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DESIGN AND CHARECTARISATION OF FAST DISSOLVING SUBLINGUAL FILM OF PERINDOPRIL ERBUMINE USING VARIOUS POLYMERS

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ABSTRACT

Sublingual route is the one among the most significant route of administration of drugs especially for those which need to avoid the first pass metabolism and required in lesser doses. Here the attempt was made to formulate fast dissolving sublingual film of Perindopril erbumine an antihypertensive agent belongs to ACE inhibitors by solvent casting method using different concentration of polymers HPMC E15, Pullulan for increase the convenience and compliance to the elderly and dysphagic patients and evaluated for the drug polymer compatibility by FTIR studies. The prepared films were evaluated for physico-chemical parameters such as weight uniformity, thickness uniformity, folding endurance, *In-vitro* disintegration time, *In-vitro* dissolution studies and *In-vitro* permeation studies. Skin irritation and stability studies were performed. It was found that all characteristic features show significant results. Formulation F1 and F7 showing best release of 95.93% and 92.47% at the end of 180sec respectively. *In-vitro* permeation studies of F1 formulation showed highest drug permeation of 93.97% at the end of 5min. No significant change was observed in the physical appearance, drug content, and *In-vitro* dissolution studies during stability studies at 40±20˚C/75±5% RH up to 90 days.

KEYWORDS: Perindopril erbumine, sublingual film, ACE-inhibitor, physicochemical parameters.

INTRODUCTION

Fast Dissolving Drug Delivery System is one of the major approach than the conventional dosage forms since the drug gets rapidly disintegrate and dissolves in the saliva without the use of water.[1] Many patients find difficult to swallow tablets and hard gelatin capsules particularly pediatrics and geriatric patients. In some cases such as motion sickness, sudden episode of allergic attack or coughing, fear of choking and an unavailability of water, the swallowing of tablet or capsules may become difficult. To overcome these difficulties, several fast dissolving films can be replaced.[2] Which placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for Oro-mucosal absorption. These films are suited for the drug which undergo high first pass metabolism, smaller and moderate molecular weight with the dose less than 30mg are preferable. Due to high permeability and rich blood supply, the sublingual route can produce rapid onset of action by improving bioavailability with reducing dosing frequency to mouth plasma peak levels, which in turn minimize adverse effect and also make it cost effective.[3] The mechanism for the absorption of the drug in to oral mucosa is via passive diffusion into the lipoidal membrane. The absorption of the drug through the sublingual route is 3 to 10 times greater than oral route. Perindopril is a long acting ACE inhibitor used to treat high blood pressure, heart failure, or stable coronary artery disease in the form of perindopril erbumine or perindopril arginine. Perindopril is freely soluble in water. The half-life of perindopril erbumine is 1-2hrs and dose range starts from 2mg for hypertension and gradually increases up to 4mg.[3]

MATERIALS

Perindopril erbumine, HPMC E 15, Croscarmellose, sodium starch glycolate, citric acid and sucrose were obtained as a gift sample from Yarrow Chem Products. Pullulun is obtained from kumar organics and PEG 400 is obtained as gift sample from loba chemie. All other chemicals used were analytical grade.

METHODS

Organoleptic characteristics

Colour, odour, and taste of the Perindopril erbumine were characterized and recorded using descriptive terminology.

Solubility

The solubility study was conducted by taking excess amount of the drug in 10 ml in respective solvents. Then the samples were kept in the water bath shaker and agitated for 24 hr at 37±0.5°C. The samples were filtered and diluted suitably with respective solvents. The samples were analyzed spectrophotometrically at 213nm. The concentration of drug was determined using standard graph.

Drug-excipient compatibility study

Compatibility Studies were carried out by using FTIR for finding possible chemical interaction between the drug and polymer. A physical mixture of drug, polymer and other excipients were prepared. It was scanned from 4000 to 400 cm^{-1} in a FTIR spectrophotometer. The FTIR spectrum of the physical mixture was compared with those of pure drug and with the polymer and peak matching was done to detect any appearance or disappearance of peaks.

Formulation of fast dissolving films of Perindopril Erbumine

Table 1: Model formula for oral film.

Sl No.	Ingredients	Percentage	Use
1	Perindopril erbumine	1-25%	Active Pharmaceutical Ingredients
2	Pullulan	40-50%	Polymer
3	HPMC E15	40-45%	Polymer
4	Crosscarmellose	2-6%	Super disintegrating agent
5	Sodium Starch Glycolate	2-6%	Super disintegrating agent
6	Citric acid	2-6 %	Saliva stimulating agent
7	PEG 400	0-20%w/v	Plasticizer
8	Sucrose	1-2 %	Sweeting agent

Formulation of fast dissolving oral films containing Perindopril erbumine[7]

The fast dissolving films of perindopril were prepared by solvent casting technique using film forming polymers pullulan or HPMC E15. The calculated amount of polymer was dissolved in three forth volume of water with continuous stirring. The calculated amount of perindopril was incorporated in the polymeric solutions. Sodium starch glycolate or croscarmellose sodium was then added to polymeric solution and stirred vigorously. Then citric acid and PEG 400 were added and the final volume was adjusted up to 10ml with distilled water. The resulting bubble free viscous solution was casted on to Petri dish (area of 63.58 cm^2) then kept in hot air oven at 40ºC for 24 hours. The films were cut in to size of 2cm×2cm containing 2 mg of perindoril erbumine.

