

# Fabrication of Specially Designed Novel Mold for Casting of Perindopril Erbumine Mouth Dissolving Film

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**Abstract** In present investigation attempt was made to design novel mold with aim to overcome the problems occurs during the casting of mouth dissolving films. Placebo and Perindopril Erbumine containing mouth dissolving film (MDF) were prepared with Pullulan, HPMC E-15 as film forming agent and other excipient by solvent casting method on specially design mold and regular petri dish. The HPMC E-15 125mg and Propylene Glycol 30  $\mu$  ml as plasticizer contains MDFs formulation (H2) were found to be optimized when compared with Pullulan on the basis of physical evaluation parameters like weight variation, drug, thickness in the range 0.01 – 0.03 mm, disintegration time in <17sec. And release of drug from the film was found to <60sec and other parameters were found within acceptable limits. The prepared optimized stable mouth dissolving films were characterized by SEM, FT-IR, DSC etc. And various new equipments were used first time in PMDFs preparation for cutting, pill-out and water level indicator for balancing novel mold in the oven, which was widely used in other field like engineering and physics. Especially design mold for casting of the film was found to be more efficient than regular petri dish due to easily scale up and avoid problems occurs during preparation of stable mouth dissolving film which leads to reduce the wastage of active ingredients and excipients.

**Keywords** Novel mold, Solvent Casting Method, Pullulan, & HPMC E-15, Perindopril Erbumine and Mouth Dissolving Film

## 1. Introduction

Mouth dissolving films (MDFs) that disintegrate and dissolve upon contact with a wet surface within seconds in oral cavity is gaining increasing popularity day-by-day (1-4). Due to its easy administration, avoidance of water use, (4-7) and first pass metabolism; quick onset of action, and convenient way of dosing medications, (5,7,8). These MDFs are not merely meant for special population groups with

swallowing difficulties like children and the elderly, but also for the general population. (3,4,7) The MDFs allow multidirectional drug transport, but by applying a backing layer even unidirectional drug transport can be achieved. Drug loaded MDF were reported by various researchers for various physiological and neurological conditions like dysphasia, motion sickness, allergic attacks, or coughing, hand tremors, rheumatoid arthritis, degenerative arthritis and gout (2,4,5,7).

The MDF was prepared by various method like rolling method, hot melt extrusion, solid dispersion extrusion, solvent casting method, semisolid casting method (10). Among these methods, solvent casting method is reported widely in literature (11), due to its simplicity and convenience but these methods have some limitations like deposition of drug solution at the edges of petri dish, cracking of the film, un-uniform distribution of excipient, variation in thickness and wastage during cutting of film and wastage of drug solution.

In the light of the above literature an effort was made for designing of novel mold (NM) for casting MDFs prepared by solvent casting method. In this research, Perindopril Erbumine (PEM) an ACE inhibitor, which is widely used in the treatment of high blood pressure was selected as model drug for preparation of MDFs. The effect of plasticizer and film forming agent concentration was examined and further characterized by different evaluation parameters like disintegration time, dissolving time, thickness, weight variation, content uniformity, surface pH, tear resistance, folding endurance, percent elongation, and tensile strength. (7,8,9) and first time we're using new equipments required for cutting, stripping down, leveling of NM during preparation of films.

## 2. Material

Perindopril Erbumine (PEM) was obtained as a gift sample from Dr. Reddy's Lab, R and D, Hyderabad. Pullulan (Hayashibara, Okayama, Japan) was generously gifted by Gangwal Chemical Pvt. Ltd, Mumbai India. Neotame was

obtained as a gift sample from Kawaralal and Co. Chennai, India. All other chemicals and reagents used were of analytical grades and used as received.

### 3. Method

#### Preparation of placebo mouth dissolving film

Placebo MDFs (PMDFs) were prepared by commonly used solvent casting method. In this method water-soluble polymers (HPMC E-15 and Pullulan as film former) were dissolved in distilled water and other excipients like Propylene glycol and PEG-400 as plasticizer, Neotame as sweetening agent, Amaranth die as coloring agent and citric acid as saliva stimulating agent were added with continuous stirring and finally casted into regular shape (circular) in petridish (10,11) and dried in hot air oven at optimized 50 °C for next 24 h (4,12) and cut each PMDF in size 2 x 2 cm. and stored in dry and well-closed container. (12,13) and evaluated by different evaluation parameters.

#### Fabrication of PMDF using conventional technique

During preparation of PMDF some defects were observed in solvent casting method like deposition of solution at the edges of petri dish, cracking of film, un-uniform distribution of excipients, variation in thickness and wastage during cutting of film, summarized in (Fig.1) In this method, solution was cast in regular shape (circular) using petri dish. Most of the MDFs were square in shape; this method resulted in only 55% practical yield and 45% loss during preparation film. The wastage occurred during cutting of the film was significant. Consequently there was a need of modification of this technique for casting of the film, which will reduce

the wastage of active ingredient and other excipients.

