Formulation and Evaluation of Transdermal Patches of an Antihypertensive Drug for Controlled Release

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Abstract: The objective of the research work was to formulate and evaluate transdermal patches of Enalapril maleate, an antihypertensive drug, for controlled release. The transdermal formulation was prepared by solvent casting method by incorporation of various polymers like Gum rosin, PVP in different proportions. PEG 400 and Glycerin were used as Plasticizer and DMSO Permeation enhancer. The prepared patches were evaluated for various physiochemical properties like Folding endurance, Moisture Uptake, Moisture content, Weight variation ,Film thickness, Drug content and In-vitro drug release studies. FT-IR and DSC studies revealed that there was no interaction between the drug and polymers used in the study. The drug release studies were performed for 16 h at 37°C ± 1°C.The optimized formulation F9 was found to be clear, with pH 7.4 and the drug content was found to be more than 85 % in ethanol and showed release of drug up to 89.23 % in 16 h. It showed no significant changes on stability studies when stored at 40 ± 2°C/ 75%RH ± 5% for two months according to ICH guidelines. The drug release of optimized formulation was found to follow Zero order. The n-value of Korsmeyer–Peppas plot was found 1.0013 indicating that most formulations may have followed non-Fickian diffusion mechanism, The R^2 value for F9 was found to be 0.9742, 0.8211. 0.9037, 0.921, Zero order, First order, Higuchi model, Peppas model respectively. So, it follows the Zero order of drug release.

Key words: Transdermal patch; Enalapril maleate; Controlled release; Gum Rosin; Polyvinyl Pyrrolidone; Permeation enhancer;

I. INTRODUCTION

Controlled drug delivery system is defined as any drug delivery system that maintains adequate and desired release of drug over an extended period of time. The major role of ideal drug delivery system is to provide proper amount of drug at regular time intervals and at exact site of action to maintain therapeutic range of drug in blood plasma. Hydrophilic polymer matrix is extensively used polymer for making formulations. [1]

Transdermal drug delivery system is defined as the self-controlled discrete dosage forms, applied to the intact skin, deliver the drug through the skin at controlled rate to the systemic circulation. The transdermal route of drug administration is considered as most potential route of drug administration over conventional dosage form because of its local and systemic delivery of the drug, it offers many advantages over conventional dosage form such as greater convenience, enhanced efficacy, improved safety, improved patient compliance, and also it bypasses the hepatic metabolism. It excludes the problems that affect the drug from the gastrointestinal track such as enzyme activity pH and drug interaction with the food. [2]
Enalapril maleate is Belongs to class of ACE inhibitors and it's a prodrug which when administered orally, hydrolyzed to release the active converting enzyme inhibitor enalaprilat. Enalapril maleate is 60% absorbed and 40% bioavailable as Enalaprilat. Both compounds undergo hepatic metabolism so the oral bioavailability is less [3]

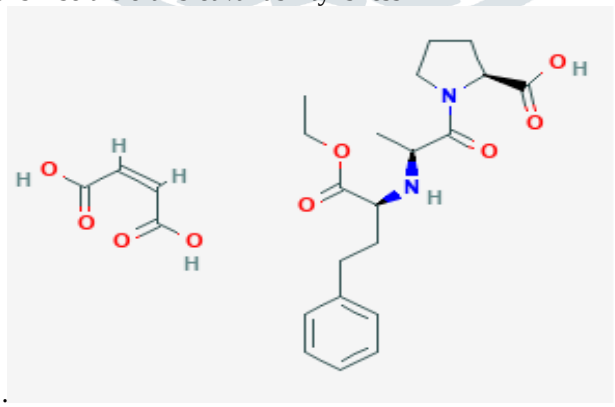

Figure 1: Structure of Enalapril Maleate

The intact skin is considered as the port of drug administration to the human body and has been recognized from ancient years. But the skin is a very difficult barrier to the ingress of material allowing only small quantity of drug to penetrate over a period of time. The thorough understanding of morphological, physicochemical and biophysical structure and properties of the skin is extremely important in order to deliver the therapeutic agent through the skin. [4]

MATERIALS AND METHOD

Materials: Pure Enalapril Maleate drug was purchased from yarrow chem. Products. Mumbai. The polymers Gum Rosin and Polyvinyl pyrrolidone (PVP) and Chemicals such as DMSO, PEG-400.Glycerine were procured from yarrow chem. Mumbai and all other chemicals and solvents used were of analytical grade.

Methods: It is the major important requirement in formulating of any drug delivery system. Preformulation studies were carried out on drug which includes Melting point, solubility and compatibility studies.