Table 2: Composition of Perindopril erbumine sublingual films.

	Formulations											
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Perindopril erbumine in mg	31.79	31.79	31.79	31.79	31.79	31.79	31.79	31.79	31.79	31.79	31.79	31.79
Pullulan (mg)	200	300	400				200	300	400			
HPMC E15 (mg)				200	300	400				200	300	400
Crosarmellose Na (mg)	20	20	20	20	20	20						
Sodium starch glycolate (mg)							20	20	20	20	20	20
Citric Acid (mg	30	30	30	30	30	30	30	30	30	30	30	30
Sucrose (mg)	20	20	20	20	20	20	20	20	20	20	20	20
PEG 400 (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Menthol(Mg)	5	5	5	5	5	5	5	5	5	5	5	5
Distilled water up to	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml

Evaluation of Fast Dissolving Films

Thickness Measurement[1]

The thickness of the fast dissolving film (2cmx2cm) was determined by using a screw gauge. The thickness of each film at three different places was determined mean standard deviation was also calculated.

Drug content uniformity[11]

Fast dissolving film of size (2cm x 2cm) was cut into small pieces and transferred into a graduated glass stoppered flask containing about 100 ml of phosphate buffer. Solution was filtered and the amount of drug present was determined by uv-spectrophotometric method with suitable dilutions.

Weight variation[1]

Three individual batches of fast dissolving films of size (2cm x2cm) were weighed on an electronic balance and the average weight and standard deviation was calculated.

Surface pH[8]

The surface pH of fast dissolving film was determined in order to investigate the possibility of any side effect *in-vivo*. A combined pH electrode was used for this purpose. Oral film was slightly wetted with the help of water. The pH was measured by bringing the electrode in contact with the surface of the oral film. The procedure was performed in triplicate and average with standard deviation was reported.

Tensile strength[10]

The film size of 6cm x 2cm was selected for performing tensile strength test. The tensile strength apparatus has two clamps, the upper one is fixed and the lower is movable. The film

sample was clamped between the two clamps. The force at tearing and elongation were determined.

Tensile strength = Break force/ L

Where, L = elongated length of the film.

Results were reported in N/cm^2 $units^{-1}$

Percentage elongation[4]

The film size of 6cm x 2cm was selected for performing percentage elongation test. Percent elongation was mainly based on tensile strength of films. Percentage elongation was calculated by measuring the increase in length of the film after tensile strength measurement using the following formula.

$$\text{Elongation (percent)} = \frac{LF-Lo}{Lo} X\ 100$$

Where, L_F = final length, Lo= initial length. % elongation results are reported in percentage.

Folding Endurance[5]

The film size of 4cm x 2cm was selected for performing the folding endurance test. Folding endurance measures the ability of patch to withstand rupture, higher the folding endurance lower was chances of film to rupture easily and vice versa. This parameter was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking give the value of folding endurance.

Percentage Moisture content[6]

Moisture content was determined to evaluate the integrity of films at dry condition. Film of 4 cm^2 area was cut out and weighed accurately and kept in a desiccator containing fused anhydrous calcium chloride. After 24 hours the film was removed and weighed. Percentage moisture content of film was determined as follows.

$$\text{Moisture content} = \frac{W1-W2}{W1} X100$$

Where w_1=initial weight & w_2=final weight

Percentage moisture content results are reported in percentage.

***In-vitro* disintegration Test**[9]

The disintegration time is the time when a film breaks or disintegrates. The film size required for dose delivery (2cmx2cm) was placed on glass petri dish containing 10 ml of 0.1N

phosphate buffer. The time required for breaking of film was noted as *in-vitro* disintegration time.

In-vitro dissolution test[10]

The dissolution studies were carried out using USP XXIII type1 dissolution apparatus at 37° ± 0.5 °C and at 50 rpm using 0.1N phosphate buffer (250ml). Each film with dimension (2cm x 2cm) was placed on a basket. The film sample placed on the basket was submerged into dissolution media. Samples (5ml) were withdrawn at 0, 30, 60, 90, 120, 150 and 180 seconds and were analyzed by measuring the absorbance in UV spectrophotometer at 213nm. To maintain the volume, an equal volume of fresh dissolution medium was added after withdrawing samples.

