	C-N	1180-1360	1270	1297

Characterization of Omeprazole Transdermal Patches

Table No 4: Weight, thickness and folding endurance of Omeprazole transdermal patches

Formulation	Weight (mg)	Thickness (mm)	Folding endurance
F1	48±2.23	0.15±0.11	251±1.59
F2	47±1.16	0.14±0.9	210±2.60
F3	43±2.19	0.13±0.42	256±2.93

F4	49±0.82	0.17±0.09	279±3.07

Values ± S.D, n=6

Table No -5. Drug content and % Moisture content of Omeprazole transdermal patches

Formulation	Drug content (%)	% Moisture content
F1	93.6±0.40	1.33±0.16
F2	97.8±0.59	1.46±0.33
F3	95.5±0.53	1.38±0.31
F4	98.1±0.38	1.49±0.29

Values ± S.D, n=6

Table No-6. Swelling Index of Omeprazole transdermal patches

TIME (Hrs)	F1	F2	F3	F4
0	0	0	0	0
1	32±0.68	70±0.23	48±0.39	62±0.23
2	68±0.59	102±0.46	75±0.58	98±0.36
4	83±0.57	139±0.23	105±0.33	143±0.32
8	101±0.71	172±0.49	129±0.39	168±0.63
16	138±0.68	189±0.38	--	192±0.43
24	--	198±0.42	--	201±0.29

Values ± S.D, n=6

***Invitro* Release Studies**

Table No-7. Cumulative percent release of Omeprazole from transdermal patches

TIME (Hrs)	F1	F2	F3	F4
0	0	0	0	0
1	09±0.51	13.9±0.48	17±0.15	8±0.26
2	21±0.36	25.4±0.35	34±0.42	19±0.29
3	32±0.42	32.5±0.33	39±0.09	32±0.17
4	41±0.31	41.6±0.27	46.5±0.32	49±0.15
6	50±0.13	52.1±0.37	51.8±0.27	61±0.39

8	62±0.29	59.2±0.21	58±0.38	72±0.23
12	70±0.41	61.4±0.16	65.2±0.16	79±0.49
16	78±0.17	68.4±0.22	69.2±0.44	86±0.23
20	84±0.43	72.4±0.19	76.5±0.52	92±0.38
24	89±0.22	78.6±0.46	80±0.38	100.1±0.44

Values ± S.D, n=6

Flux Rate Determination

The profiles of *invitro* permeation of Omeprazole from patches prepared with different penetration enhancers were shown in **Table no. 8** From the table it is found that flux rate is highest for the PEG 400. The order is PEG 400>Olive oil>Castor oil> Capryol 90.

Table No -8 Flux Rate

Formulation Code	Flux rate µg/cm^2 /hr
F1	106
F2	93.97
F3	95.64
F4	119.56

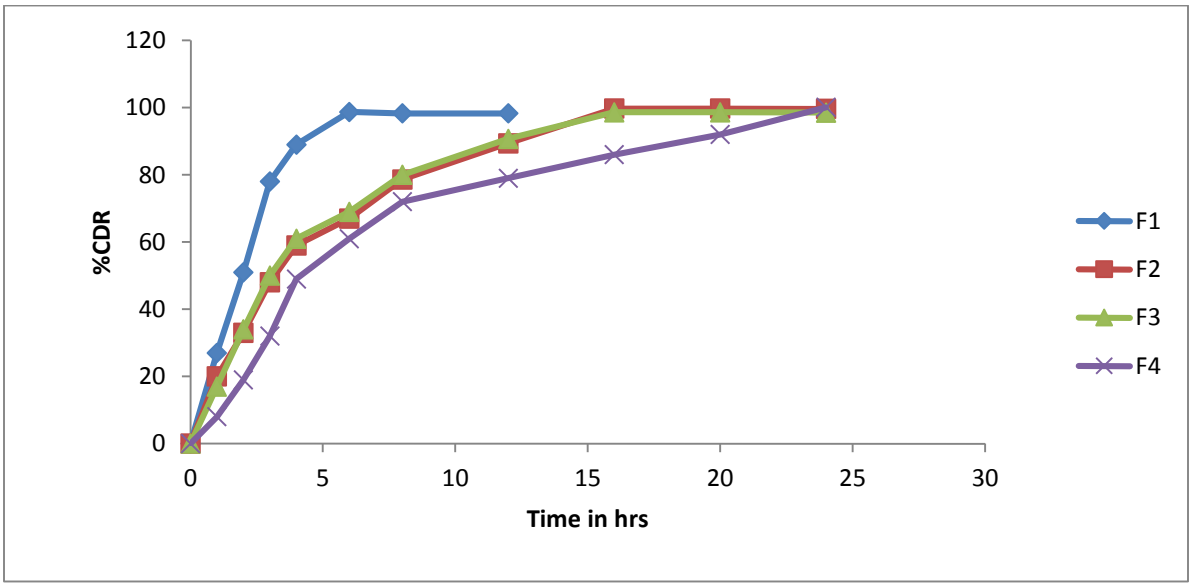

Fig No.4 Cumulative percent release of Omeprazolefrom transdermal patches F1-F4

***In vitro* Drug Release Studies from Transdermal Patches**

The cumulative amount of drug released from Transdermal patches are shown in the **Table**. No-10 The results indicate that there was highest amount of drug release was found with. Formulations F4 exhibited greatest (100.1%)percentage of drug release values when compared with the other formulations. In the present study it was observed that as the use of ethyl cellulose with PEG 400 has showed highest amount of drug release rate substantially.