Preformulation studies:

Description: Enalapril Maleate was physically examined for color, odor etc.

solubility: Solubility of Enalapril Maleate was performed in Water, ethanol, Chloroform, and Phosphate buffer pH 7.4

Drug-polymer interaction studies: The compatibility studies were done by FTIR and DSC

FTIR: The FTIR spectra (Bruker) was taken and analyzed for any interaction between the drug and the polymers.

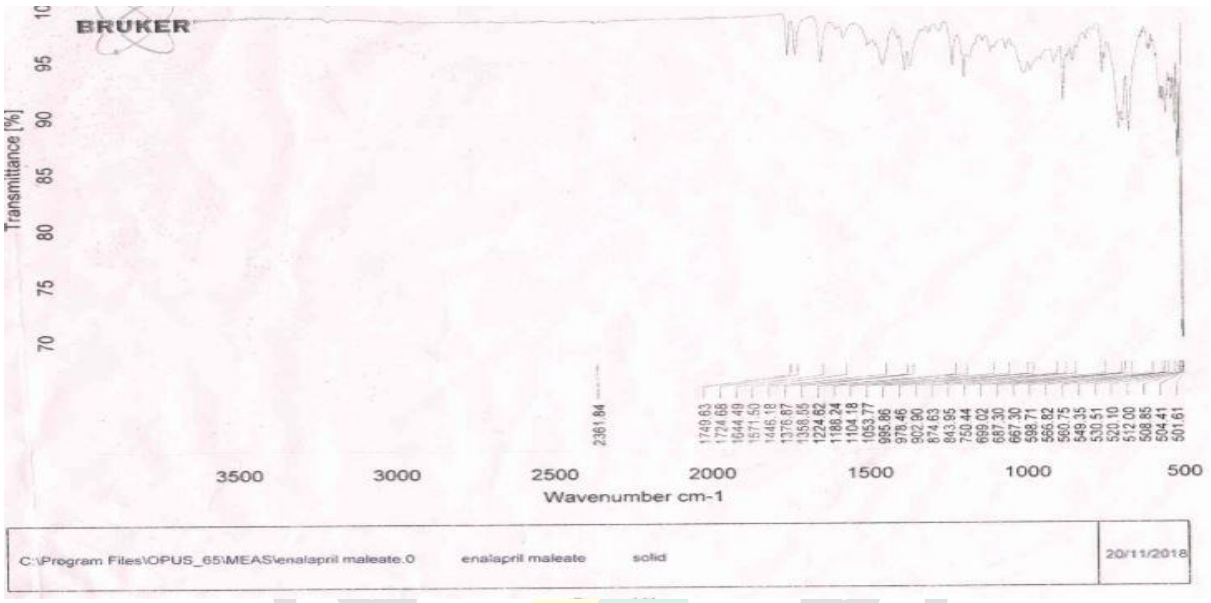

Figure 2: FTIR spectrum of pure drug Enalapril Maleate

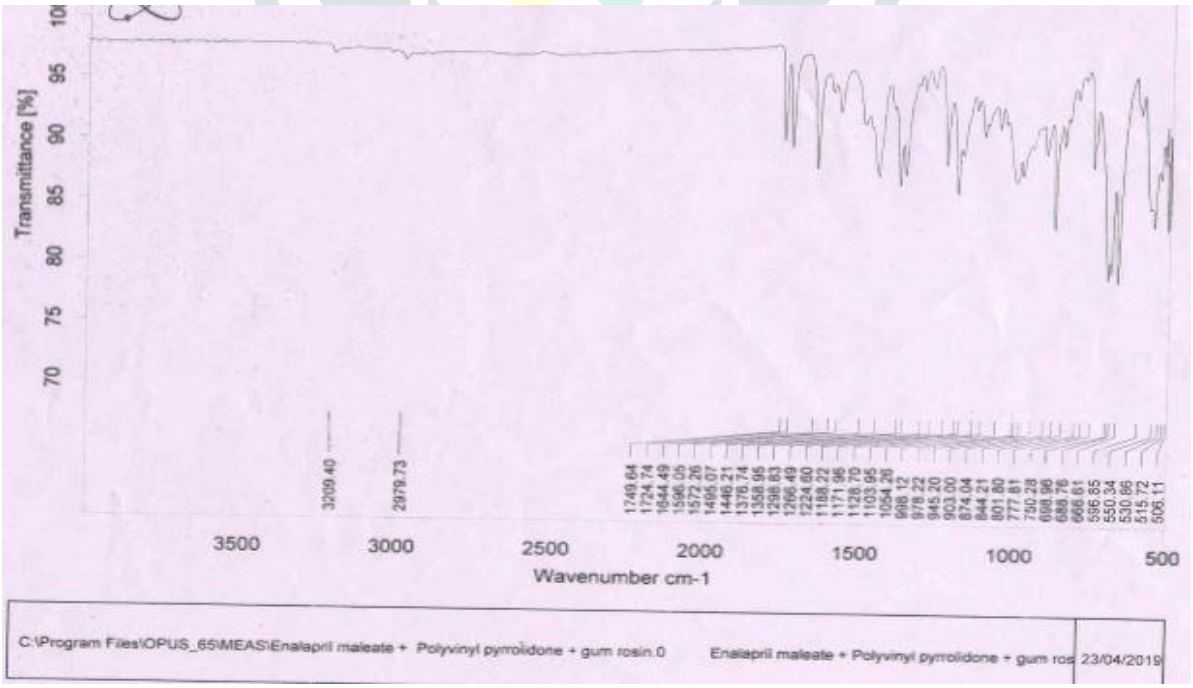

Figure 3: FTIR spectrum of Pure drug Enalapril Maleate with PVP and Gum Rosin

Table 1: FTIR peaks of Enalapril Maleate and mixture drug with polymer

Functional group	Range	Observed wavenumber for Enalapril Maleate	Observed wavenumber for Enalapril Maleate and gum rosin	Observed wave number for Enalapril Maleate and PVP	Observed wave number for Enalapril Maleate and PVP and Gum rosin
O-H stretch N-H stretch	3200-3700	3647.12	3647.58	3209.68	3209.40