In-vitro permeation studies[12]

In-vitro permeation studies through cellophane membrane were carried out using the Franz diffusion cell of internal diameter of 2.5 cm. The cellophane membrane was mounted between the donor and receptor compartments. The receptor compartment was filled with 100 ml of 6.8 pH phosphate buffer which was maintained at 37± 0.5°C. One film of dimension 2cm x 2cm was previously moistened with a few drops of phosphate buffer and placed in donor compartment. The donor compartment was filled with 5ml of 6.8pH phosphate buffer. 1 ml samples from receptor compartment were withdrawn at suitable time interval which was then replaced with 1 ml of 6.8 pH phosphate buffer. The percentage of perindopril permeated was determined by measuring the absorbance in UV spectrophotometer at maximum absorption.

Stability studies[6]

The 3 batches of formulations which show better evaluation parameter results were selected and were subjected to stability studies as per International Conference on Harmonization (ICH guidelines), the sample was packed in an aluminum foil. Then stored in stability chamber controlled at accelerated testing condition at 40±2°C / 75±5% RH for Three months and evaluated for their physical appearance, drug content and drug release studies at monthly intervals of time and results were reported.

RESULTS AND DISCUSSION

Preformulation studies of Perindopril erbumine

Organoleptic characteristics and solubility

Table No 3: Preformulation studies of Perindopril erbumine.

Properties	Reported		Observed	
Appearance	White powder		White powder	
Crystallinity	Crystalline Powder.		Crystalline Powder.	
Taste	Slightly metallic		Slightly metallic	
Odor	Odorless		Odorless	
Solubility	Water	60mg/ml	Water	59.8mg/ml
	Ethanol	54mg/ml	Ethanol	53.33mg/ml
	Phosphate buffer	51mg/ml	Phosphate buffer	50.22mg/ml
Melting Point	126ºC-128ºC		125ºC	
Identification(UV)	210nm		204	

Drug Excipients Compatibility Studies

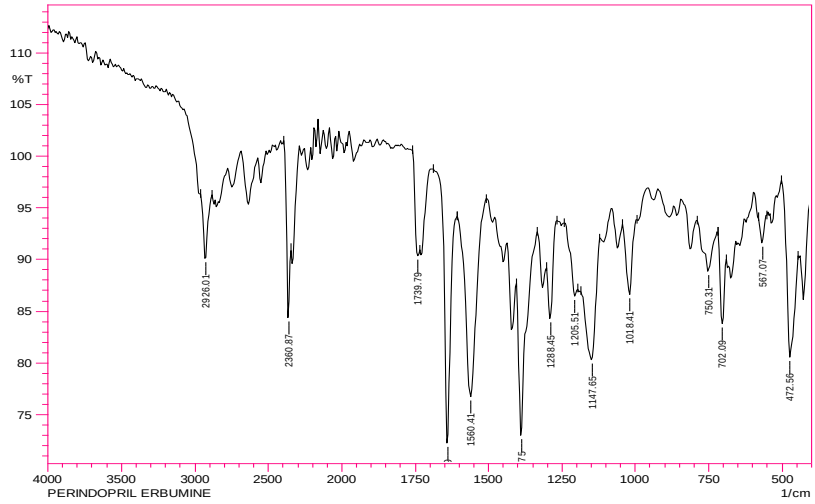

Fig. 1: FTIR Spectra of Perindopril erbumine.

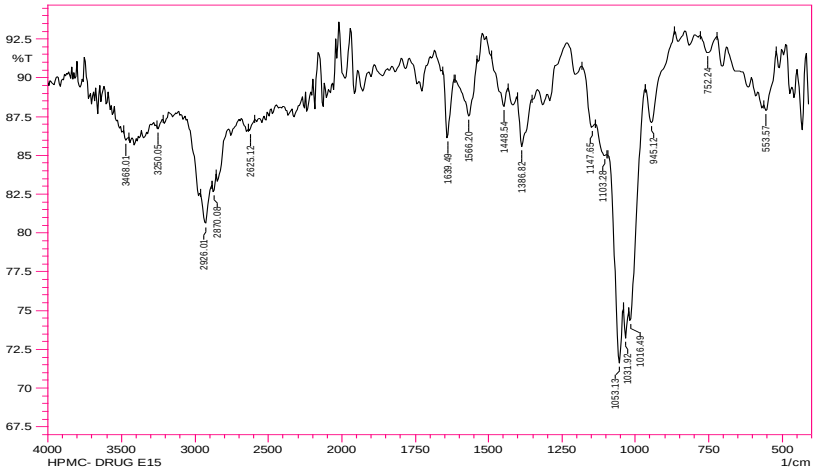

Fig. 2: FTIR Spectra of Perindopril erbumine + HPMC E15.

