Development of a Polymer Film Dosage Form for Buccal Administration In the treatment of Hypertension

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Abstract: The objective of the study was to develop buccal films of Enalapril Maleate for the treatment of hypertension with minimal side effects, controlled release and patient compliance. The buccal films are orally administered medicament that deliver drug for local or systemic effects at a predetermined and controlled rate. Buccal drug delivery system avoids hepatic first pass metabolism and gastrointestinal irritation.

The Enalapril maleate buccal films were prepared by solvent casting method by incorporation of polymers like gum rosin, ethyl cellulose. . The Enalapril maleate buccal films were evaluated for swelling index, folding endurance, film thickness and in-vitro drug release. The drug release study was performed by using phosphate buffer 7.4 pH.

The optimized formulation (F9) provides controlled release of drug up to 87.73 % in 16 h. The optimized formula showed no significant changes on stability studies when stored at 40ºC/75% RH for two month according to ICH guidelines The r^2 values of zero order of F9 formulation have shown higher values which indicates the drug release is directly proportional to time which means release of Enalapril maleate follows zero order

Keywords: Enalapril Maleate; Gum rosin; Ethyl cellulose; DMSO; Glycerol; buccal films; Solvent casting

I. INTRODUCTION

Buccal drug delivery system is the one of the mucosal routes that has been studied from several years. The advantages of buccal drug delivery system are to avoidance of hepatic first- pass metabolism and degradation of drug in gastro intestinal tract. The flexibility, softness and small size of Mucoadhesive films are favorable for buccal mucosa compared to tablets.[1] The delivery system of oral films are more flexible and easier to administrate to pediatric, geriatric and mentally ill patients that experience difficulties swallowing oral solid dosage forms. Due to their size and thickness, buccal films are easy to handle, administer, improving patient compliance; these oral films are economically effective. These oral films are placed up and below the tongue it will dissolve or disintegrate in a saliva within a few minutes. Buccal mucosa helps to fast uptake of drug into systemic circulation and enhances the bioavailability[2]

Rich blood supply in Buccal mucosa is relatively permeable compared to low patient compliance of rectal, vaginal, sublingual and nasal drug delivery for controlled release.[3] The oral cavity is easily agree for self-medication, hence it is safe and agree by patients , the buccal films are easily applied and withdraw from administered site ,withdraw the input of the drug when it desired[4]

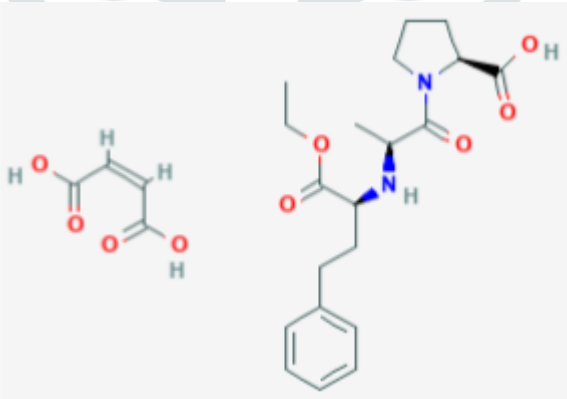

Figure 1: Enalapril Maleate

From the buccal delivery drug absorption is promptly terminated in case of toxicity from the site by removing the dosage form. Mucosal drug delivery provides a safer method of drug utilization. Buccal drug delivery is most advantageous because it abundant blood supply in buccal mucosa, bypassing the hepatic first pass effect.[5]

II . MATERIALS AND METHODS

Materials : Pure Enalapril Maleate drug was purchased from yarrow chem. Products. Mumbai. The polymer Gum Rosin and Ethyl Cellulose(EC) and chemicals such as DMSO, Glycerine were procured from yarrow chem. Mumbai and all other chemicals and solvents used were of analytical grade.