C=O Stretch	1640-1810	1724.68 1749.63	1724.31 1749.32	1724.94 1749.76	1724.74 1749.64
C-O Stretch	1050-1150	1053.77 1104.18	1053.79 1103.76	1054.38 1104.08	1054.26 1103.95
C-N stretch	1200-1350	1224.62 1358.55	1224.50 1359.35	1224.73 1266.75	1224.60 1266.49
C=C stretch	1640-1680	1644.49	1644.82	1644.70	1644.49

DSC: DSC was used to determine thermal characteristics of Enalapril Maleate, physical mixture and drug loaded film. The thermogram of drug, polymer was measured with a DSC-60 instrument.

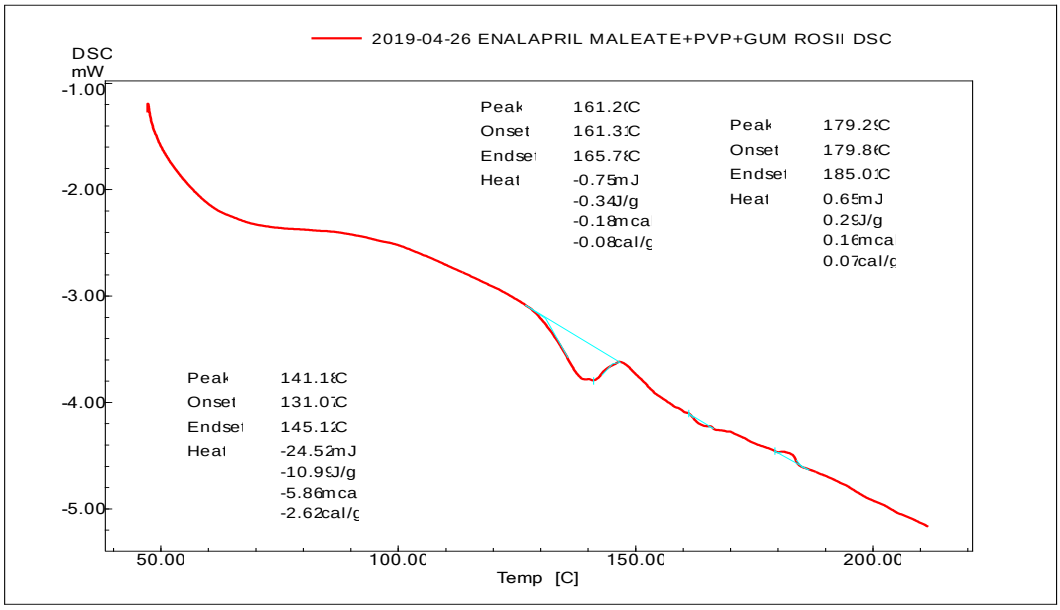

Figure 4: DSC graph of mixture pure drug Enalapril Maleate with PVP and Gum rosin

Standard Calibration Curve of Enalapril Maleate:

Preparation of pH 7.4 phosphate buffer [5,6,7]: Dissolve 2.38 g of disodium hydrogen phosphate,0.19 g of potassium dihydrogen phosphate and 8.0 g of sodium chloride in sufficient water to produce 1000ml

Procedure:

Weigh accurately about 0.25g of Enalapril maleate and transfer to a 25mL volumetric flask, dissolve and make up to the mark with phosphate buffer of pH 7.4 this is a stock solution for the UV detection.