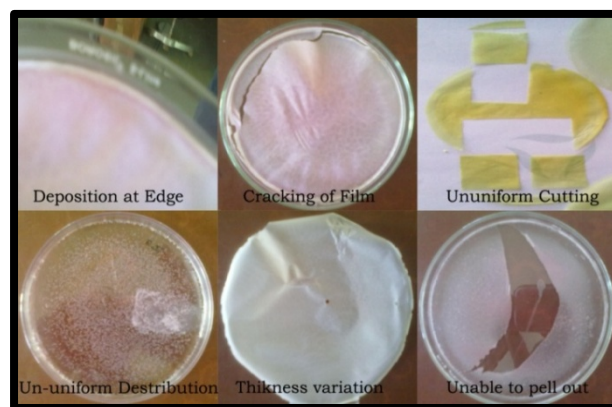


Figure 1. Defects in mouth dissolving films

#### Design of Specially Design Novel mold

The mold was fabricated by using thick glass which provides resistance to thermal stress, with thickness of 0.5cm with dimension of 30 x 30 cm. Left the space 5×5cm all sides and fixed glass plate with the help of Araldite glue which having thickness 0.4cm and width 1cm, square shape novel mold were design having inner size diameter 19 x 19cm area, which was used for casting of the film (Fig.2). During the casting of film on NM were using water leveling meter to achieve the proper thickness of all film, which is widely used for the wall leveling purpose in construction of buildings, Roll and Draw scale for cutting of film which is widely used in engineering drawing and forceps were used for pill-out of film.

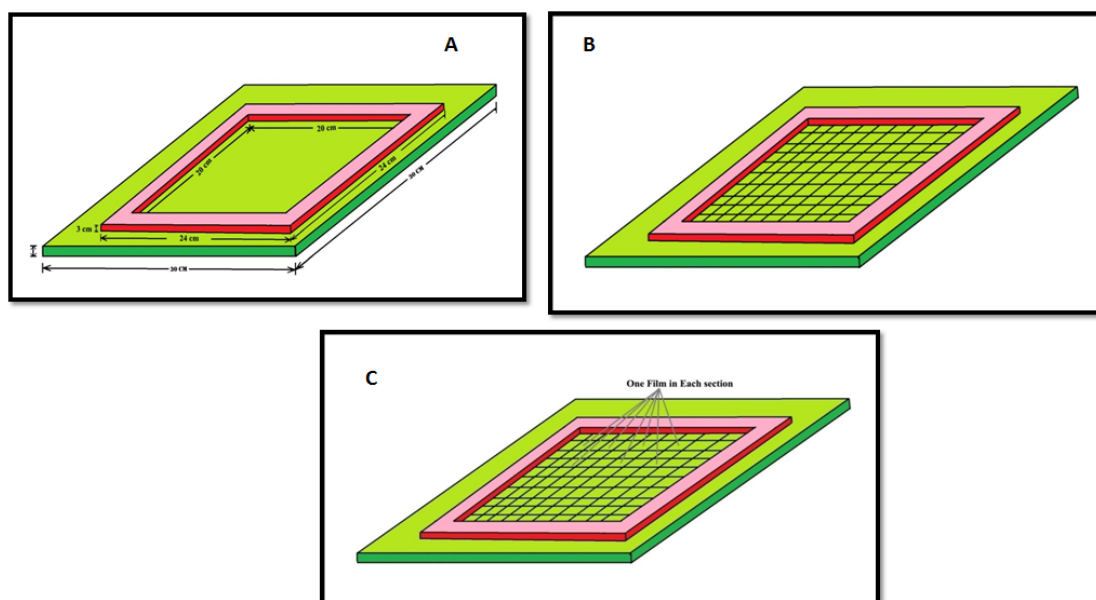


Figure 2. Designed novel mould for mouth dissolving film

**Table 1.** Effect of HPMC E15 & Pullulan as film forming agent

Formulation Ingredient (mg)	H1 P1	H2 P2	H3 P3	H4 P4	H5 P5	H6 P6	H7 P7	H8 P8	H9 P9	H10 P10
HPMC E-15 [H1-H10]	100	125	150	175	200	225	250	275	300	400
PULLULAN [P1-P10]	350	400	450	500	550	550	600	650	700	750
Dist. Water (ml)	14	14	14	14	14	14	14	14	14	14

**Table 2.** Effect of Polyethylene Glycol & PEG400 as plasticizer

Formulation Ingredient (mg)	A1 B1	A2 B2	A3 B3	A4 B4	A5 B5	A6 B6	A7 B7	A8 B8
HPMC E15 [A1-A8]	125	125	125	125	125	125	125	125
Pullulan [B1-B8]	450	450	450	450	450	450	450	450
Propylene Glycol	10		20		30		40	
PEG-400		10		20		30		40
Distilled water (ml)	14	14	14	14	14	14	14	14