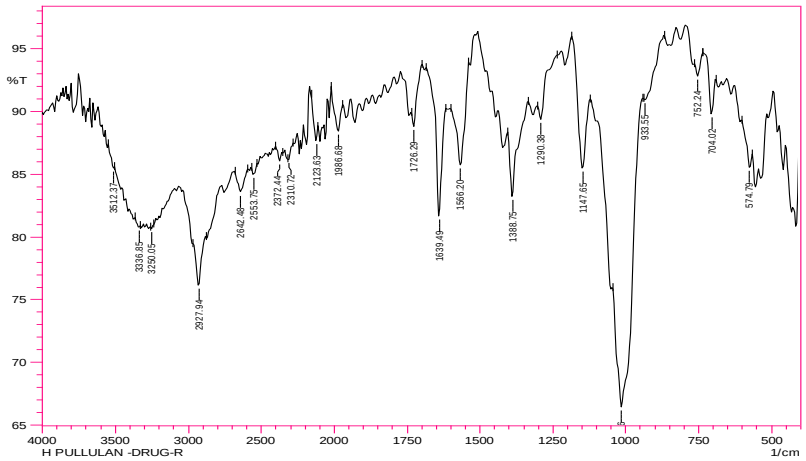

Fig. 3: FTIR Spectra of Perindopril erbumine + pullulan.

Table 4: Interpretation of FTIR spectra.

	C=0 Stretch cm^{-1} (1500 to 1600)	C-H Stretch cm^{-1} (3300 to2800)	OH Stretch cm^{-1} (1100 to 1300)	Aromatic and enes (700 to 800)cm^{-1}
DRUG	1566.29	2926.95	1147.26	750.26
DRUG+ pullulan	1566.30	2927.03	1147.26	752.11
DRUG+HPMC E15	1566.20	2926.95	1088.27	756.11

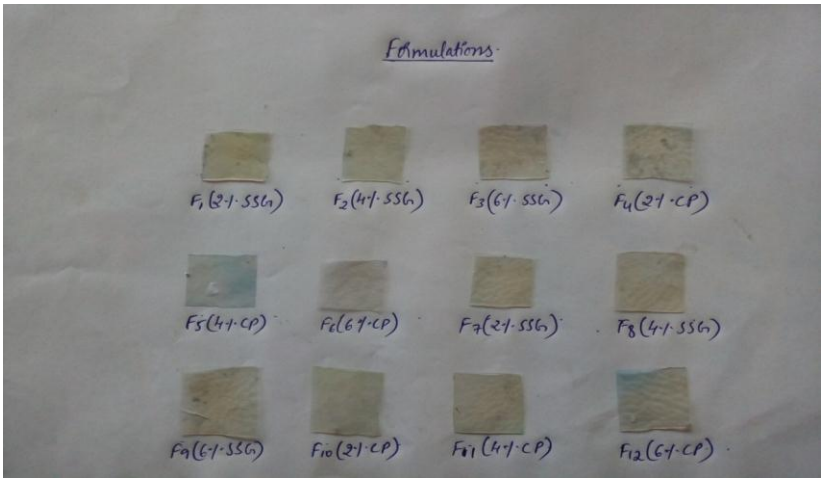

Fig. 4: Formulations of Perindopril erbumine films.

Results of various evaluation parameters

Table 5: Evaluation of fast dissolving films containing Perindopril erbumine.

Formulation code	Film Thickness (mm±SD*)	Drug Content (%±SD*)	Average Weight (mg±SD*)
F1	0.20±0.012	93.2±0.96	50.52±0.30
F2	0.21±0.015	92.1±1.34	62.26±0.40
F3	0.23±0.017	91.8±0.14	74.54±0.90
F4	0.21±0.015	90.1±0.81	52.48±0.14
F5	0.23±0.02	88.2±0.41	66.48±0.17
F6	0.25±0.08	89.2±2.29	79.57±0.17

F7	0.22±0.13	92.6±0.22	53.59±0.26
F8	0.26±0.08	91.2±1.62	70.25±0.13
F9	0.25±0.09	90.13±0.96	80.27±0.126
F10	0.24±0.12	90.02±0.11	56.56±0.16
F11	0.28±0.08	89.06±0.92	66.55±0.17
F12	0.29±0.04	88.5±1.37	82.32±0.14

**All values represented are mean of 3 readings (n = 3)*

Table 6: Characterization of fast dissolving films containing Perindopril erbumine films.