From the above stock solution pipetted out 0.25mL of solution into 25ml volumetric flask make up to mark with phosphate buffer this will give the solution of concentration. 100µg/mL and this is known as sub stock solution pipetted out 0.2, 0.4, 0.6, 0.8 and 1.0 mL 0f solution into separate 10mL volumetric flasks make up to mark with phosphate buffer7.4 to give solution of concentration 2, 4, 6, 8, 10µg/mL detect the solution in UV spectrophotometer at the wavelength of 226 nm

Table 2: Spectrophotometric data for construction of standard graph of Enalapril Maleate

Concentration	Absorbance
0	0
2	0.15
4	0.308
6	0.441
8	0.632
10	0.701

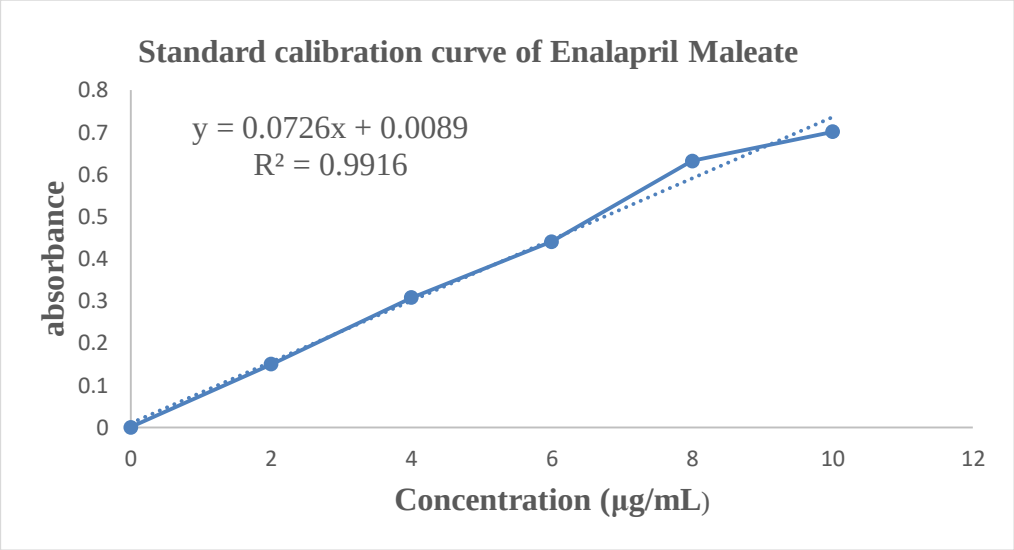

Figure 5: Standard graph of Enalapril Maleate in Phosphate buffer 7.4

Preparation of Enalapril Maleate transdermal films

The matrix-type transdermal patches containing enalapril maleate were prepared by solvent casting method, using different ratios of rosin and PVP. The polymers in different ratios were dissolved in 4 ml of solvent. Then the drug [Enalapril maleate] was added slowly in the polymeric solution and stirred on the magnetic stirrer to obtain a uniform solution. PEG 400 and DMSO was used as the penetration enhancer. Glycerin was used as plasticizers. The solution was poured into the Petridis and dried at room temperature for 24 hrs. An inverted funnel was placed over the mold to prevent fast evaporation of the solvent. Patches of 2.0 cm diameter were prepared by cutting and packed in an aluminum foil and stored in a desiccator until further use. [8, 9, 10]

Table 3: Formulation design of Enalapril Maleate transdermal Films by Response Central Surface Design (using JMP 14 Trial)

Formulation code	Enalapril Maleate [mg]	Gum Rosin [mg]	PVP [mg]	PEG -400 [mL]	Glycerine [mL]	DMSO mL	Solvent (Ethanol)
F1	15	55	30	1	1	0.6	4
F2	15	55	40	0.7	1	0.6	4
F3	15	67.5	20	1	1.5	0.6	4
F4	15	80	40	0.5	0.5	0.6	4
F5	15	80	40	1	0.5	0.6	4
F6	15	67.5	40	1.5	2	0.6	4
F7	15	55	20	1	1	0.6	4
F8	15	80	30	1	1	0.6	4

Evaluation of Enalapril Maleate transdermal films

1. Physical appearance

All the prepared transdermal patches were visually inspected for clarity, color, flexibility and smoothness.

2**. Weight Variation**:

Weight variation was studied by individually weighing 3 randomly selected films. Such determination was performed for each formulation.

3**. Film Thickness:**

The thickness of prepared patch was measured at three different places using a Screw gauge and mean values were calculated. [11,12]

4. Folding Endurance:

Folding endurance test was performed 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 the folding endurance value.