Preformulation studies: Preformulation studies such as physical appearance ,solubility ,Melting point and drug excipient compatibility were done by FTIR and DSC

Physical appearance: Pure Enalapril Maleate was examined for its color, odor, etc**.**

Solubility : The solubility of the selected drug was determined in distilled water, ethanol , chloroform and Phosphate Buffer pH7.4.

Melting Point Determination: The melting point was determined by using little amount of Enalapril Maleate in a capillary tube closed at one end. The tube is kept in the electrically operator melting point apparatus. The drug start to melt in the apparatus and the temperature at which drug melts was recorded the average value of three experiments was calculated.

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.

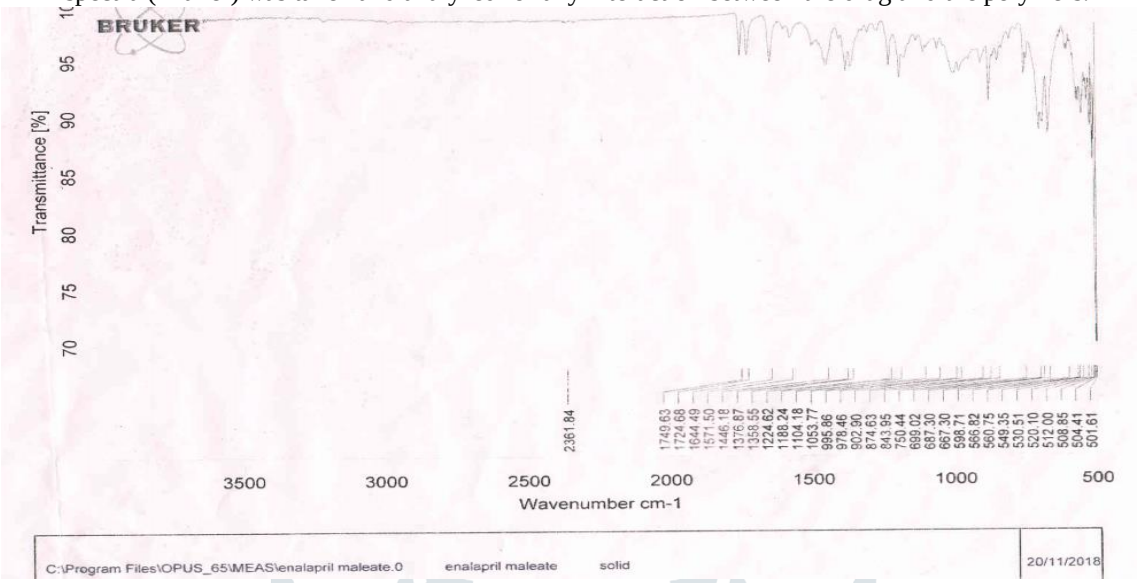

Figure 2: FTIR Spectra of Enalapril Maleate

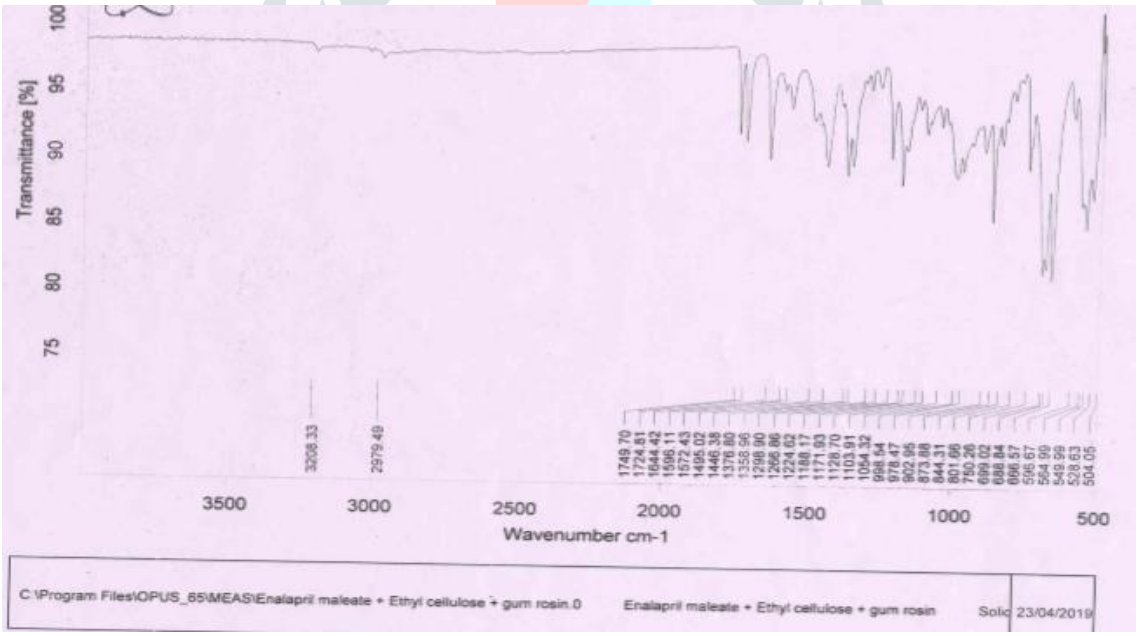

Figure 3: FTIR Spectra of Enalapril Maleate, Ethyl Cellulose And Gum Rosin

Table 1: FTIR Interpretation

