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DESIGN AND EVALUATION OF ESOMEPRAZOLE TRANSDERMAL PATCH FOR ENHANCED THERAPEUTIC ACTIVITY

M. Sakthivel[1], M. Pavithra[1]*, S. P. Senthil[1] and R. Senthamari[2]

[1]Department of Pharmaceutics, Periyar College of Pharmaceutical Sciences, Tiruchirappalli, Tamilnadu, India - 620 021.

[2]Department of Pharmacognosy, Periyar College of Pharmaceutical Sciences, Tiruchirappalli, Tamilnadu, India - 620 021.

***Corresponding Author: M. Pavithra**

Department of Pharmaceutics, Periyar College of Pharmaceutical Sciences, Tiruchirappalli, Tamilnadu, India - 620 021.

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ABSTRACT

The main aim of the work was to formulate and evaluate the Esomeprazole magnesium transdermal patch for enhanced therapeutics activity using different concentration of polymers, permeation enhancer and plasticizers by solvent casting method. The polymer are HPMC, pectin and sodium alginate; permeation enhancer are Dimethyl Sulfoxide which playing role of releasing hydroxide agents to penetrate through the skin; plasticizer are glycerin were to get thin, transparent, smooth, stable and high permeable transdermal patches. The patches undergoes physicochemical evaluation, *in vitro* drug release, in that P2 formulation shows maximum drug release of 99.03±0.09% when compared with other formulation, release kinetics of P2 formulation which follows zero order kinetics and non-fickian diffusion case II. The transdermal patch of P2 formulation which may improves the patient compliance and avoid first pass metabolism.

KEYWORDS: Transdermal Drug Delivery System, Esomeprazole magnesium, Solvent casting method, Physicochemical evaluation, *in vitro* drug release.

INTRODUCTION

Transdermal drug delivery system can be defined as the topically administered medication is self contained, discrete dosage form of patches which when applied to the skin deliver the drug to systemic circulation at a predetermined and controlled rate over a prolonged period of time in order to increase the therapeutic efficacy and reduces side effect of drug.[1] Transdermal drug delivery system is capable of transporting the drug through the skin into the systemic circulation. Transdermal route which gives an alternative dosage form for oral and IV route which avoid first pass metabolism and invasive nature. This type of drug delivery system which faster pace in last two decades which improves patient compliance and self access medication, which also attract by many scientists and patient.[2]

Esomeprazole magnesium is a proton pump inhibitors which reduces the acid secretion by covalently binding to sulfhydryl group of cysteines found on the H^+/ K^+ ATPase as in gastric parietal cells. Esomeprazole is the S- isomer of omeprazole. It is used in the treatment of Peptic Ulcer Disease (PUD), gastroesophageal reflux (GERD), Zollinger Ellison syndrome, risk reduction of NSAID-associated gastric ulcer, *Helicobacter pylori* eradication.[3] Peptic ulcer disease is a global problem with a lifetime risk development which is due to improper hygienic and sanitary conditions, combined with effective treatment and judicious use of NSAIDs. PUD is characterized by discontinuation in the inner lining of the gastrointestinal tract because of gastric acid secretion or pepsin. A peptic ulcer in the stomach is called gastric ulcer and an ulcer in the duodenum is called duodenum ulcer.[4]

The major, most potent and effective antiulcer medication is the selective histamine type 2 receptor blockers and the Proton pump inhibitors. Proton pump inhibitors are more rapid onset of action compared with histamine type 2 receptor blocker. This most widely used as class of Antisecretory medication. They do not show the tolerance effect even long term of treatment.[5]

MATERIALS AND METHODS

Esomeprazole magnesium trihydrate was received as a gift sample from Vertex Pharma chemical (Pondicherry); HPMC E5 LV and Pectin was purchased from Hi Media laboratories (Chennai); Sodium alginate, Dimethyl Sulfoxide (DMSO) and Glycerin was purchased from Merck limited (Mumbai). All other reagents used were analytical grade.

Preformulation Studies[6]

In this study the physical appearance of the drug which identified color, taste and odor. Melting point of the drug was determined by capillary tube method. This method which involves small amount of drug packed tightly in capillary tube and placed in apparatus. Solubility study of the drug (10mg) was dissolved in 10 ml with various solvent at room temperature. Fourier Transform Infrared Spectroscopy was to determine the compatibility studies between the drug and polymer. The drug and polymer sample was added in dry sample after triturated to the approximately amount of dry potassium bromide and make into disc placed in the FTIR apparatus, scanned under the range of 4000 and 500 cm^{-1}.