5. Determination of Drug Content in the Film [7]:

The specific area of prepared film was cut and added to a beaker containing 100 ml of Ethanol. The medium was stirred [500rpm] with Teflon coated magnetic bead for 5 hours. The contents were filtered by using Whatman filter paper and the filtrate was analyzed by U.V. Spectrophotometer at 226 nm for the drug content against the blank solution

6. Percentage of Moisture Content:

The films were weighed individually and kept in desiccator containing activated silica at room temperature for 24 h. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.[13]

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

7. Percentage of Moisture Uptake:

A prepared patch was weighed and kept in a desiccator at room temperature for 24 h was taken out and exposed to 84% relative humidity (a saturated solution of aluminum chloride) in a desiccator until constant weight for the film was obtained. The percentage of moisture uptake was calculated as the difference between final weight and initial weight with respect to initial weight.[13]

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

8. In vitro drug diffusion studies

In vitro diffusion studies were performed by using a Franz diffusion cell with a receptor compartment capacity of 150 ml. The dialysis membrane was mounted between the receptor and donor compartment of the diffusion cell. The prepared film was placed on cellulose acetate membrane and covered with aluminum foil.

The receptor compartment of the diffusion cell was filled up with phosphate buffer pH 7.4. The whole assembly was fixed on a hot plate magnetic stirrer, and solution in the receptor compartment was continuously and constantly stirred by use of magnetic beads and the temperature was mentioned at 37 ± 0.5°C. The samples were withdrawn at different intervals of time and analyzed the drug content in U.V. spectrophotometer. The receptor phase was replenished with an equal volume of phosphate buffer (pH 7.4) at each sample withdrawal. [13, 14, 15]

9. Stability Studies:

The purpose of stability testing is to provide the evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as humidity, temperature, and light and to establish a retest period for the drug substance or a shelf life for the drug product and for recommended storage conditions. To assess the drug and formulation stability, stability studies were done according to ICH guidelines Q1C. Stability studies were carried out on the films of most satisfactory as per ICH Guidelines Q1C. The most satisfactory formulation stored in sealed in aluminum foil. These were stored at room temperature for 2 months. Films were evaluated for In vitro drug release, In vivo diffusion study and various physical characteristics.[16]

OPTIMIZATION:

Optimization is an approach to search along process variables of input variables to satisfy a goal such as maximizing/minimizing/targeting a response variable. Amount of plasticizers addition, base (Gum Rosin, PVP, PEG -400.DMSO. Glycerin), different base was selected as design factor and the other parameters were kept constant in the formulation. The ultimate goal of the DOE was to optimize the critical process parameters to achieve desired thickness, Tensile strength and Drug release profiles. Response central surface design was selected to carry out with 10 experimental runs for each base was optimize the formulation of Transdermal patch. The DOE runs were performed by 2*4 response surface design in a random order. The analysis was performed, ANOVA, interaction profile, prediction profiler,3D surface graph, actual Vs. predicted and optimization were conducted in JMP 14 Trial (SAS institute Inc., NC).

II. RESULTS AND DISCUSSION

Preformulation studies: it showed white colored amorphous Enalapril maleate was poorly soluble in water and freely soluble in ethanol and Phosphate buffer pH7.4 .Melting point of drug was found to be 142.66 .Interaction of drug with polymers was confirmed by carrying out by FTIR and DSC .It shows that there are no interaction found between the drug and polymer.

Physicochemical evaluation of transdermal patches of Enalapril Maleate

Table 4: Physicochemical evaluation of formulation F1 to F8

Formulation code	Weight variation Mean ±SD (mg)	Film thickness Mean SD (mm)	Folding endurance Mean ±SD	% Drug content	% Moisture content Mean ±SD	% Moisture Uptake Mean SD
F1	320±0.01	0.26 ± 0.02	110 ± 0.8	92.6 ± 0.13	2.02 ±1.42	1.51 ± 1.55
F2	365±0.033	0.23 ± 0.01	96 ± 6	86.2 ± 0.14	1.88 ± 1.32	2.59 ± 1.01
F3	325±0.01	0.29 ± 0.06	108 ± 0.9	85 ± 0.23	1.97 ± 0.73	1.67 ± 0.67
F4	355±0.02	0.20 ± 0.04	105 ± 1.6	87.4 ± 0.31	1.94 ±0.91	1.55 ± 2.17
F5	332±0.03	0.25 ± 0.03	111 ± 1.2	96 ± 0.13	1.65 ± 1.65	3.06 ± 0.56
F6	321±0.07	0.17 ± 0.02	97 ± 5	95.9 ± 0.11	2.17 ± 0.37	1.65 ± 1.99
F7	368±0.03	0.21 ± 0.06	102 ± 3	91.6 ± 0.14	1.32 ± 0.32	1.59 ± 1.2
F8	354±0.09	0.23±0.07	107 ± 1.9	88 ± 0.15	2.12 ± 0.21	2.36 ± 0.9

n*=3 ±SD

Physicochemical characterization of Enalapril Maleate transdermal films

All the physicochemical evaluation parameters were shown in table: 04). The weight variation of prepared patches was found to be in the range of 320 ± 0.01 to 368 ± 0.03 and thickness of the prepared films was found to be range of 0.17 ± 0.02 to 0.26 ± 0.02. The low SD values indicates the uniformity of film thickness.