Functional group	Range	Observed wavenumber for Enalapril maleate	Observed wavenumber for Enalapril maleate and gum rosin	Observed wavenumber for Enalapril maleate, Ethyl Cellulose	Observed wavenumber for Enalapril Maleate, Ethyl cellulose , Gum rosin
O-H stretch N-H stretch	3200-3700	3647.12	3647.58	3646.06 3209.19	3208.33
C=O Stretch	1640-1810	1724.68 1749.63	1724.31 1749.32	1724.79 1749.66	1724.81 1749.70
C-O Stretch	1050-1150	1053.77 1104.18	1053.79 1103.76	1054.22 1103.90	1054.32 1103.91
C-N stretch	1200-1350	1224.62 1358.55	1224.50 1359.35	1224.66 1266.76	1224.62 1266.86
C=C stretch	1640-1680	1644.49	1644.82	1644.47	1644.42

Differential Scanning Calorimetry (DSC) :DSC was used to determine thermal characteristics of Enalapril Maleate, physical mixture and drug loaded film. The thermo gram of drug, polymer and film were measured with a DSC-60 instrument.

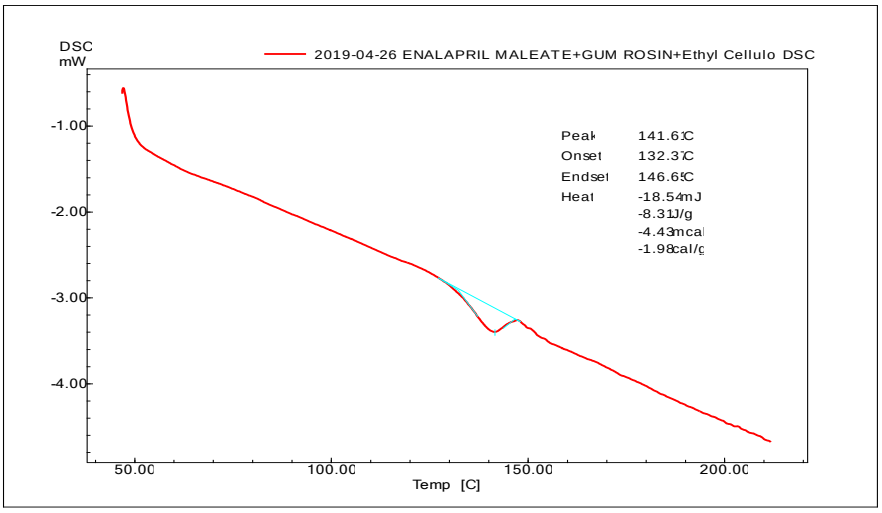

Figure 4: Enalapril Maleate, Gum Rosin and Ethyl Cellulose

Standard Calibration Curve of Enalapril Maleate:

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 buffer to give solution of concentration 2, 4, 6, 8, 10µg/mL detect the solution in UV spectrophotometer at the wavelength of 226 nm.[6]

Table 2: Standard calibration curve of Enalapril maleate by phosphate buffer 7.4 pH

Absorbance	Concentration
0	0
2	0.21
4	0.341
6	0.481
8	0.612
10	0.751

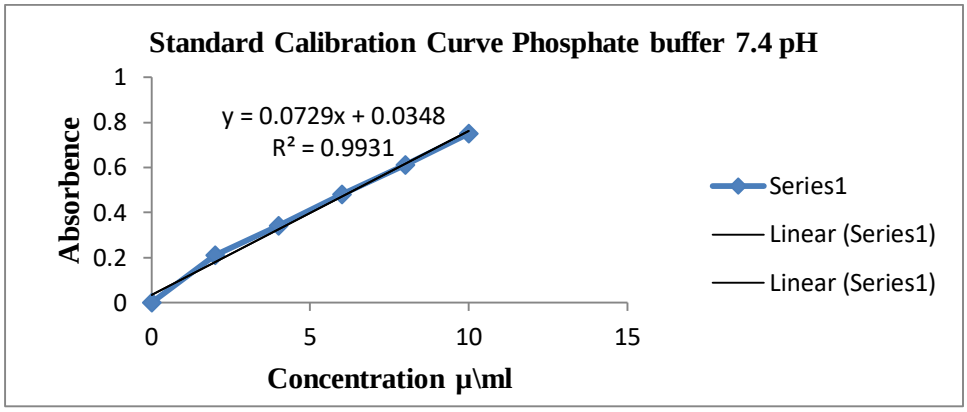

Figure 5: Standard Calibration Curve of Enalapril Maleate by phosphate buffer 7.4 pH

Preparation of buccal patches:

Table 3: Composition of preparation of buccal patches:

Enalapril maleate	Drug candidate
Gum rosin	Film forming agent + plasticizer
Glycerol	plasticizer
Ethyl cellulose	Film forming agent
DMSO	Permeation enhancers