Preparation of Standard curve

Accurately weighed amount of drug (100mg) was dissolved in small quantity of ethanol and then made upto 100ml with phosphate buffer pH 7.4. Each ml of the stock solution contains 1mg of drug. From this stock solution different standard of working standard solution 2, 4, 6, 8, 10µg/ml were made up with phosphate buffer pH 7.4 and absorbance was measured at 205nm using phosphate buffer pH7.4 by UV spectroscopic method. (Fig. 1)

Preparation of transdermal patch[7]

Esomeprazole Transdermal patch was prepared by solvent casting method. The Patches were prepared in a petriplates had the diameter of 9 cm with 7ml to 9 ml capacity. Weighed quantity of polymer was dissolved in calculated quantity of water and heated on hot plate. The drug Esomeprazole (40 mg) dissolved in 1ml ethanol. Then dissolved drug was added to the polymeric solution and allowed to stir well to obtain homogenous solution. The calculated quantity of plasticizer and permeation enhancer was added and stirred well to get homogenous solution. The finally patch were casted on the Petri plate and air dried at 24 hrs. After 24 hrs the dried patch were removed by using sharp blade, wrapped in aluminium and stored in desiccators. (Table. 1)

Table 1: Formulations of Transdermal patch of drug.

S.No	Ingredients	HPMC E5 LV (H)			PECTIN (P)			SODIUM ALGINATE (S)		
		H1	H2	H3	P1	P2	P3	S1	S2	S3
1.	Esomeprazole magnesium (mg)	40	40	40	40	40	40	40	40	40
2.	Polymer (mg)	320	400	480	320	400	480	320	400	480
3.	Dimethyl Sulfoxide (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
4.	Glycerin (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
5.	Water (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Physicochemical evaluation of Esomeprazole Transdermal patches[8]

Formulated films were subjected to the preliminary evaluation tests. Patch with any imperfections, entrapped air, or differing in thickness, weight (or) content uniformity were excluded from further studies. (Table. 03)

Uniformity of weight

This was done by weighing five different patches of individual batch taking the uniform size at random and calculating the average weight of three. The tests were performed on patch which was dried at 60˚C for 4hrs prior to testing.

Thickness of the Patches

The thickness of the patch was assessed by using digital Vernier caliper at different points of the patch. From each formulation three randomly selected patches were used. The average value for thickness of a single patch was determined.

Drug content determination

The patch were taken and added in a beaker containing 200ml of Phosphate buffer pH 7.4. The medium was stirred magnetic bead for 24 hrs. The solution was later filtered and analyzed for drug content with proper dilution and scanned at 205 nm in UV spectrophotometrically.

Folding Endurance

The number of times the patch could be folded at the same place without breaking gave the value of folding endurance. This was determined by repeatedly folding one patch at the same place till it breaks.

Percentage Moisture uptake

The patch were weighed accurately and placed in desiccators at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs, the patch were taken out and reweighed. The percentage moisture uptake was calculated as the difference between final and initial weight with respect to initial weight. It is calculated by using following formula.

$$\text{Percentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Percentage Moisture content

The patch were weighed and kept in desiccators containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the patch were taken out and reweighed. The percentage moisture content was calculated using the following formula.

$$\text{Percentage moisture content} = \frac{\text{Initial weight– Final weight}}{\text{Initial weight}} \times 100$$

Determination of surface pH

The patches were allowed to swell by keeping them in contact with 1 ml of distilled water for 2 hrs at room temperature and pH was noted down by bringing the electrode in contact with the surface of the patch, allowing it to equilibrate for 1 min.

Percent Elongation

When stress was applied, a patch sample stretches and this is referred to as strain. Strain is basically the deformation of patch divided by original dimension of the sample. Generally elongation of patch increases as the plasticizer content increases. It is calculated by using following formula.

$$\text{Percentage elongation} = \frac{\text{Increase in length of patch}}{\text{Initial length of patch}} X100$$

Tensile strength

Tensile strength is the maximum stress applied to a point at which the patch specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the patch as given in the equation below.

$$\text{Tensile Strength} = \frac{\text{Load at failure}}{\text{Patch thickness x Patch width}} \times 100$$

Drug Permeation Studies

The *in vitro* drug release rate of prepared transdermal patches were evaluated by open ended tube through using Phosphate buffer pH 7.4 as diffusion medium up to 8 hrs studies. The cellophane membrane was tided in one end of the tube and then immersed in the receptor compartment containing 200ml of Phosphate buffer pH 7.4.Which was stirred at medium speed and maintained at 37°C±2°C. Samples were withdrawn at regular time intervals and the same volume was replaced by fresh diffusion medium. The samples were analyzed using UV visible spectrophotometer (Shimadzu UV1700) set at 205 nm.