The folding endurance were found to vary from 96 ± 6 to 111 ± 1.2 this value indicates good strength and elasticity; Folding Endurance of the film increases with increase in the Gum rosin and PVP proportions.

Drug content uniformity of prepared films was found to be range of 86.2 ± 0.14 to 96 ± 0.13. Moisture content of the developed formulations F1 to F8 varied from 2.17 to 1.32% And Moisture uptake of prepared films was varied from 3.06 to 1.51%. The moisture content and Moisture uptake of the prepared formulations was low, which help the formulations could remain stable and reduce brittleness during long term storage.

In-vitro Drug Release Studies from Transdermal Patches of Enalapril Maleate:

Figure06 Shows the release profile of Enalapril maleate from the transdermal patches. Formulation F1 to F8 exhibits greatest (82% ,90%) percentage of drug release values (Table 5) In these present observed that depending on the concentration Gum rosin and PVP the releasing of the drug is substantially increased.

The optimized formulation F9 showing controlled release of drug. (Table: 8)

Table 5: Comparative data of percentage drug release from the formulation F1 to F8

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	3.236	2.69	4.47	6.28	5.48	3.07	4.42	5.82
2	7.203	6.83	8.7	12.38	9.62	9	8.7	12.34
3	10.86	10.74	13.62	17.06	13.74	13.74	13.8	18.52
4	17.35	27.68	17.42	23.38	20.6	21.48	20.63	23.38
5	23.27	33.89	18.62	41.18	27.06	27.27	27.72	27.54
6	27.49	36.55	22.78	44.69	35.3	36.22	35.38	36.25
7	31.62	40.84	27.52	45.42	41.29	38.29	41.29	41.29
8	35.37	43.01	31.54	45.67	48.15	41.24	44.28	50.33
9	39.88	47.6	36.61	46.99	54.61	44.82	50.38	56.33
10	43.93	51.79	41.29	50.39	61.5	45.23	55.06	64.71
11	49.42	54.61	44.76	54.95	65.23	49.23	58.33	68.85
12	54.586	57.24	50.68	58.59	69.58	44.5	63.85	78.48
13	58.27	61.95	44.49	63.89	75.36	50.82	68.67	82.45
14	68.26	68.38	53.66	68.38	80.63	60.06	71.83	84.5
15	76.59	79.73	68.36	73.31	85.32	70.32	80.74	86.23
16	85.63	82.49	87.05	89.8	90.12	85.69	85.81	89.98

n*= 3 ±SD

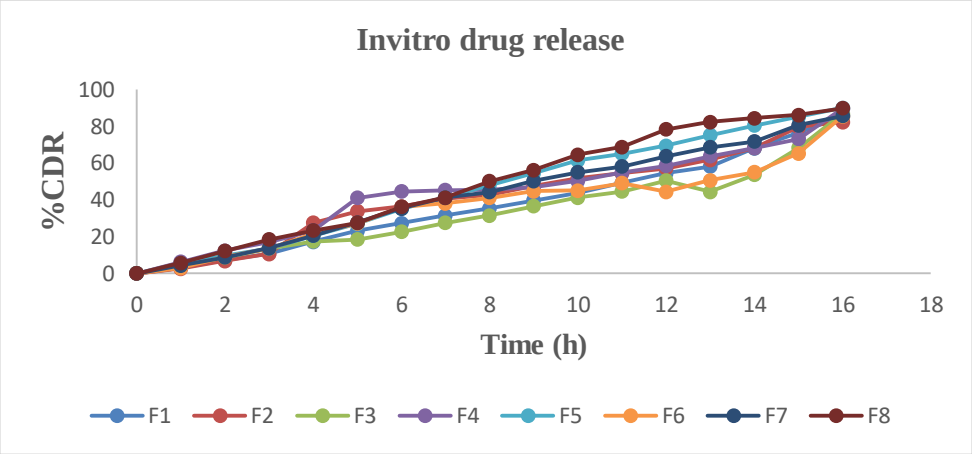

Figure 6: Comparison of *In vitro* diffusion study of formulation F1 to F8

OPTIMIZATION OF GUM ROSIN AND POLYVINYLPYRROLIDONE BASED TRANSDERMAL PATCHES

Table 6: Optimization design

QBD	Enalapril Maleate Transdermal patches
Version	JMP 14 trial version
Design	DOE
Model	2*4
Variables	Gum Rosin and PVP
Responses	Folding endurance, Drug diffusion at 5h,8h,16h