Solvent casting method

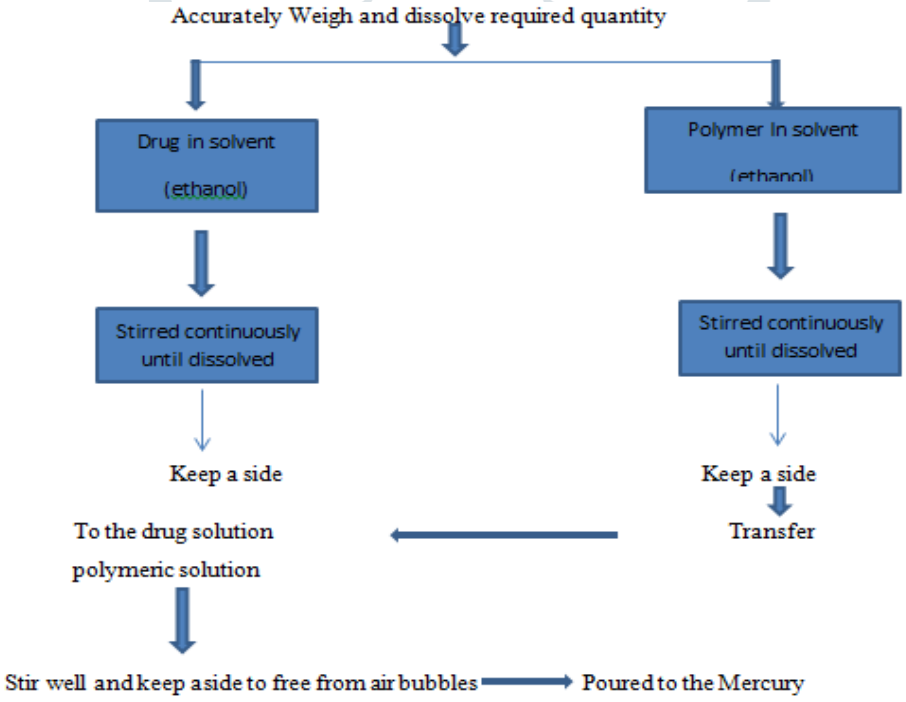

Figure 6: Preparation of Buccal films

Figure 7: Buccal films of Enalapril maleate

Table 4: Composition of Enalapril Maleate Formulation for buccal films Response central surface design (using 14 Trial)

Formulation Code	Drug (mg)	Gum rosin (mg)	Ethyl Cellulose (mg)	Glycerol	Solvent (Ml)	DMSO (ML)
F1	15	65	10	0.4	4	0.5
F2	15	77.5	10	0.4	4	0.5
F3	15	90	22.5	0.5	4	0.5
F4	15	77.5	35	0.6	4	0.5
F5	15	90	10	0.7	4	0.5
F6	15	65	22.5	0.5	4	0.5
F7	15	65	35	0.54	4	0.5
F8	15	90	35	0.5	4	0.5

Evaluation of Mucoadhesive buccal films:

Film weight [7]: Three films of each formulation were taken and weighed individually in analytical balance. The average weights were calculated.

Film thickness [6]: The thickness of films was measured at three different places using a Screw gauge and mean values were calculated.

Folding Endurance [8]: Randomly selected three films from each batch were taken to measure the folding endurance. The films were rapidly folded at the same place till it broke. The films folded up to 300 times manually was considered satisfactory value. The number of times of films could be folded at the same place without breaking gave the value of the folding endurance.

Surface pH [9]: An agar plate was prepared by dissolving 2% (w/v) agar in warmed simulated saliva and allowed to solidify at room temperature. Buccal patches were placed and allowed to swell for 2 h on the surface of an agar plate. The surface Ph was measured by bringing a combined glass electrode in contact with the surface of the swollen patch, allowing it to equilibrate for 1 min. The experiment was repeated thrice and the averages were taken.

Swelling index: The water uptake was determined by gravimetrically. The dried films fixed to stainless steel support were immersed in a beaker containing 25Ml distilled water at room temperature. At specific intervals up to 3h, the swollen sample with the pre-weighed mesh were weighed after removal of excess surface water by light blotting with filter paper. The experiment was discontinued when films begins to disintegrate or dissolved. The swelling index percentage was calculated as follows.

Swelling index % =(W2-WI/W1) ×100
W1=initial weight,
W2=final weight,
SI=Swelling index

Drug Content in the Film [10]: The patches were tested for the Content Uniformity. A patch of size 2x2cm2 was cut and placed in a 100 ml volumetric flask containing 100 ml Ethanol solution The contents were kept for 24 hours to complete dissolve the patch. After making proper dilution to the stock solution if necessary, the absorbance of the solution was measured against the corresponding blank solution at 412 nm.

In Vitro Drug Diffusion Studies: In Vitro Drug 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 donor and receptor compartment of the diffusion cell. The film was placed on cellulose acetate membrane and covered with aluminum foil. The receptor compartment of the diffusion cell was filled with phosphate buffer Ph 7.4. The whole assembly was fixed on a hot plate magnetic stirrer, and solution in the receptor compartment was constantly and continuously stirred using magnetic beads and the temperature was mentioned at 37± 0.5°C. The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically at 226 nm. The receptor phase was replenished with an equal volume of phosphate buffer after each sample withdrawal.