Evaluation of *In vitro* release kinetics[9]

In order to examine the drug release mechanism sample from the prepared transdermal patch of the formulations, the results of the percent cumulative drug release was examined in accordance to the kinetic models such as Zero-order, First-order, Higuchi equation, Korsmeyer Pappas equation and Hixson–Crowell equation.

Zero-Order Model

In many of the modified release dosage forms particularly controlled or sustained release dosage forms (those dosage forms that release the drug in planned, predictable and slower than normal manner) is Zero-order kinetics.

$$Q = K_0 t$$

Where-Q is the amount of drug release at time t and K_0 is the release rate constant. A plot of cumulative percentage drug released versus time is linear.

First-order Model

Most conventional dosage forms exhibit this dissolution mechanism. Some modified release preparations, particularly prolonged release formulations, adhere to this type of dissolution pattern.

$$\text{Log } Q = K_1 t$$

Where- Q is the percent of drug release at time t and K_1 is the release rate constant. A plot of log cumulative percentage drug remained versus time is linear.

Higuchi Model

A large number of modified release dosage forms contain some sort of matrix system. In such instances, the drug dissolves from this matrix. The dissolution pattern of the drug is dictated by water penetration rate (diffusion controlled) and thus the following relationship applies:

$$Q = K_2 t^{1/2}$$

Where-Q is the percentage of drug release at time $t^{1/2}$ and K_2 is the diffusion rate constant. In Higuchi model, a plot of cumulative percentage drug released versus square root of time is linear.

Hixson-Crowell Model

Some specialized dosage forms contain many drug particles of the same size and shape of their agglomerates that dissolve evenly. In such instances the cube-root law can express the dissolution process. If the dissolution pattern of the drug is dictated by the actual dissolution of drug molecules, then the following relationship applies:

$$(100-Q)^{1/3} = 100^{1/3} - K_3 t$$

Where-Q is the amount of drug release at time t and K_3 is Hixson Crowell Constant. In this model the cube root of cumulative percent drug retained versus time is linear.

Korsmeyer and Pappas Model

If n=1, the release is zero-order, and if n=0.5, the release is best explained by Fickinian diffusion, and if $0.5 < n < 1$ then the release is through anomalous diffusion or case II diffusion.

$$Q = Kt^n$$

Where, Q is the fraction of drug release at time t^n and K is the diffusion rate constant and n is diffusional exponent. In this model, a plot of log cumulative percent drug released versus log time is linear.

RESULTS AND DISCUSSION

Preformulation study

Physical appearance

Color- off white
Odor- Bitter
Taste- Bland
Melting point: 185.2^{O}C

Solubility study: The drug was soluble in ethanol, methanol, and other organic solvents like Dimethyl Sulfoxide, Slightly soluble in water and soluble in pH 7.4 phosphate buffer at room temperature.

Calibration curve of Esomeprazole magnesium

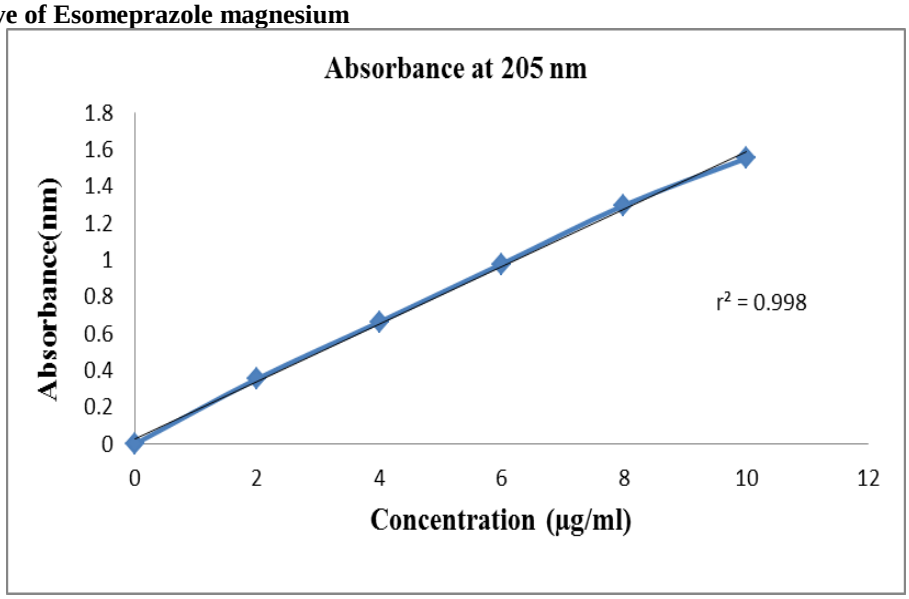

Fig. 1: Calibration curve of Esomeprazole magnesium.