#### Fabrication of PMDF using novel mold

Modify the existing solvent casting method which is required for specially designed novel mold, In this method, Divide equal amounts of solvent (water) in two portions denoted as Part (A) and Part (B). In Part (A), distilled water used as solvent, mix film forming agent HPMC E-15 and Pullulan in different concentration of 125-750mg and 450-950 mg respectively and study the effect of film forming agent on film formation, shown in (Table 1) and Propylene glycol and PEG-400 as a plasticizer in 10,20,30,40  $\mu$ /ml and study the effect of plasticizer on film formation, shown in (Table 2) Neotame, Amaranth die and citric acid was used as sweetening, coloring and saliva stimulating agent respectively. In Part (B) 72mg of active ingredient (Perindopril Erbumine) was dissolved in distilled water for preparation of 18 films containing 4mg of dose and mixed both part carefully with continuous stirring on magnetic stirrer at 500 rpm for 2h. Dispersion was carefully cast in novel mold and kept in hot air oven for drying at 60°C for 24 hours (Fig.2). The PMDFs were cut and pill-out into size 2×2cm containing 4 mg of perindopril erbumine with help of roll and draw scale and forecep respectively. Prepared PMDFs were stored in the dry and airtight container. The outcome of the film forming agent and plasticizer concentration was examined and various new equipments were used first time in PMDFs preparation for cutting, pill-out and water level indicator for balancing novel mold in the oven, which was widely used in other field like engineering and physics

#### 4. Evaluation of MDF

#### Thickness

Thicknesses of PMDF were measured by Digimatic Caliper (Mitutoyo, Japan) with range 0-10 mm and resolution 0.01 mm. Anvil of the thickness gage was lifted and 4mg single dose PMDF was inserted after making sure that the pointer was set to zero. The MDF was held on the anvil and the reading on the dial was noted. The average of three readings was taken as mean thickness. (14)

#### Weight variation

The prepared PMDFs were evaluated for their uniformity of weights. Ten films were weighed on digital weighing balance (AS-220/X, RADWAG wagi Elektroniczne, Poland) individually and average weight was calculated. Individual film weights were compared to the average weight. (15)

#### Drug content

Equivalent to 4mg PMDF was dissolved in 4ml distilled water and sonicated for 15min. This solution was filtered through the whatmann number 1 filter paper. PMDF extract (1mg mL<sup>-1</sup>) was diluted with water to give a final concentration (500  $\mu$ g mL<sup>-1</sup>) and determined the concentration of Perindopril Erbumine by using UV/VIS spectrophotometer (Shimadzu- 1800) was found to be  $\lambda_{max}$  213nm, which was coming under the vacuum range of UV/VIS spectrophotometer, thus Chandra Bala Sekaran *et al* spectrophotometric method was used to increase  $\lambda_{max}$  213nm for analysis of Perindopril Erbumine. In this method 1 mL of 0.5 N HCl and 0.5ml of 0.5% Bromophenol blue was transferred in suitable aliquot and mixed well. The funnels were shaken vigorously with 5 mL of chloroform for

2 min and then allowed to stand for clear separation of the two phases. The chloroform phase thus separated was transferred into a 10 mL volumetric flask. Then the extract was made up to the mark with chloroform and mixed well. The absorbance of the chloroform phase was measured at  $\lambda_{\max}$  425nm against a reagent blank prepared similarly omitting the drug.(15).This spectrophotometric measured  $\lambda_{\max}$  425nm were used for further analysis of Perindopril Erbumine

### Content uniformity

Ten PMDFs equivalent to 40mg were dissolved in 40ml and sonicated for 15min. this solution was filtered through the whatmann number 1 filter paper. PMDF extract (1mg  $\text{mL}^{-1}$ ) was diluted with water to give a final concentration (500  $\mu\text{g mL}^{-1}$ ). Above mention spectrophotometric method was used for analysis of content uniformity of Perindopril Erbumine. The content uniformity of PMDF, and the content of Perindopril Erbumine was determined by UV/VIS spectrophotometer (Shimadzu- 1800) at  $\lambda_{\max}$  425nm. In USP27, the contents of major component in the preparation should be within a range between 85% and 115%, and the relative standard deviation should be less than or equal to 6.0%.

### Surface pH:

The prepared PMDF was placed in a petri dish and moistened with 0.5 ml of distilled water and kept it for 30 second. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the film and allowing equilibration for 1 min. The average of three determinations for each film was done.

### Disintegration Time:

In vitro disintegration time is determined visually in a glass dish of 25ml distilled water with swirling every 10 Sec. The disintegration time is the time when the film starts to split or disintegrates. (10)

### Tensile strength

Tensile strength of PMDF was analyzed on tensile grip was fixed to the base of the Brookfield CT3 Texture Analyzer, while the other one was attached to the load cell, sample was placed between both tensile grips on the Texture Analyzer, Rupture force was taken as the maximum force required to break the sample and the tensile strength was calculated by the following equation. (3,13,17,18)

$$\text{Tensile strength} = \frac{\text{Rupture force}}{\text{Thickness} \times \text{width}}$$

Percentage elongation: Percentage elongation of PMDF was determined by using Brookfield CT3 Texture Analyzer When stress applied 500g trigger load, speed 0.3mm/sec, PMDF sample was stretches with final load 73g and work 35.5mJ required for deformation at peak load 0.84mm was referred to as strain. Strain is basically the deformation of strip divided by the original dimension of the sample.

Generally elongation of strip increases as the plasticizer content increases. (13)

$$\% \text{Elongation} = \frac{\text{Increase in length of strip} \times 100}{\text{Initial length of strip}}$$

### Tear Resistance

Tear resistance of PMDF was determined by using Brookfield CT3 Texture Analyzer Principally low rate of loading 51 mm (2 in.) / min is in employment to determine the strength to initiate tearing. The maximum tension necessary to tear the variety is recorded as the tear resistance value in Newton's. and Tear resistance of film is a composite of its final resistance to break. (19)

### Folding endurance

Folding endurance was determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film was folded without breaking is computed as the folding endurance value.