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 aluminium 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.[11]

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 (Rosin, Ethyl Cellulose, DMSO and 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 Folding endurance, 6h Drug release, 12h Drug release and 16h Drug release. Response central surface design was selected to carry out with 10 experimental runs for each base was optimize the formulation of Buccal films. 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.

III. 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 142-144°**c** .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.

Evaluation of Enalapril maleate Buccal Films.

Table 5: Drug Content, Swelling Index, Folding Endurance and Film Thickness

Formulation code	Film weight (mg)	Drug content (%)	Swelling index (%)	Folding endurance	Film thickness (mm)
F1	104	94.60	86.04	87	0.25
F2	103	93.59	91	85	0.29
F3	105	93.71	84.13	90	0.26
F4	104	94.32	92.06	94	0.27
F5	103	95.39	90.65	92	0.25
F6	105	93.44	87.11	91	0.30
F7	102	94.98	89.05	89	0.28
F8	106	94.30	90.04	94	0.31

n=3

Physicochemical characterization of Enalapril Maleate Buccal films

All the physicochemical evaluation parameters were shown in table :5). Weight variation of the developed formulation F1 to F8 varied from 102 to 106 mg and Thickness of the developed formulations F1 to F8 varied from 0.25 to 0.31 mm and was found to be uniform.

Folding Endurance of the developed formulations F1 to F8 varied from 85-94 (Table 5). Folding Endurance of the film increases with increase in the Rosin Proportion. Good uniformity in drug content was observed in all buccal patches as evidenced by (Table 5). The drug content is ranged from 93.44% to 95.39%. The comparison of swelling index of the developed formulation F1 to F8 varied from 84.13% to 92.0%. The Water Content remained in F4 was found to be more so The formulation F4 which is having high % Swelling Index. The formulation F3 which is having less % swelling was found to be 84.04%.

In vitro Drug Release of Enalapril Maleate:

(Table 6) shows in- vitro release of Enalapril Maleate from the prepared buccal formulation was studied in Ph 7.4 phosphate buffer for 16 h. From Formulation (F1-F8) exhibits highest percentage drug release value is %. As the ratio of polymer increased, the drug release decreased proportionally. The release rate from prepared formulation containing low polymer concentration was remarkably faste87.32 to 89.98 This may be due to the combination of other factors such as Ethyl Cellulose. In-vitro drug release of all formulations was represented in (Figure 8).

The optimized formulation F9 shows the percentage drug release value is87.73%. it showing controlled release of drug(table 8).

Table 6: Comparison 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	4.97	3.51	4.12	5.62	4.1	5.82	7.29	6.25
2	10.82	9.54	9.45	13.52	8.07	12.82	11.92	11.92
3	15.85	15.11	16.88	16.88	15.13	18.21	17.8	18.12
4	17.28	21.92	25.45	26.92	21.92	25.54	24.25	25.4
5	21.39	27.4	27.4	31.71	27.28	32.44	30.19	29.24
6	25.63	33.69	33.69	33.14	33.71	38.97	36.88	35.61
7	27.43	39.75	40.67	40.67	40.67	43.14	42.85	40.64
8	33.85	43.84	44.32	45.7	44.37	50.17	50.17	46.61
9	39.72	50.72	49.82	49.82	50.79	53.48	54.71	54.67
10	43.75	54.86	54.84	56.55	56.61	59.31	61.04	59.75
11	50.65	61.59	59.32	64.29	64.49	66.7	66	66.7
12	56.26	67.92	67.16	71.5	70.35	73.41	71.34	71.34
13	65.65	73.47	70.31	77.61	76.79	76.96	75.28	76.86
14	73.59	80.86	78.03	80	80.89	80.98	81.63	81.38
15	80.87	82.59	84.01	84.23	84	85.32	86.14	85.95
16	87.32	88.63	89.02	89.2	88.5	89.63	89.82	89.98