Table 2: Calibration curve of Esomeprazole magnesium.

Concentration (µg/ml)	Absorbance at 205 nm
0	0
2	0.354
4	0.663
6	0.978
8	1.297
10	1.552

The calibration curve yields a straight line (r^2= 0.998) which shows drugs obeys Beer-Lambert's law in the range of 2-10µg/ml.

Drug-Excipient compatibility studies

FTIR Spectroscopy was performed to find the compatibility between dug and selected polymers. The pure sample and drug- excipients were scanned separately and spectral were studied. FTIR spectra show that there was no interaction between Esomeprazole magnesium and polymers because no extra peak or broadening peak was observed.

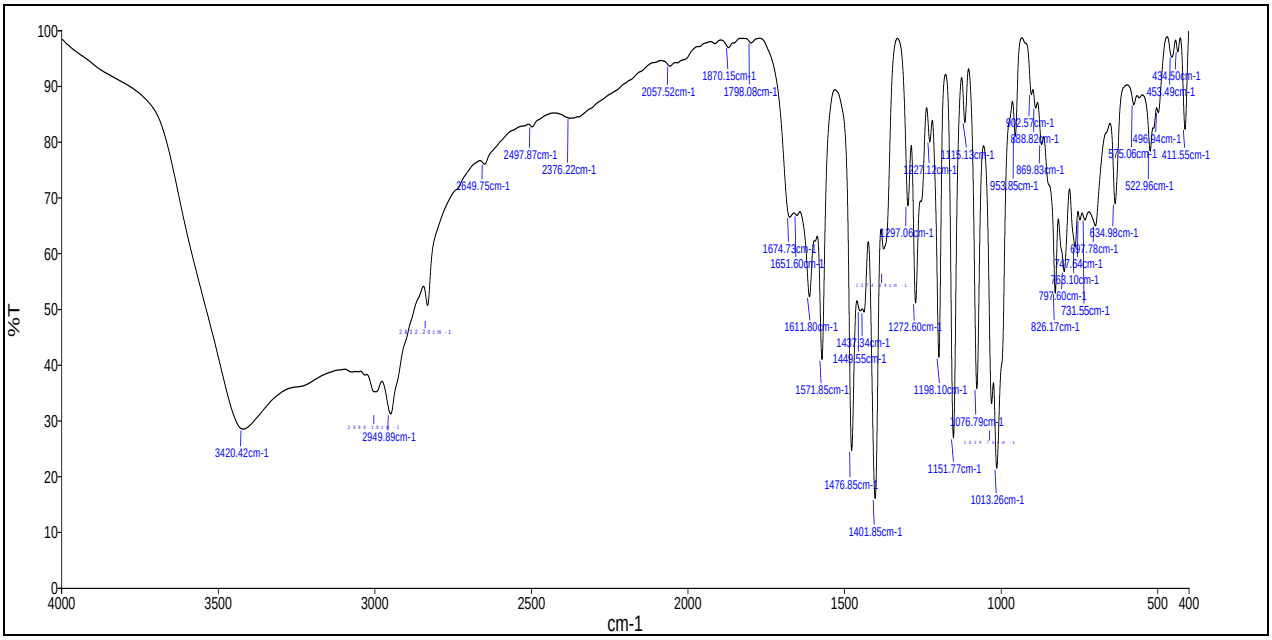

Fig. 2: FTIR of Pure sample.