Formulation code	Surface pH (*)	Percentage Elongation (%±SD*)	Percentage moisture content (%±SD*)	Folding endurance (*)
F1	6.60±0.01	12.44±2.07	1.59±0.54	205±2.05
F2	6.66±0.03	16.82±1.35	1.34±0.58	201±1.69
F3	6.71±0.08	19.81±2.29	1.85±0.47	207±3.09
F4	6.73±0.05	21.74±2.07	1.24±0.43	209±2.82
F5	6.80±0.05	23.59±2.24	2.30±0.37	204±1.24
F6	6.71±0.03	22.80±1.37	1.47±0.49	208±0.94
F7	6.85±0.04	23.57±1.96	1.65±0.81	205±2.86
F8	6.82±0.06	27.90±2.45	1.94±0.41	211±0.47
F9	6.63±0.05	27.82±2.18	1.47±0.35	212±1.24
F10	6.65±0.08	26.36±1.18	1.39±0.38	206±1.57
F11	6.68±0.03	29.02±2.11	2.17±0.46	208±2.28
F12	6.66±0.09	30.02±2.08	2.47±0.52	212±3.17

**All values represented are mean of 3 readings (n = 3)*

Table 7: Characterization of fast dissolving films containing Perindopril erbumine

Formulation code	Tensile Strength (N/cm2±SD*)	*In-vitro* disintegration time (seconds±SD*)
F1	4.0±0.02	29.10±1.62
F2	4.4±0.01	30.24±2.06
F3	5.3±0.02	30.23±2.02
F4	4.7±0.03	35.55±1.49
F5	4.6±0.09	37.12±1.57
F6	5.1±0.04	39.94±1.28
F7	5.4±0.02	34.66±1.18
F8	5.1±0.21	34.11±2.01
F9	4.7±0.04	35.36±1.05
F10	4.4±0.03	40.60±1.82
F11	5.0±0.05	42.11±2.01
F12	5.5±0.07	42.52±2.05

**All values represented are mean of 3 readings (n = 3)*

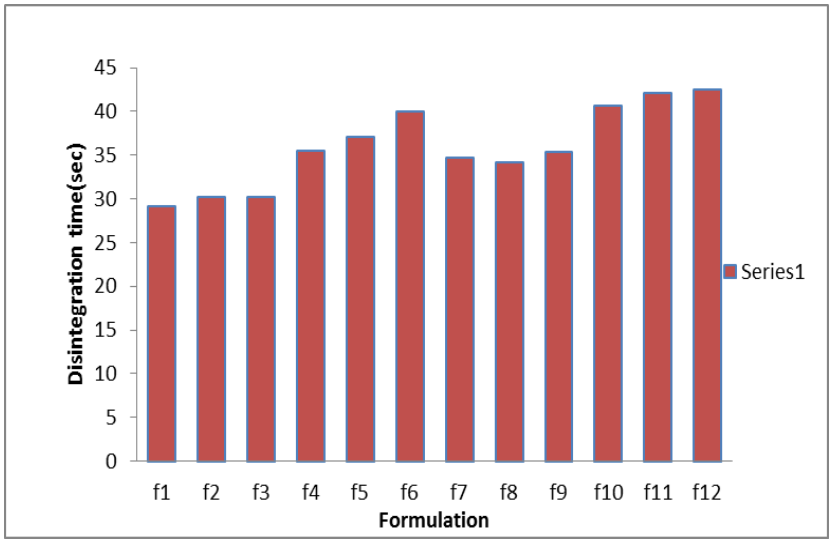

Fig. 5: *In-vitro* disintegration study of F1 – F12.

***In-vitro* drug release study of formulations**

Table 8: *In-vitro* drug release study of F1 to F6.

Time (sec)	Percentage Cumulative Drug Released					
	F1	F2	F3	F4	F5	F6
0	--	--	--	--	--	--
30	34.61	22.13	19.35	28.17	14.21	10.23
60	47.63	37.17	30.08	41.18	25.03	21.49
90	58.74	48.85	48.91	57.68	45.22	36.27
120	70.32	62.83	66.03	64.32	58.94	56.58
150	80.66	80.91	81.32	80.61	73.13	70.35
180	95.93	93.23	92.17	91.61	89.17	87.62

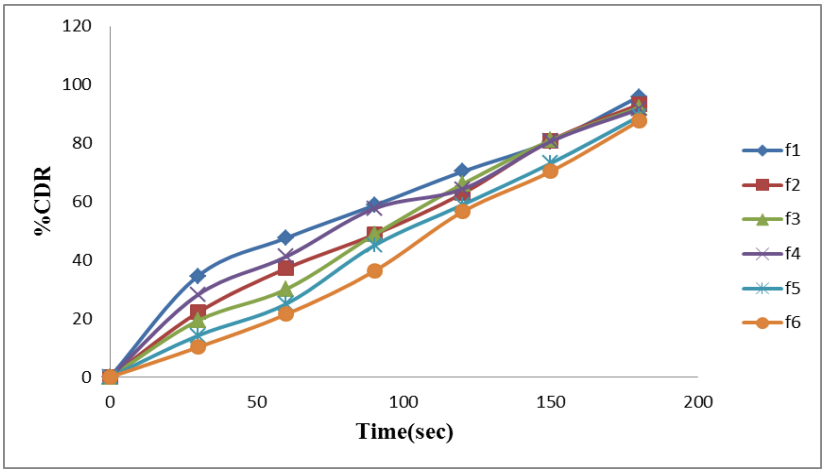

Fig. 6: *In-vitro* dissolution study of F1 to F6.