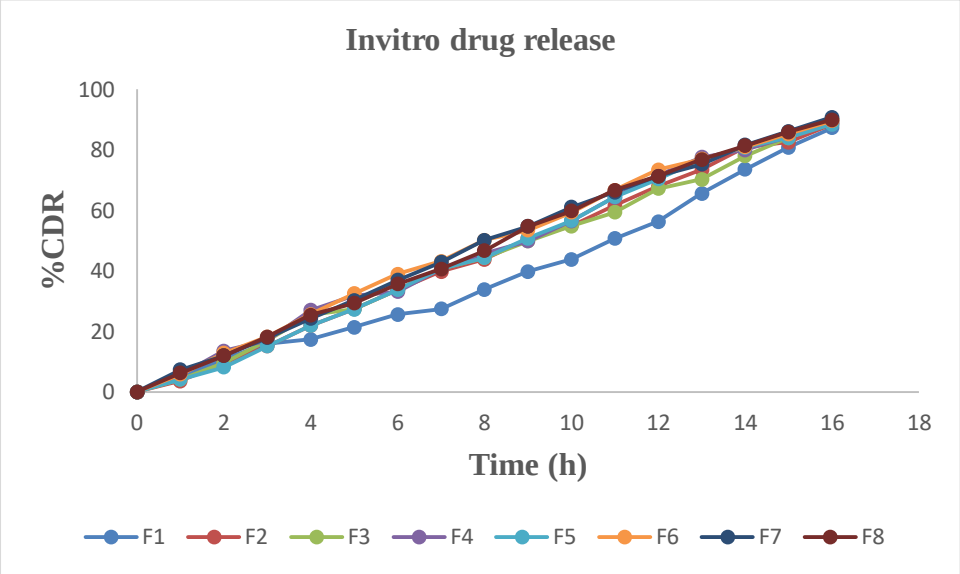

Figure 8: Comparison of In vitro dissolution study of F1 –F8 formulation

Optimization of Enalapril maleate films

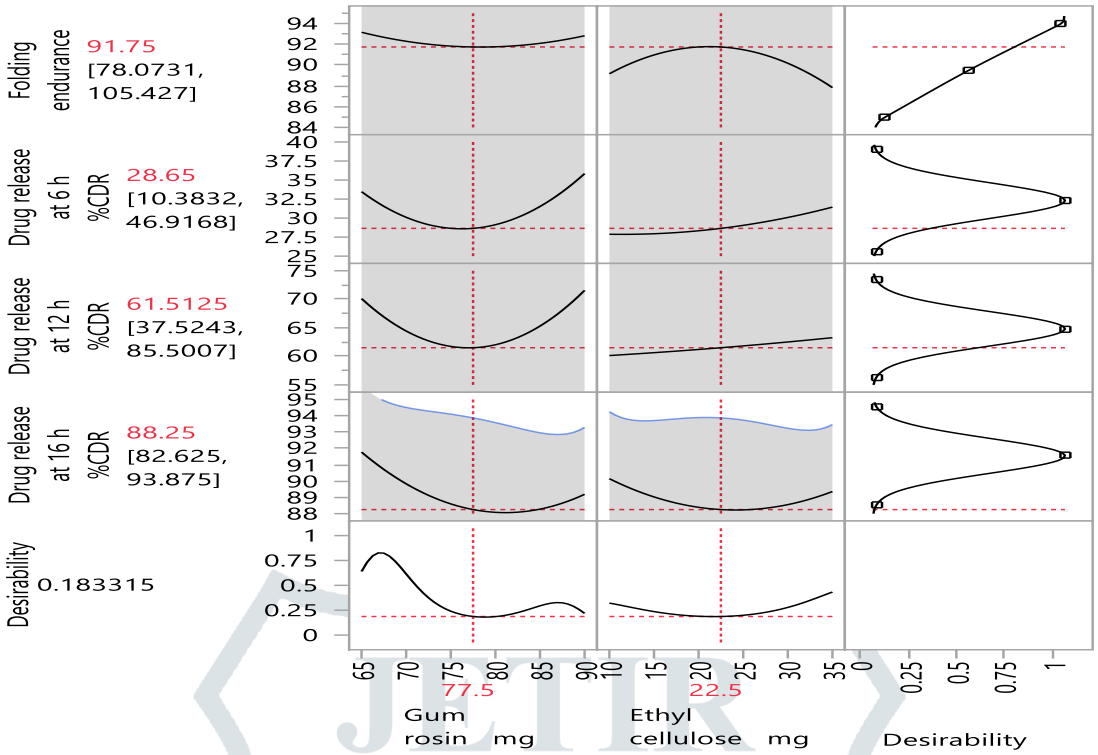

Figure 9: Prediction Profiler

Table 7: Composition of Optimized Formula (F9)

Ingredients	**Quantity**
Drug(mg)	15
Rosin(mg)	77.5
Ethyl Cellulose(mg)	22.5
Glycerol(Ml)	0.5
DMSO	0.5
Ethanol(Ml)	4

Table 8: Evaluation of Enalapril Maleate Buccal Films

time (hr)	**%CDR**
0	0
1	4.128
2	8.395
3	13.56
4	17.22
5	22.29
6	27.5
7	35.06
8	40.71
9	45.55
10	53.44
11	56.52
12	60.51
13	68.43
14	76.00
15	81.87
16	87.73

Table 9 : Comparison between the experimentalI and Predicted(P) values for the Optimized Formulation(F9)

Optimized Formulation	Drug Release at 6 h	Drug Release at 12 h	Drug Release at 16 h	Folding Endurance
Predicted	28.65	61.51	88.25	91.75
Experimental	27.57	60.51	87.73	90

Table 10 : Kinetic Data for Optimized Formulation of Enalapril Maleate Buccal Film for optimized formulation (F9)

Formulation(F9)	Zero Order	First Order	Korsmeyer Peppas	Higuchi	N Value
R^2 values	0.9959	0.9062	0.9985	0.9565	1.1169

Release kinetics

The drug release mechanism from the optimized formulation 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 Korsemeyer- Peppas equation, the results were shown in Table (10)

The R^2 value for F9 was found to be 0.9959, 0.9062. 0.9565, 0.9985, zero order, first order, higuchi model, peppas model respectively. So, it follows the Zero order and first order of drug release.