## 5. In-vitro Dissolution Study

The in-vitro dissolution studies of PMDF were carried out using USP dissolution test apparatus Type-II Paddle Method (Dissolution test TDT-08L plus, Electrolab, USP) at 50 rpm. The dissolution study was conducted in 250 ml of phosphate buffer having pH 6.8 as a dissolution medium at  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$  temperature. Optimized batches of PMDF HF&PF were suspended in reported dissolution media. Aliquot 5 mL of dissolution medium was withdrawn at specified time intervals and immediately replaced with an equal volume of fresh medium. Samples were suitably diluted and analysed for percent drug release by using UV spectrophotometer (Shimadzu UV-1700 Pharmaspec, Shimadzu, double beam spectrophotometer) at  $\lambda_{\max}$  425nm. All the tests were carried out in triplicate. (10,20)

## 6. In-vitro Disintegration Test

Vitro disintegration test was carried out by taking 10 ml of water at  $37^{\circ}\text{C}$  placed in a petri dish having 10 cm diameter. The PMDF carefully positioned in the center of the petri dish and noted time required to disintegrate completely. Disintegration time of PMDF was measured in replicates (n=6) and mean  $\pm$  SD values were recorded.

### Characterization

Identification of drug is a part of preformulation study and prior to the development of dosage form with the drug, it is essential to determine certain fundamental physical and chemical properties of the drug molecule and other derived properties of the drug. This information will dictate many of the subsequent events and possible approaches in the development of the formulation.

### UV Spectroscopy

Perindopril Erbumine is freely soluble in distilled water and sample solution of drug (concentration 10 to 60 µg/ml) was prepared. Then scan the spectrum was scanned at range 200 to 400nm on a UV spectrophotometer (Shimadzu-1800) and the spectrum was compared with standard spectra of drugs.

#### Fourier transforms infra-red spectroscopy

The FTIR study of Perindopril Erbumine was carried out to identify the functional group present in the material. For FTIR spectroscopy, Perindopril Erbumine was mixed with dried KBR in the ratio 1:100. Then the IR spectrum was taken on a FTIR spectrophotometer (IR Infinity, Shimadzu) by the DRS technique (Diffuse reluctant substance) and the result was shown in (Fig.4)

#### Differential scanning calorimetry

The thermal behavior of Perindopril Erbumine was examined by DSC. The DSC curve of the samples was obtained by a differential scanning calorimeter (Mettler Toledo). Each sample was placed in an aluminum pan and then crimped with an aluminum cover. The heating and cooling rate were 20°C/min and all measurements were performed over temperature range 40–300 °C. obtained result was shown in (Fig.5)

## 7. Drug–Excipients Interaction Study

#### Differential scanning calorimetry (DSC)

Physical mixtures of drug and excipients were filled in the prewashed vial and sealed. The sealed vial was kept at  $37 \pm 0.5^\circ\text{C}$  for 28 days in stability chamber. At the end of 28 days vials were removed from stability chamber and investigated for interaction study. Drug-exci-pient interaction study was done by using DSC. In this study thermogram of pure drug Perindopril Erbumine, Pullulan, HPMC E15, physical mixture was taken (Fig.5). The DSC curves of the samples were obtained by a differential scanning calorimeter (Mettler Toledo). Each sample was placed in an aluminum pan and then crimped with an aluminum cover. The heating and cooling rates were 20°C/min and all measurements were performed over temperature range 40–300°C.

#### Fourier transforms infrared (FT-IR) spectroscopy

IR spectroscopy was also used to determine the molecular interaction between polymer and drug (Fig.4). Infrared spectra of Pure drug, Pullulan, HPMC E15 physical mixture were obtained using FT-IR spectrophotometer (IR Infinity, Shimadzu) by the DRS technique (Diffuse reluctant substance).

#### Surface morphology

Sample of PMDF prepared by fracturing the films in liquid nitrogen, mounted on aluminum stubs, and sputter coated with platinum and surface morphology of PMDF was studied by scanning electron microscopy (SEM) with magnification of X25,000. (JEOL 5400, Tokyo, Japan).

#### Stability Study

The stability study of PMDFs was carried out according to the ICH guidelines for zones III and IV. The formulations were stored at  $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{RH}$  for 3 months by storing the samples in a stability chamber. At the end of 1, 2 & 3 month PMDFs were tested for thickness, drug content, disintegration time.(21)

## 8. Result and Discussion

Placebo MDFs were prepared by widely used solvent casting method. Some defects were observed in MDF like deposition of solution at the edges of petri dish, cracking of film, un-uniform distribution of excipients, variation in thickness and wastage during cutting of film, show at (Fig.1) In this method regular circular shape of petri dish was used as mold, It gives only 55% practical yield and 45% loss during cutting of square shape film, comparison of design novel mold for MDF (Fig.3) gives 90% practical yield and 10% loss. Therefore, square shape novel mold were designed for casting of the film having inner diameter 20 x 20 cm in area, show at (Fig.2). This will reduce the wastage of active ingredient and other excipients. Forceps, Roll and Draw scale, water leveling meter were used to reduces losses occurs during cutting and pill-out of film, which leads to reduce the cast of films and to achieve uniformity of MDF thickness.