Table. 9: *In-vitro* drug release study of F7 to F12.

Time (Sec)	Percentage Cumulative Drug Released					
	F7	F8	F9	F10	F11	F12
0	--	--	--	--	--	--
30	32.1	22.06	14.98	20.91	21.21	16.23
60	43.21	38.57	31.39	38.01	39.41	28.42
90	58.43	49.77	45.32	50.24	50.48	44.11
120	70.29	60.54	58.88	62.97	60.79	60.32
150	83.43	77.38	73.91	75.55	72.65	78.86
180	92.43	90.69	90.06	90.71	88.57	85.94

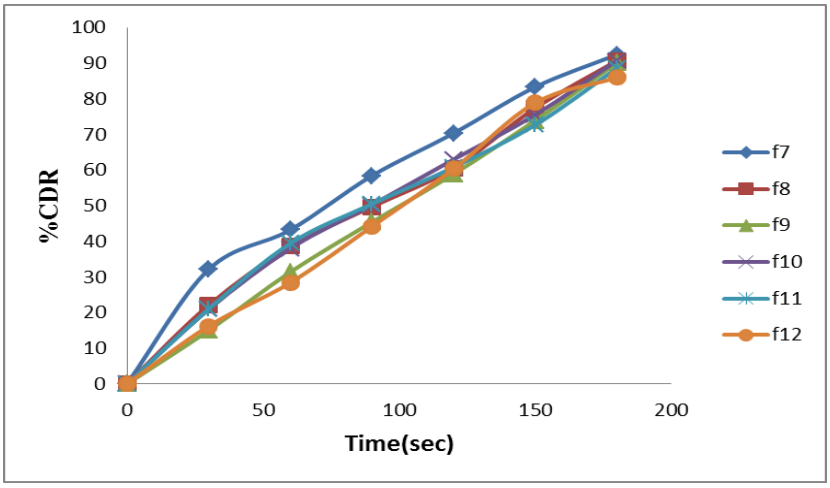

Fig. 7: *In-vitro* dissolution study of F7 to F12.

***In-vitro* Permeation studies**

Table. 10: Permeation studies data of formulations F1 to F6.

Time (sec)	Percentage Cumulative Drug Released					
	F1	F2	F3	F4	F5	F6
30	16.54	15.32	13.43	15.65	14.10	12.43
60	23.43	21.13	20.11	20.77	21.01	19.45
90	30.32	29.57	29.43	25.56	24.74	22.33
120	42.45	36.87	32.45	30.98	33.34	29.54
150	49.33	42.22	42.06	40.45	40.43	39.04
180	57.22	54.65	52.67	56.11	53.45	49.23
210	65.78	62.65	61.98	63.54	64.65	57.44
240	73.66	72.87	71.12	72.87	70.66	65.34
270	85.66	83.96	82.22	81.89	82.10	80.54
300	93.97	92.26	90.09	92.10	90.32	89.98

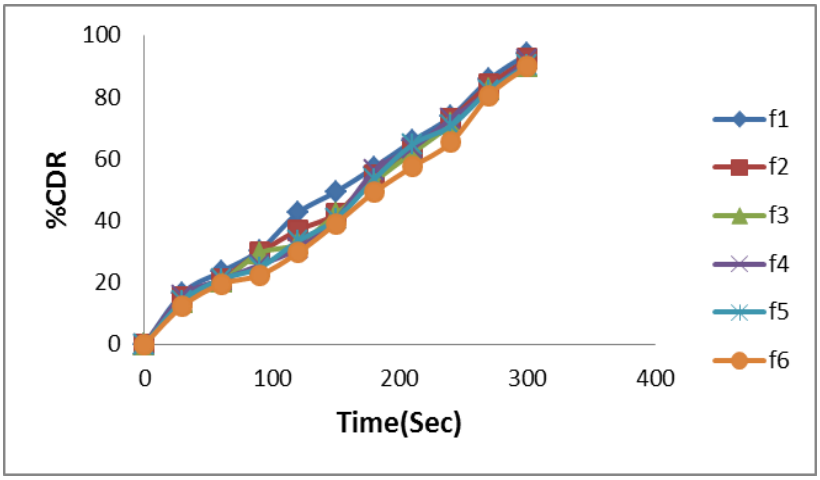

Fig. 8: *In-vitro* permeation pattern of F1 to F6.

Table. No. 11: Permeation studies data of F7 to F12.