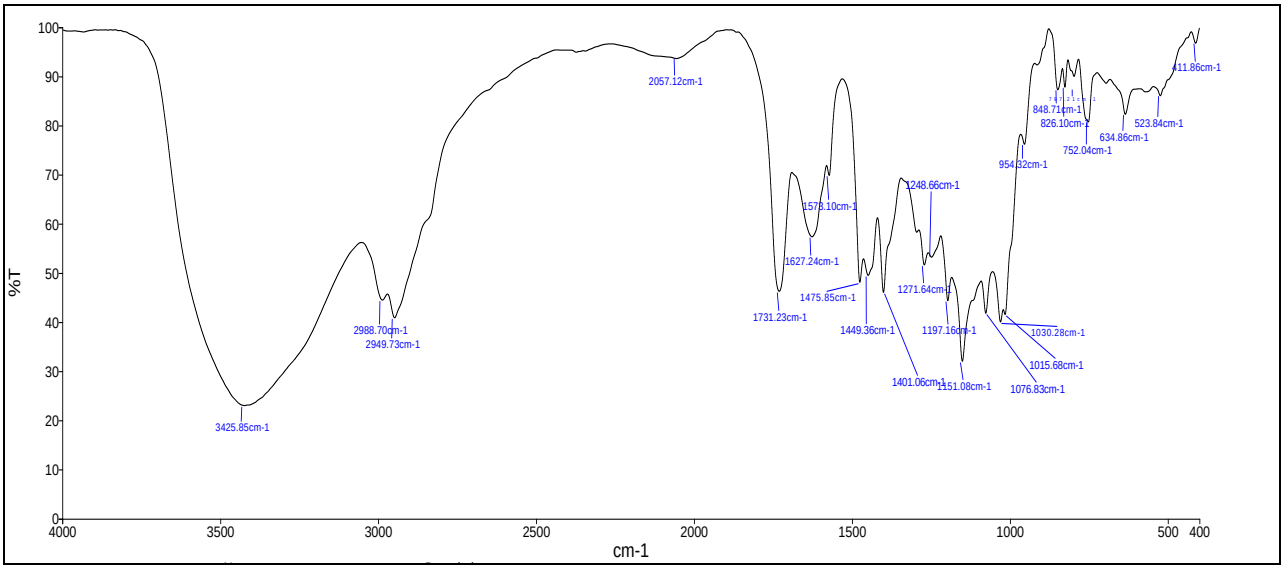

Fig. 3: Physical mixture of Esomeprazole magnesium with HPMC E5LV, Pectin, Sodium alginate.

Physicochemical Evaluation of Esomeprazole magnesium Transdermal patch

Table 3: Physicochemical evaluation of Esomeprazole magnesium Transdermal patch.

Formulation code		Uniformity of weight (g)	Thickness (mm)	Drug Content (%)	Folding Endurance(no's)	Moisture Uptake (%)	Moisture Content (%)	Surface pH	Percent Elongation (% mm)	Tensile Strength (Kg/mm^2)
Transdermal Patch of HPMC E5 LV (H)	H1	0.37±0.07	0.38±0.57	98.31±0.74	249±0.51	2.93±1.73	2.327±0.91	7.0±0.87	90±0.23	5.88±0.32
	H2	0.41±0.03	0.42±0.73	98.28±0.33	251±0.77	2.80±0.97	1.932±0.87	7.1±0.38	89±0.99	6.03±0.10
	H3	**0.43±0.08**	**0.46±0.86**	**98.97±0.54**	**253±0.63**	**2.62±0.12**	**1.431±0.37**	**7.2±0.49**	**88±0.68**	**6.234±0.72**
Transdermal Patch of Pectin (P)	P1	0.41±0.10	0.44±0.29	98.71±0.89	237±0.69	2.46±0.21	2.698±0.60	7.1±0.26	90±0.27	6.475±0.49
	P2	**0.44±0.05**	**0.46±0.07**	**99.93±0.49**	**251±0.81**	**2.24±0.93**	**2.403±0.52**	**7.3±0.80**	**88±0.05**	**6.628±0.49**
	P3	0.52±0.85	0.51±0.85	99.01±0.04	263±0.94	2.08±1.43	2.193±0.56	7.5±0.65	86±0.87	6.801±0.27
Transdermal Patch of Sodium alginate (S)	S1	0.41±0.30	0.39±0.11	98.45±0.93	243±0.22	2.85±0.87	2.897±0.75	7.0±0.83	91±0.74	5.846±0.35
	S2	**0.45±0.10**	**0.47±0.01**	**99.27±0.11**	**248±0.32**	**2.41±0.34**	**2.634±0.89**	**7.2±0.96**	**89±0.03**	**6.482±0.74**
	S3	0.53±0.51	0.53±0.51	98.92±0.39	267±0.53	2.01±0.14	2.499±0.90	7.5±0.77	87±0.87	6.628±0.21

Mean± S. D: n= 3

The Nine (H1, H2, H3, P1, P2, P3, S1, S2, S3) batches of drug loaded patches with different ratios of three different polymer were subjected to various physicochemical evaluation. Based on thickness, drug content, uniformity of weight, folding endurance, percentage moisture uptake, moisture content and tensile strength, the formulation H3, P2, S2 were selected for further studies.

Pictures of optimized Transdermal Patch

Fig. 4: Transdermal patch of H3.

Fig. 5: Transdermal patch of P2.

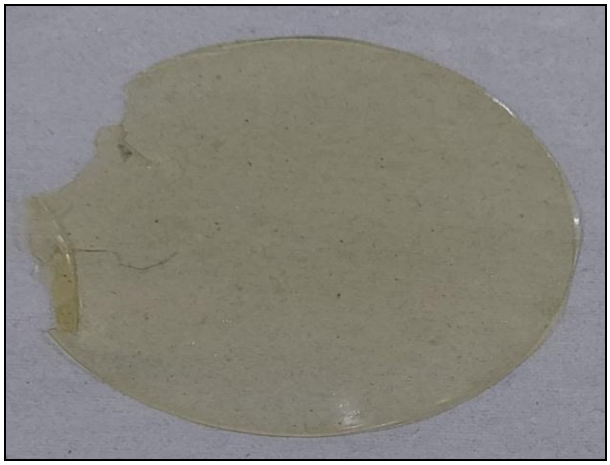

Fig. 6: Transdermal patch of S2.