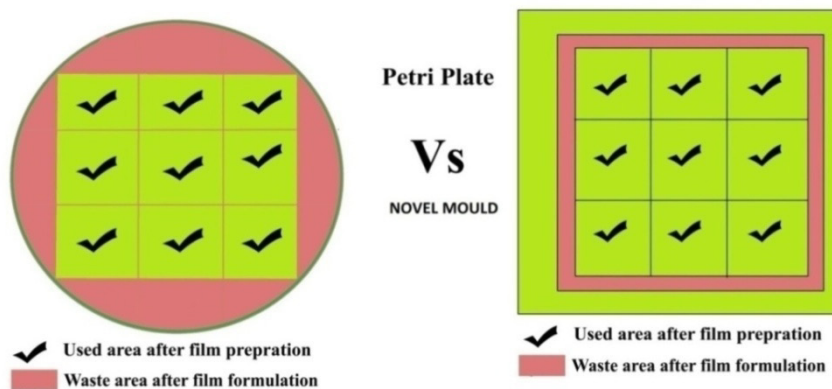


Figure 3. Comparison of design novel mould & Petri plate for casting MDF

### Formulation and evaluation of mouth dissolving film

Placebo MDF (H1-H10 and P1-P10) batches were prepared on specially designed novel mould by modified solvent casting method and study the effect of film forming agent (HPMC E-15 and Pullulan) in different concentration in the range of 125-750 mg and 450-950 mg respectively on film formation, From result, it was reveals that, as concentration of HPMC E-15 and Pullulan increased as film the disintegration and dissolution time were increased but transparency of film decreased with increased in concentration of film forming agent. MDF Batch H1 and P1 unable to peel out at concentration 100 mg and 350 mg. Hence, batches H2 contain 125mg of HPMC E-15 and P2 contain 450 mg of Pullulan were optimized on the basis of low disintegrating time and low dissolution time, good transparency and sufficient peel out properties. Therefore, this two batches were selected for further study, shown in (Table 3).

**Table 3.** Evaluation of film forming agent HPMC E15 and Pullulan

Formulation	Disintegration Time (sec) SD (n=3)	Dissolution Time (sec) SD (n=3)	Formulation	Disintegration Time (sec) SD (n=3)	Dissolution Time (sec) SD (n=3)
H1	8 ± 0.471405	29 ± 1.699673	P1	6 ± 0.471405	28 ± 0.471405
H2	<b>8 ± 0.471405</b>	<b>32 ± 0.471405</b>	P2	<b>10 ± 1.699673</b>	<b>43 ± 0.816497</b>
H3	11 ± 1.699673	49 ± 0.942809	P3	25 ± 1.247219	52 ± 0.942809
H4	22 ± 1.247219	52 ± 1.247219	P4	41 ± 1.699673	71 ± 0.816497
H5	33 ± 1.632993	55 ± 0.471405	P5	44 ± 1.699673	95 ± 0.471405
H6	40 ± 0.942809	60 ± 00	P6	90 ± 0.471405	149 ± 0.471405
H7	47 ± 0.471405	60 ± 2.054805	P7	117 ± 0.816497	201 ± 1.699673
H8	48 ± 0.816497	64 ± 1.247219	P8	157 ± 4.966555	280 ± 2.867442
H9	50 ± 0.471405	75 ± 2.054805	P9	202 ± 0.942809	301 ± 1.414214
H10	55 ± 2.357023	90 ± 2.054805	P10	223 ± 0.816497	355 ± 2.054805

**Table 4.** Evaluation of Plasticizer with film forming agent

Bach No.	Disintegration Study SD (n=3)	Dissolution Study SD (n=3)	Tensile Strength SD (n=3)	Percentage Elongation SD (n=3)
A1	12 ± 1.41421	40 ± 0.81649	3.73761	21.5
A2	13 ± 0.470140	49 ± 0.47140	3.743496	22.5 %
A3	<b>14 ± 0.01</b>	<b>45 ± 0.47140</b>	<b>3.81609</b>	<b>35.5 %</b>
A4	14 ± 0.42411	45 ± 0.81647	3.811185	32.5 %
A5	14 ± 0.57735	49 ± 1.24729	3.808733	24.5 %
A6	16 ± 0.471405	50 ± 0.471405	3.771945	24 %
A7	30 ± 0.81649	65 ± 0.47145	3.751344	33.5 %
A8	40 ± 0.94280	74 ± 0.47145	3.743496	23.5 %
B1	11 ± 0.81647	50 ± 0.87977	3.792546	31 %
B2	13 ± 0.00	48 ± 0.81647	3.796961	32.5 %
B3	13 ± 0.47545	56 ± 0.81648	3.795489	32 %
B4	14 ± 0.81647	54 ± 0.47587	3.801866	33.5 %
B5	<b>18 ± 0.471405</b>	<b>53 ± 0.816497</b>	<b>3.826391</b>	<b>38.5 %</b>
B6	16 ± 0.81649	54 ± 0.94257	3.810204	34 %
B7	32 ± 1.91274	78 ± 0.47145	3.800995	34 %
B8	50 ± 0.47145	84 ± 0.47145	3.792546	25.5 %