Time (Sec)	Percentage Cumulative Drug Released					
	F7	F8	F9	F10	F11	F12
30	14.33	13.33	11.57	12.76	10.66	8.87
60	21.54	19.43	19.54	18.65	14.66	13.76
90	29.66	26.65	26.55	25.54	21.54	19.66
120	38.45	35.54	36.67	30.11	29.33	26.66
150	48.67	40.32	48.76	38.43	37.32	38.66
180	58.76	50.22	57.32	54.44	46.33	48.88
210	66.87	65.33	63.65	62.43	53.43	54.44
250	76.66	73.55	71.45	70.12	66.77	66.76
270	85.67	81.23	80.65	79.89	79.65	75.44
300	91.32	89.88	89.43	87.54	86.23	84.11

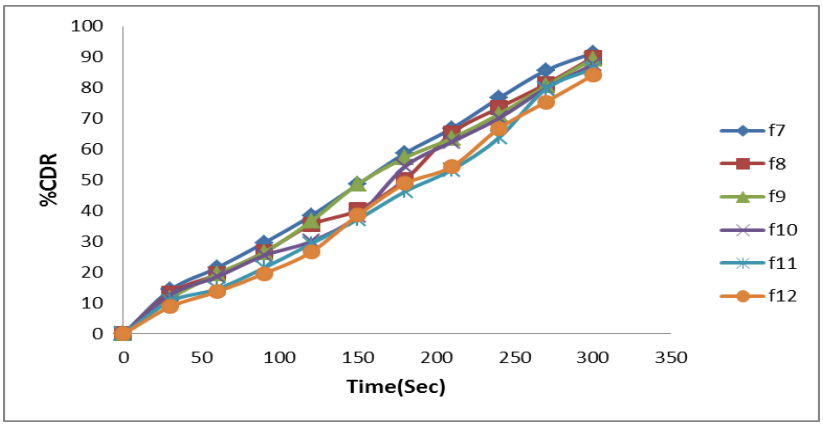

Fig. 9: *In-vitro* permeation pattern of F7 to F12.

Stability Studies of best formulations

Table. 12: Stability study data of F1.

Time (months)	Appearance	Drug content (%)
	*	*
Zero	transparent	93.20
First	transparent	92.88
Second	transparent	92.12
third	Transparent	92.12

** 40±2°C and 75±5% RH*

Table 13: Drug release under stability study of F1.

TIME(Sec)	%CDR40±1°C and 75 % RH			
	0 Day	30 Day	60 Day	90 day
30	34.66	33.21	33.18	33.15
60	47.03	46.13	46.10	46.05
90	58.74	57.11	56.79	55.69
120	70.33	69.33	68.65	68.12
150	80.61	78.88	78.11	79.50
180	95.93	94.76	94.01	94.00

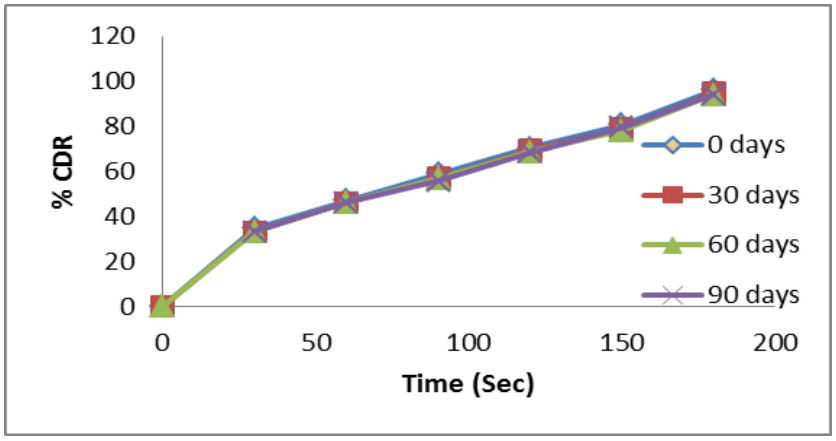

Fig. 10: *In-vitro* dissolution study of F1 under stability study.

Stability study on F7 (PULLULAN+SSG)

Table. 16: Stability study data of F7 (PULLULAN +SSG).

Time (months)	Appearance	Drug content (%)
	*	*
Zero	transparent	92.60
First	transparent	92.11
Second	transparent	91.77
Third	transperant	91.78

** 40±2°C and 75±5% RH*

Table. 17: Drug release under stability study of F7 (pullulan +ssg).