All the optimized transdermal patches of H3, P2 and S2 were visually appearance like color, clarity, flexibility and smoothness.

***In vitro* drug release study**

Table 3: *In vitro* drug release of optimized formula of Transdermal patch.

Time in min	% Drug release		
	HPMC E5LV (H3)	Pectin (P2)	Sodium Alginate (S2)
0	0	0	0
5	0.2±0.18	0.82±0.64	0.59±0.88
10	0.82±0.63	1.55±0.55	1.12±0.52
15	1.69±0.26	2.99±0.09	2.11±0.49
30	2.93±0.16	5.53±0.15	4.07±0.97
45	7.89±0.37	9.78±.0.11	7.99±0.56
60	13.02±0.86	17.89±0.45	15.89±0.73
120	25.89±0.99	30.99±0.98	28.92±0.55
180	33.73±0.56	42.9±0.32	39.58±0.11
240	41.47±0.78	54.87±0.22	49.2±0.22
300	50.01±0.05	66.53±0.32	59.85±0.20
360	64.86±0.43	78.99±0.21	70.01±0.32
420	77.99±0.65	88.01±0.13	80.59±0.52
480	89.67±0.67	99.03±0.20	92.83±0.14

Mean± S. D: n= 3

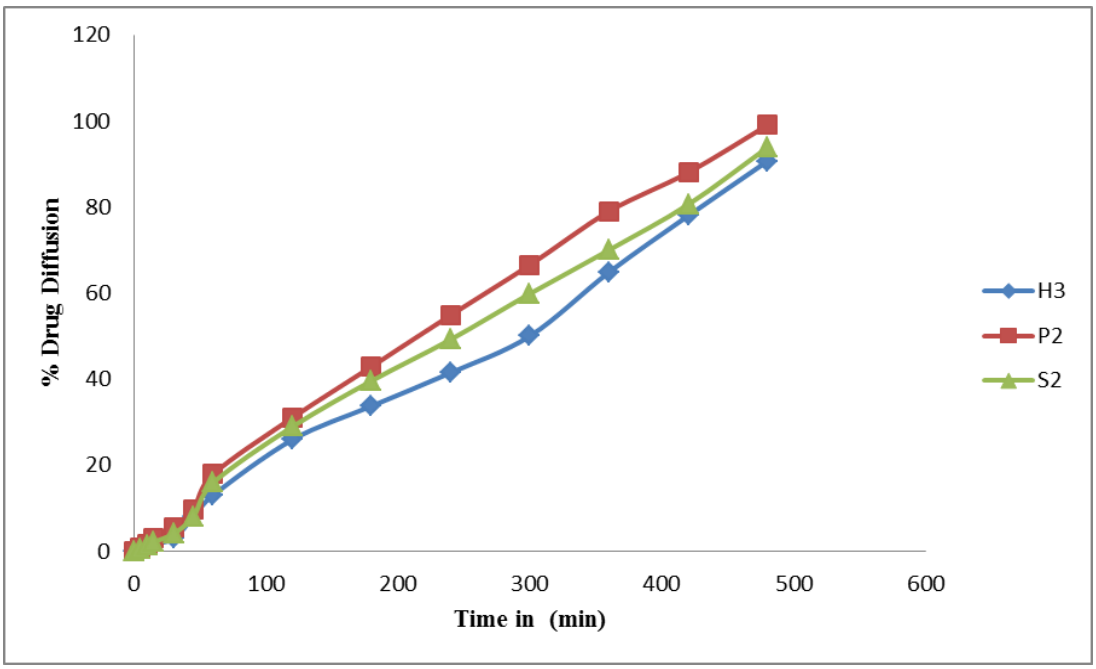

Fig. 7: In vitro drug release of optimized formula of Transdermal patch.

The optimized transdermal patches of H3, P2, S2 were studied in vitro drug diffusion profile shows that 89.67 ± 0.67, 99.03 ± 0.20, 92.83 ± 0.14. From this P2 transdermal patch shows maximum drug release.

Release kinetics

Table 4: Release kinetics of Optimized formula of Transdermal patch.