Propylene glycol and PEG-400 as a plasticizer in 10,20,30,40  $\mu$ /ml was added and prepared batches from (A1-A8 and B1-B8) and optimized the effect of plasticizer with a film forming agent in film formation. Plasticizer effects on the physical integrity of the film was observed after evaluation of parameters like Percentage elongation, Tensile strength, shown in the (Table 4). Dissolution time and disintegration time, Tensile strength and % elongation were increased with increasing concentration of plasticizer, which produces soft film. Hence, batches A3 and B5 20 $\mu$ /ml and 30 $\mu$ /ml plasticizer Propylene glycol show short disintegration time and dissolution time with sufficient Tensile strength and % elongation and without plasticizer film show more brittleness which is easy to break, shown in (Table 4).

**Table 5.** Formulation of Perindopril Erbumine containing mouth dissolving films

Batch Ingredient	HF	PF
Perindopril (mg)	72	72
HPMC E15 (mg)	125	---
Pullulan (mg)	---	450
Propylene Glycol ( $\mu$ ml)	30	20
Neotame (mg)	30	30
Citric Acid (mg)	55	55
Pine App. Flv (ml)	0.5	0.5
Amaranth (mg)	0.25	0.25
Dist. Water ( ml )	14	14

**Table 6.** Evaluation of PMDF

Parameters	HF	PF
<b>Physical Properties</b>		
Thickness	0.01mm	0.01mm
Weight variation	8.5 $\pm$ 0.345	15.2 $\pm$ 0.443
Content Uniformity	99.3 $\pm$ 0.3	101.25 $\pm$ 0.1
pH	6.7	6.7
Disintegrating time	11 $\pm$ 0.4924	17 $\pm$ 0.1125
<b>Tensile Properties</b>		
Tensile Strength (N/mm <sup>2</sup> )	3.7501	3.796961
% Elongation	23 %	32.5%
Tear resistance(N)	2.336851	2.51457
Folding endurance	325	410

Perindopril Erbumine containing optimized concentrations of film forming agent, plasticizer and other excipients were added and prepared HF and PF batch of specially designed novel mold by modifying solvent casting methods, shown in (Table 5). The results stated that, the all batches were acceptable in terms of weight variation (100 $\pm$ 10%), and drug contents are described in (Table 6). Thickness was found to be in the range 0.01 – 0.03 mm, In vitro disintegration time of all MDF batches were studied

and all MDF show disintegration time in <17sec. In MDF; concentration of plasticizer was changed with constant film former concentration. The result reveals that batch contain 20  $\mu$ /ml PG have less disintegration time compared to batches contain 40, 30, 20  $\mu$ /ml PG. It indicates that MDF are easily dissolved when placed in the mouth. The pH of the film is slightly acidic to facilitate saliva secretion. The tensile strength was performing to assess strength and elasticity of the film. As the concentration of plasticizer increased tensile strength, % elongation, tear resistance and folding endurance increased. The all MDF batches have sufficient strength and elasticity to withstand mechanical stress during transport.

Identification and confirmation of pure drug (Perindopril Erbumine) were carried out by using UV spectroscopy, infrared spectroscopy and differential scanning calorimeter. Perindopril Erbumine solution was scanned at 200 nm to 400 nm, an absorbance maximum observed at 219nm in pH 6.8 phosphate buffer. FTIR principal peaks corresponds to the structural features of Perindopril Erbumine are shown in (Fig.4) and found 1743.86  $\text{cm}^{-1}$  peak of confirming presence of C=O stretching, broad peak at 2500 -3000  $\text{cm}^{-1}$  and peak at 1292.61  $\text{cm}^{-1}$  confirm the acid group, further peak at 3111.78 with 1640.12  $\text{cm}^{-1}$  confirm presence of amine with amide linkage. Peak at 1743.86 with 1207.44  $\text{cm}^{-1}$  confirm the presence of the ester group. The peak at 2860.37  $\text{cm}^{-1}$  confirms the presence of C-H stretching of primary carbon. The peak at 2929.87  $\text{cm}^{-1}$  confirms the presence of C-H stretching in aromatic group. DSC thermogram of Perindopril Erbumine exhibits in (Fig.5) and found sharp exothermic peak at 128 $^{\circ}$ C means that it has a crystalline structure corresponding to its melting and decomposition. The reported peak temperature was 125-129  $^{\circ}$ C. The spectrum and thermogram of Perindopril Erbumine shows the desired peak as per reported in the USP pending monograph.