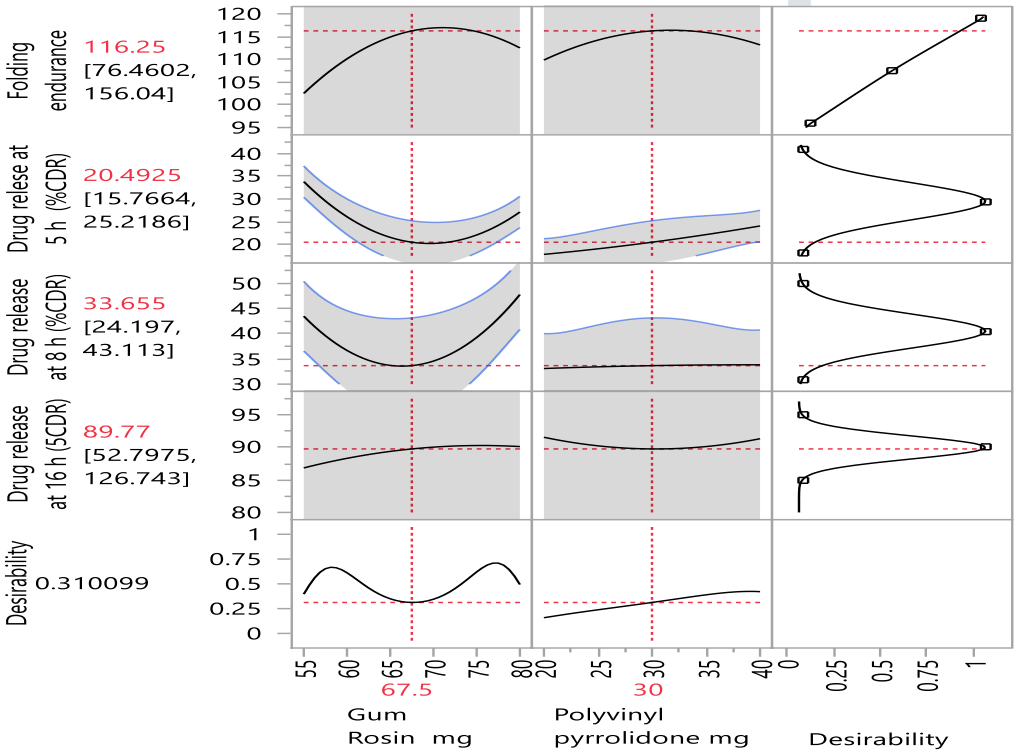

Figure 07: Prediction Profiler

OPTIMIZED FORMULATION (F9)

Table 7: Optimized formulation of *Enalapril* Maleate transdermal patch

Ingredients	Amount
Enalapril Maleate(mg)	15 mg
Gum Rosin (mg)	67.5
Polyvinylpyrrolidone (mg)	30
Glycerine (ml)	1
PEG-400 (ml)	1
DMSO (ml)	0.5
Amount of ethanol (solvent) (ml)	4

Table 8: Drug release studies of optimized formula (F9)

Time (h)	%CDR
0	0
1	5
2	10.86
3	15.92
4	17.35
5	20.10
6	25.74
7	27.54
8	32.99
9	39.88
10	43.93
11	50.86
12	56.50
13	65.92
14	73.89
15	81.21
16	89.23

Table 9: Comparison between the experimental (E) and predicted (P) values for the Optimized Formulation(F9)

Optimized Formula(F9)	Drug release at 5h	Drug release at 8h	Drug release at 16h	Folding endurance
Pred.	20.49	33.655	89.77	116
Expt.	20.10	32.99	89.23	110

Table 10: Kinetic data for optimized formulation of Enalapril Maleate Transdermal Patch

Formulation code F9	Zero order	First order	Higuchi	Korsmeyer & Peppas	N Value
R^2 Values	**0.9742**	**0.8211**	**0.9037**	**0.921**	**1.0013**

Release kinetics

The drug release mechanism from the optimized formulation(F9) was determine by fitting the data obtained from in vitro diffusion studies from the optimized formulation i.e. F9 were fitted in different models viz. Zero order, first order, Higuchi and Kielmeyer- Peppas equation, the results were shown in (Table 10)

The R^2 value for F9 was found to be 0.9742, 0.8211. 0.9037, 0.921, zero order, first order, higuchi model, peppas model respectively. So, it follows the Zero order of drug release.

The 'n' value (1.0013) it indicates that amount of released drug was by non-fickian diffusion super case 2.