Formulation code	Correlation coefficient (r^2)				'n' Diffusion Exponent
	Zero order	First order	Higuchi	Korsmeyer Peppas	
H3	0.9919	0.9770	0.9609	0.9671	1.278
P2	0.9958	0.9756	0.9688	0.9904	1.004
S2	0.9937	0.9918	0.9715	0.9949	1.067

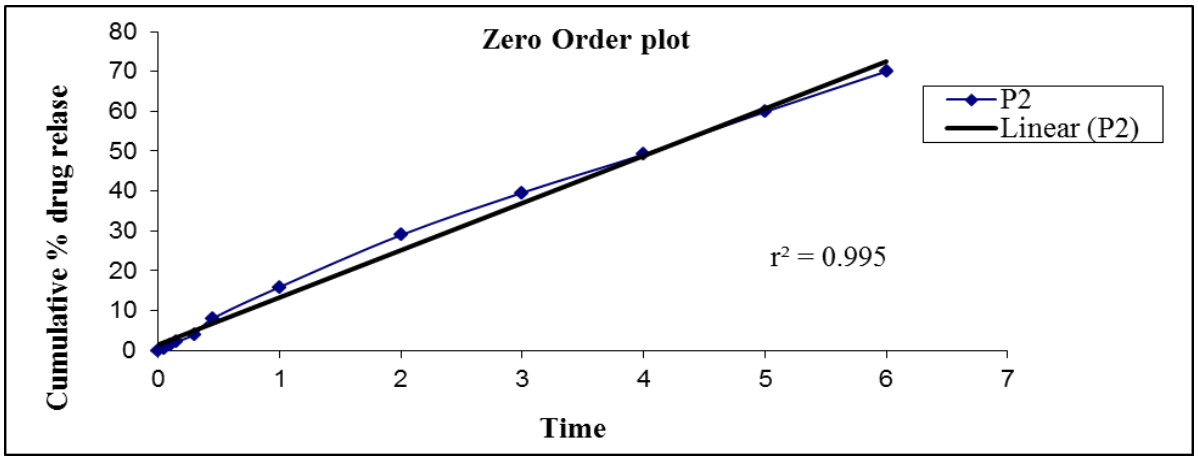

Fig. 8: Zero order kinetic plot of P2.

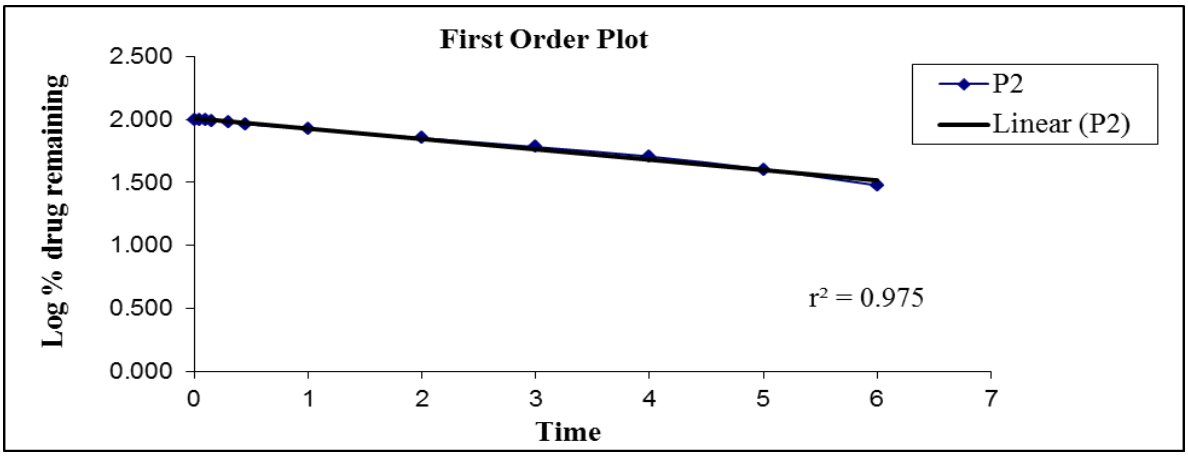

Fig. 9: First order kinetic plot of P2.