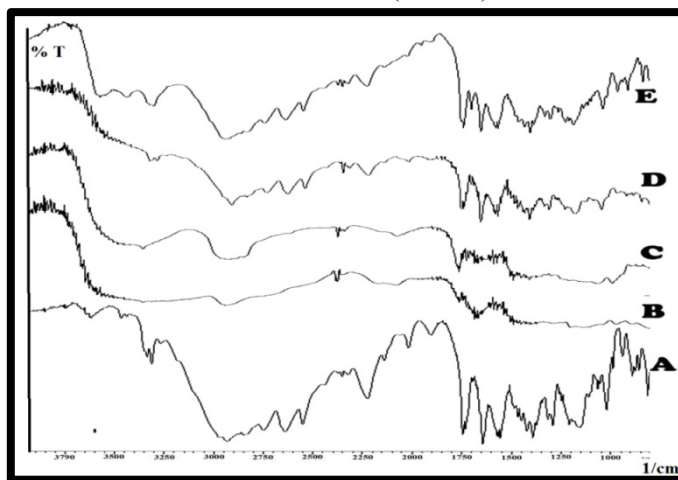
Drug-excipient interaction studies were done by using FTIR spectroscopy and used to assess the interaction between drug Perindopril Erbumine and other excipients. FT-IR spectrum drug Perindopril Erbumine, Pullulan, HPMC E15 and their physical mixtures was shown in (Fig.4). The principal peaks corresponds to the structural features of Perindopril Erbumine are observed that, Peak of 1743.86  $\text{cm}^{-1}$  confirms presence of C=O stretching, broad peak at 2500 -3000  $\text{cm}^{-1}$  and peak at 1292.61  $\text{cm}^{-1}$  confirm the acid group, further peak at 3111.78 with 1640.12  $\text{cm}^{-1}$  confirm presence of amine with amide linkage. Peak at 1743.86 with 1207.44  $\text{cm}^{-1}$  confirm the presence of the ester group. The FT-IR spectrum of the Pullulan is characterized by broad bands at 3150–3650  $\text{cm}^{-1}$  and 1031.92  $\text{cm}^{-1}$  due to aromatic O–H stretching vibrations, 1118.71  $\text{cm}^{-1}$  due to vibration of C-O-C groups. The FT-IR spectrums of the HPMC E15 contain broad peak at 3350.36 region to peak at 1012.63  $\text{cm}^{-1}$  due to aromatic O-H stretching, broad peak at 2835.36-2927.94  $\text{cm}^{-1}$  region due to C-H and C-H<sub>2</sub> vibrations. Any sign of interaction would be reflected by changes in the characteristic peaks of Perindopril Erbumine, depending on the extent of interaction (Bramhane 2011). The

FTIR spectra of the physical mixtures did not show any significant shifts in principal peak with respect to the FTIR spectra of the Perindopril Erbumine. Hence study reveals that there is no any physicochemical interaction between Perindopril Erbumine and excipients. DSC of drug perindopril Erbumine (A), Pullulan (B), HPMC E15 (C), Perindopril Erbumine: Pullulan (A: B) physical mixture and Perindopril Erbumine: HPMC E15 (A: C) physical mixture is shown in (Fig.5). The DSC curve of Perindopril Erbumine exhibiting a sharp endothermic peak at 128°C indicated melting point. Whereas Pullulan and HPMC E 15 shows melting peaks at 107.5 and 112 °C. Thermogram of Perindopril Erbumine: Pullulan physical mixture showed an endothermic peak of pullulan at 109.1°C followed by broad endotherm of Perindopril Erbumine at 124.51°C. Thermogram of Perindopril Erbumine: HPMC E15 physical mixture showed an endothermic peak of HPMC E15 at 114.9 °C followed by broad endotherm of Perindopril Erbumine at 124.79 °C. The peak of Perindopril Erbumine in the physical mixture shifted to lower scale with broad endotherm indicates the conversion of crystalline to amorphous.

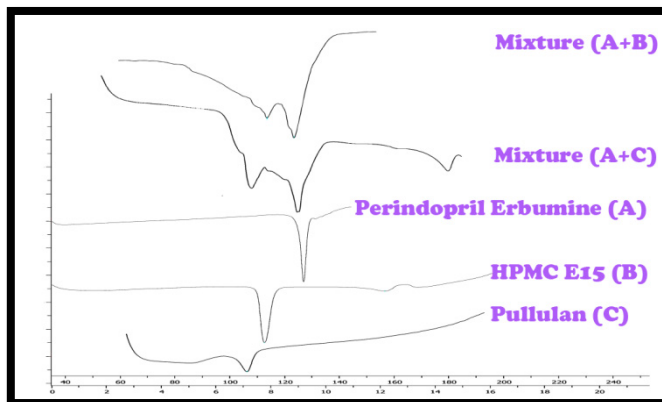
Optimized batch (HF and PF) of Perindopril Erbumine containing Mouth dissolving films was prepared on specially designed novel mold by modifying solvent casting methods and in-vitro release study of two batches was carried out at

pH 6.8 at 37°C ± 0.5 °C and shows maximum drug release more than 90% within in 4 min. and drug release optimized batch HF and PF showed 98.60 and 99.60% in 3 min respectively, shown in (Fig.7) Surface morphological study was carried out on scanning electron microscopy with 50000 x magnification values at 5 µm lengths. The image was scanned from both upper surface (A) and lower surface (B). Resulted film containing Perindopril Erbumine oral MDF was clear and colorless in nature. Smooth surface with some little pores and with few scratches or transverse striations were shown in (Fig.6)

Lower surface (B) is shown smooth as compare to upper surface (A) because of during formulation glass slide more smooth surface. Scanned image also shows a clear image, therefore it should be conclude total drug and excipients was dissolved and uniformly distributed within the formulation. The stability of optimized formulation HF was monitored up to 3 months at stress temperature and normal humidity conditions (40°C ±75 %RH). Periodically (initial, 1, 2, 3 months) samples were removed and evaluated by different parameters like thickness, content uniformity, disintegration test, weight variation.. There were no major changes observed during stability studies of Perindopril Erbumine containing mouth dissolving film. The result are summarized in (Table 7).