Accelerated Stability study:

Stability studies were carried out on most satisfactory formulation as per ICH Guidelines Q1C. The most satisfactory formulation was sealed in aluminum foil and stored in stability chamber. These were stored at room temperature for 2 months, after 2 months drug content of most satisfactory formulation was determined. (Table 11) showed that there were no significant changes found in physicochemical parameters and in vitro diffusion of the most satisfactory formulations (F9) after stability study.

Table 11: Physicochemical properties of most optimized formulation (After stability)

Formulation code		F9	
Time (Days)		30	60
Folding endurance	A	> 110	>110
% drug content	A	>85	>85
%Moisture content	A	2.10	2.10
%Moisture uptake	A	3.0	3.0

Where A: 40°C±2°C/75%±5% RH.

III. CONCLUSION:

Transdermal patch of Enalapril Maleate can be successfully prepared by using Gum Rosin and PVP as individual polymer film and in combination by solvent casting method. Optimized formulation F9 was found to be best among all batches with a consistent release rate for 16 hours and the extent of drug release 89.23 %In vitro release data fitted into various kinetic models suggested that the release obeyed Zero order and release mechanism was non Fickian diffusion

Hence, it was concluded that Enalapril maleate transdermal patch may prove to be potential candidate for safe and effective controlled drug delivery over an extended period of time.

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V. REFERENCE

1. Kushal M, Monali M, Durgavati M, Mittal P, Umesh S, Pragna S. Oral controlled release drug delivery system: An overview. Int Res J of Pharm. 2013;4(3):70-6.
2. Bharkatiya M, Nema RK, Bhatnagar M. Development and characterization of transdermal patches of metoprolol tartrate. Asian J Pharm Clin Res. 2010;3(2): 130-4.
3. Davies RO, Gomez HJ, Irvin JD, Walker JF. An Overview of the Clinical Pharmacology of Enalapril. Br J Clin Pharmacol. 1984;18(S2) :215S-29S.
4. Bala P, Jathar S, Kale S, Pal K. Transdermal Drug Delivery System (TDDS)-A Multifaceted Approach For Drug Delivery. J of Pharm res. 2014 ;8(12): 1805-35.
5. Aqil M, Chowdhary I, Sultana Y, Talegaonkar S, Ahmad FJ, Ali MM. Transdermal therapeutic system of enalapril maleate using piperidine as penetration enhancer. Current drug delivery. 2008 ;5(2): 148-52.
6. Radha GV, Swetha N, Bharthi P, Neeraj K, Formulation and Evaluation of transdermal Films of Enalapril Maleate.JPSI.2013;2(1): 57-60
7. Blaih SM, Abdine HH, El-Yazbi FA, Shaalan RA. Spectrophotometric determination of enalapril maleate and ramipril in dosage forms. Spectroscopy Letters. 2000 1;33(1):91-102..
8. Peddapalli H, Ganta RP, Boggula N. Formulation and Evaluation of Transdermal Patches for Antianxiety Drug. Asian Journal of Pharmaceutics. 2018 ;12(2): 127-36.
9. Jain S, Tiwary AK, Sapra B, Jain NK. Formulation and evaluation of ethosomes for transdermal delivery of lamivudine. Aaps Pharmscitech. 2007 ;8(4): 249.
10. Shirisha S, Joshi G, Sahoo SK, Rao YM. Preparation and Evaluation of Matrix Type Transdermal Patches of Domperidone Maleate: in vitro and ex vivo Characterization. indian journal of pharmaceutical education and research. 2017 Oct 1;51(4): 517-24.
11. Kulkarni RV, Mutalik S, Hiremath D. Effect of plasticizers on the permeability and mechanical properties of eudragit films for transdermal application. Indian journal of Pharmaceutical sciences. 2002;64(1): 28.
12. Misra A, Upadhyay P. Apparatus for preparing adhesive-dispersion transdermal patches on a laboratory scale. International journal of pharmaceutics. 1996;132(1-2): 267-70.
13. Gannu R, Vamshi Vishnu Y, Kishan V, Madhusudan Rao Y. Development of nitrendipine transdermal patches: in vitro and ex vivo characterization. Current Drug Delivery. 2007;4(1): 69-76.
14. Kim MK, Zhao H, Lee CH, Kim DD. Formulation of a reservoir-type testosterone transdermal delivery system. International journal of pharmaceutics. 2001;219(1-2): 51-9.
15. Shivaraj A, Selvam RP, Mani TT, Sivakumar T. Design and evaluation of transdermal drug delivery of ketotifen fumarate. Int J Pharm Biomed Res. 2010;1(2):42-7.
16. Shinde AJ, Garala KC, More HN.. Development and Characterization of Transdermal therapeutic system of Tramadol Hydrochloride. Asian J Pharm 2008;2(4): 265-9