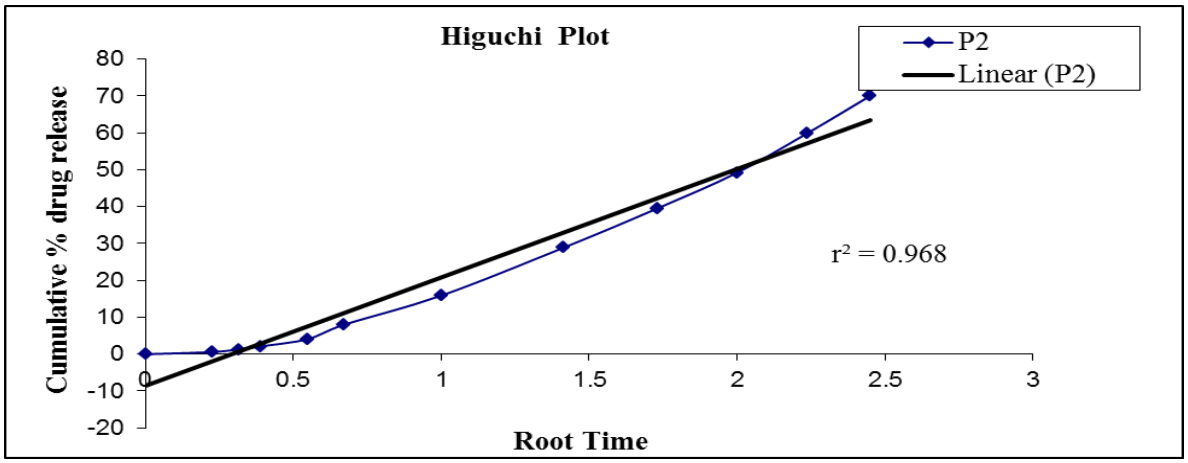

Fig. 10: Higuchi plot of P2.

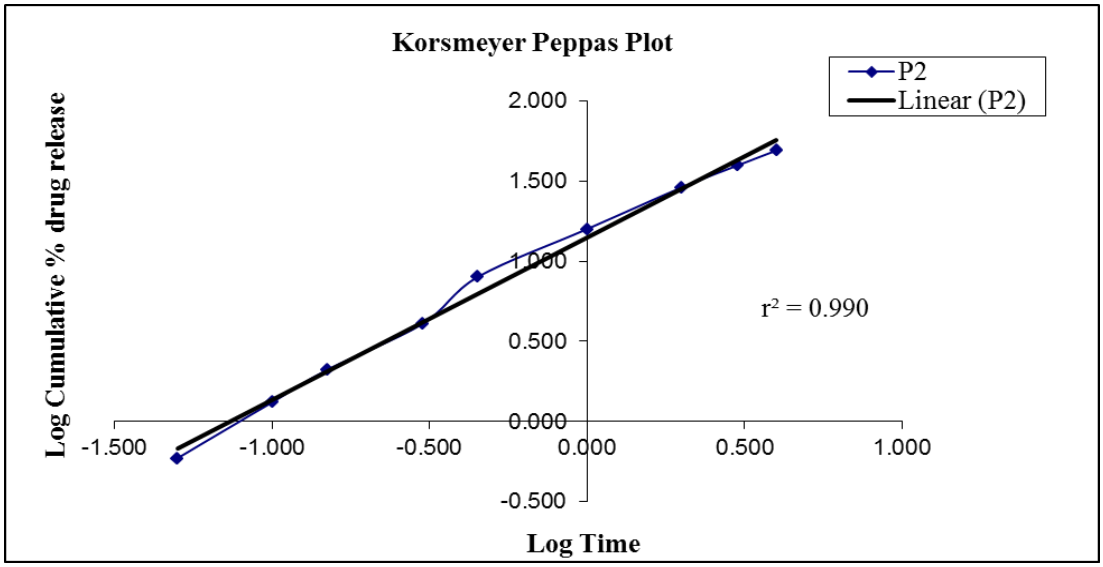

Fig. 11: Korsmeyer Peppas plot of P2.

Release kinetics study revealed that H1, P2, S2 selected patches follows zero order and non fickian diffusion model but P2 only shows the maximum release of the drug. It can be understood that P2 patch had shown regression coefficient (r^2) of 0.9958.

CONCLUSION

The formulated Esomeprazole transdermal patch using polymer like HPMC E5, Pectin and Sodium alginate carried out for the purpose of attaining maximum bioavailability by avoiding the first pass metabolism. Nine batches of patches were prepared by solvent casting techniques. The selected formulation of Transdermal patches of H3, P2, and S2 were selected based on physicochemical evaluation. The drug loaded patches exhibits satisfactory uniformity of weight, uniformity of thickness, tensile strength, percentage elongation and also exhibits optimal folding endurance without any patch variation. It was observed that patch having low average of % moisture uptake and % moisture content which was one of the physicochemical characterization in the formulation of transdermal patches. The optimization of transdermal patches of H3, P2, and S2 were studied in vitro drug release profile shows that 89.67 ± 0.67 %, 99.03 ± 0.20 %, 92.83 ± 0.14 %. The P2 transdermal patch show maximum drug release was optimized. So, this transdermal patch shows that suitable substitute for conventional and parental usage of Esomeprazole.

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