Kinetic Studies For Optimized Formulation F4

Table No -9: Release kinetics for optimized formulation

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	3.867891156	-0.06840852	21.99618526	1.023725946
Intercept	20.06204082	2.048044008	-2.69081455	0.787881927
Correlation	0.920969087	-0.95336667	0.980131134	0.853125637
R 2	0.84818406	0.908908011	0.96065704	0.727823353

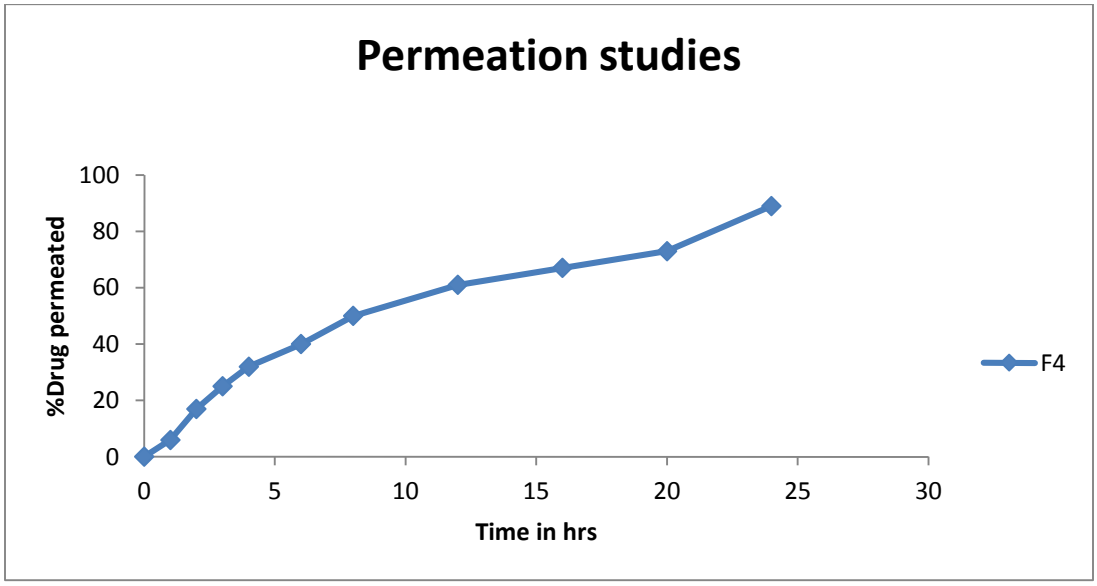

Fig No.5 permeation studies of optimized formula

Table No -9: STABILTY STUDIES FOR OPTIMIZED PATCH - PEG400 (F_4)

PARAMETER	ZERO MONTH	THREE MONTHS	SIX MONTHS
Weight Variation (mg)	49±0.82	49±0.93	50±0.13
Thickness (mm)	0.17±0.09	0.17±0.39	0.17±0.86
%Drug content	98.±0.38	98±0.35	97.8±0.46
%Moisture Content	1.49±0.29	1.52±0.36	1.53±0.52
% Swelling index	201±0.29	203±0.96	204±0.27
% Drug release	100.1±0.44	100.4±0.23	99.7±0.14
Permeation result	89±0.44	88.9±0.17	88.2±0.25

Values ± S.D, n=6

CONCLUSION

Different polymeric Patches containing Omeprazole were prepared and evaluated for physicochemical, in vitro drug release and Kinetic studies.

The IR spectral analysis of Omeprazole showed that the presence of all the characteristic bands due to functional groups in polymer mixtures suggests that there is no interaction between the drug and polymers used in the present study.

The prepared transdermal patches were evaluated for their physiochemical characteristics such as physical appearance, weight uniformity, thickness, folding endurance; moisture content, drug content were suitable for TDDS. Transdermal patches with PEG400 (F_4) showed better release than patches with OTHER permeation enhancer. The release kinetics of the optimized formulation PEG400 (F_4) followed Higuchi and release mechanism was Non-fickian diffusion rate controlled mechanism.

ACKNOWLEDGEMENTS

It is my privilege to express my gratitude to Centre For Pharmaceutical Sciences, IST, JNTUH for providing necessary reagents, chemicals & facilities for the conduct of the study. I am also thankful to Dr. Roddy's Laboratories for providing drug as a gift sample.

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