**Figure 4.** FTIR spectra for Drug-Interaction study, A= Perindopril Erbumine, B = Pullulan, C= HPMC E-15, D= Mixture of Perindopril Erbumine with Pullulan and E= Perindopril Erbumine with HPMC E-15.



**Figure 5.** DSC thermogram of Drug-Excipients Interaction Study

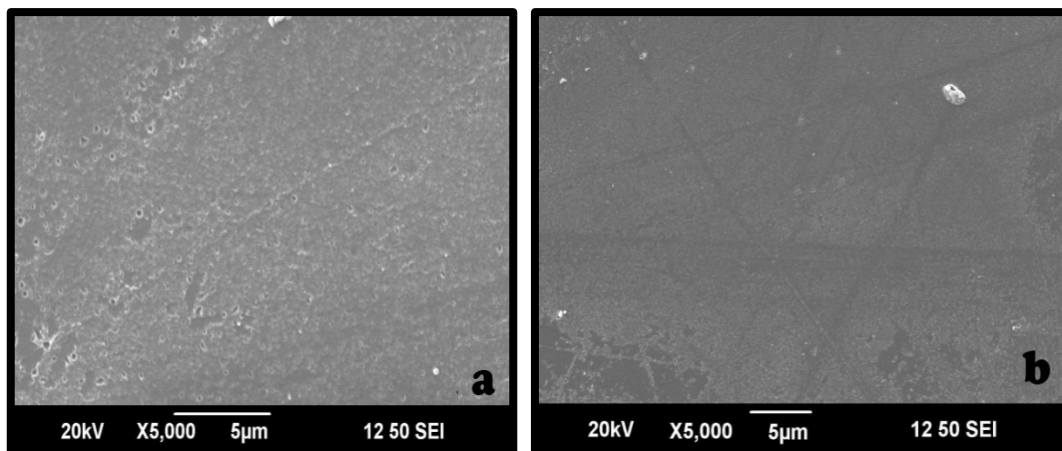


Figure 6. SEM of MDF (a) upper surface and (b) lower surface

Table 7. Stability study of PMDF (HF)

Evaluation Parameters	Before Stability	After 1 Month Storage	After 2 Month Storage	After 3 Month Storage
Thickness	0.01 mm	0.01 mm	0.01 mm	0.01 mm
Content Uniformity	99.3±0.3	99.3±0.3	99.3±0.3	99.3±0.3
Disintegration Time	10±0.4726	10±0.4790	10±0.4826	10±0.4826
Weight variation	8.9±0.3	8.9±0.3	8.9±0.6	8.8±0.3

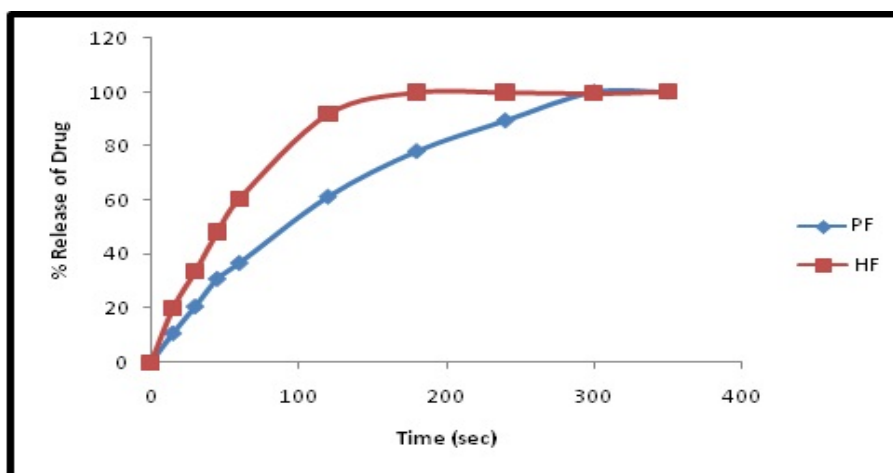


Figure 7. In-vitro release study of PMDF

## 9. Conclusion

From this study it can be concluded that, specially designed novel mold was found to be more effective than petri dish which overcome the problems occurs during the casting of mouth dissolving films. Prepared Perindopril Erbumine containing mouth dissolving film (MDF) with HPMC E-15 125mg and Propylene Glycol 30 µ ml as plasticizer concentration was found to be optimized when compared with Pullulan on the basis of physical evaluation

parameters like weight variation, drug, thickness in the range 0.01 – 0.03 mm, disintegration time in <17sec. And release of drug from film in <60sec and other parameters were found within acceptable limits and various new equipments were used first time in PMDFs preparation for cutting, pill-out and water level indicator for balancing novel mold in the oven, which was widely used in other field like engineering and physics. Especially design mold for casting of the film was found to be more efficient than regular petri dish due to easily scale up and avoid problems occurs during preparation

of stable mouth dissolving film which leads to reduce the wastage of active ingredients and excipients.

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## Conflicts of Interest

No Conflicts of Interest

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