TIME (Sec)	%CDR 40±1ºC and 75 % RH			
	0 Day	30 Day	60 Day	90 days
30	32.11	31.88	30.68	30.33
60	43.21	42.67	41.33	41.00
90	58.43	57.53	57.10	57.10
120	70.29	69.98	68.89	68.85
150	83.43	82.21	81.77	81.70
180	92.43	91.12	90.45	90.40

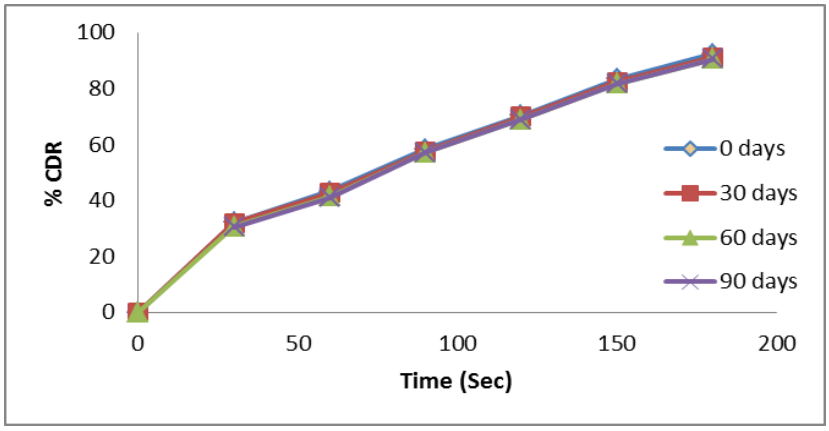

Fig. 12: *In-vitro* dissolution study of F7 (pullulan+SSG) under stability study.

DISCUSSION

Fast dissolving film of Perindopril erbumine were prepared by solvent casting method using pullulun and HPMC E15 as a polymers. It was then evaluated for physicochemical properties like organoleptic properties, melting point, solubility, drug polymer compatibility studies using FTIR. The melting point of Perindopril erbumine was found to be 125° c. Thickness of fast dissolving film varies from 0.20±0.012mm to 0.29±0.04mm. Formulation F12 showed highest thickness of 0.29±0.04. Drug content uniformity was found to be in the range 88.2±0.41 to 93.2±0.96 %. All the films passed weight variation test which were found to be in the range of 50.52±0.30 mg to 82.32±0.14 mg. The surface pH of the films F1 to F12 was ranging from 6.60±0.01 to 6.85±0.03.The percentage moisture content of the films F1 to F12 ranges from 1.24±0.43% to 2.47±0.35%. Folding endurance of the films ranges from 201±1.69 to 212±3.17. Formulation F12 had higher folding endurance of 212±3.17. Tensile strength of the films was found to be in the range of 4.0±0.02 N/cm^2 to 5.5±0.07 N/cm^2, The disintegration time of the films was found to be in the range of 33.94±1.28 seconds to 55.66±1.18, Formulation F6 showed minimum *In-vitro* disintegration time of 33.94±1.28 seconds. Rapid drug dissolution was observed in case of F1 containing 30%w/v of pullulan which released 95.93% followed by F4 containing 30%w/v of HPMC E15 which released

91.61%, at the end of 3 min. By the drug permeation study it was found that the formulation F1 containing 30%w/v of pullulan with 6%w/v of Croscarmellose sodium showed better drug permeation of 93.97% in 5 min. Short-term accelerated stability study was performed with the best formulation F1 and F12 by storing the samples at 40±2ºC with 75±5% RH for 90 days. The films were observed for physical changes, drug content and *in-vitro* drug release studies at monthly intervals. Fast-dissolving films of Perindopril were found to be physically and chemically stable as they showed no significant change in terms of physical characteristics, drug content and drug release at the above condition.

CONCLUSION

In the present study satisfactory attempt has been made to formulate and evaluate fast dissolving sublingual film of Perindopril erbumine. From the reproducible results of executed experiments it can be concluded that Pre formulation studies on Perindopril erbumine comply with the reported literature limits. The FTIR spectral data indicates that there was no interaction between drug and the polymers. Twelve formulations were prepared by solvent casting method and evaluated for physico-chemical parameters such as weight uniformity, thickness uniformity, folding endurance, drug content, surface pH, tensile strength, percentage elongation, percentage moisture content, folding endurance, *In-vitro* disintegration time, *In-vitro* dissolution studies and *In-vitro* permeation studies. All the films were flexible with smooth surface texture and transparent appearance. Formulation F1 was found to be the best formulation with a drug release of 95.93% at the end of 3min. The formulations were uniform in their weight, thickness and almost uniform on their drug content of about 93.2±0.96. *In-vitro* disintegration studies shows that time taken of the film for complete disintegration of 33.94±1.28 sec, Three month stability study of the best formulation was carried and it was found no significant changes in the appearance, drug content and dissolution parameter values after 90 days of storage at 40±2ºC with 75±5% RH. From the present study, it can be concluded that fast dissolving films of Perindopril erbumine prepared by solvent casting technique using Pullulan as shows the maximum release of the drug 95.93% within the 3min.

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