The 'n' value (1.1169) it indicates that amount of released drug was by non-fickian diffusion super case 2

Accelerated Stability Study

Table 11: Accelerated Stability Studies for the Optimized Formulation (F9)

Time	%CDR at 6h	%CDR at 12h	%CDR at 16 h	Folding Endurance
Initial	27.57	60.51	87.73	90
1st Month	27.12	59.96	87.32	89
2st Month	26.98	59.56	87.12	89

Conditions: 40°C ±2°C / 75%±5%RH

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.

IV. CONCLUSION

Buccal Films of Enalapril maleate can be successfully prepared using gum rosin (colophony) and ethyl cellulose polymers by Solvent casting method. The optimized Formulation F9 was found to be best among all batches of its consistent release rate for 16 h and the extent of drug release 87.73%. Invitro release of Enalapril maleate decreased as concentration of polymer increased.Stability Studies for two months revealed that the formulation was stable up to 40±2°C and 75 ±5% RH.

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

V. ACKNOWLEDGEMENT

We are thankful to prof. Basavaraj Ramanal, Honorable chairman, Karnataka group of institution, Bangalore, Karnataka. And Dr. K Ramesh, Director, Karnataka college of pharmacy and Ms. Rashmi Mathews. Assistant Professor, Karnataka College of Pharmacy and Dr. Beny baby. HOD pharmaceutics, Mr. Rajarajan. Assistant professor. Karnataka College of Pharmacy, Bangalore, Karnataka for providing the necessary facilities to carry out this research work.

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