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DEVELOPMENT AND CHARACTERIZATION OF ORAL DISSOLVING FILM FOR PROMETHAZINE HCl

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Keywords:

Fast dissolving oral film, Promethazine, Solvent casting, Experimental design

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ABSTRACT: Promethazine hydrochloride, one of the most effective agents for treating motion sickness, mainly acts as a strong antagonist of the H_1 receptor (antihistamine) and it blocks the action of acetylcholine on the receptors (anticholinergic effect). The purpose of present work was a development of fast dissolving oral film of promethazine HCl to overcome the limitation of current routes of administration, to provide faster dissolution rate and increase patient compliance, especially for outpatient setting. The amount of drug was calculated according to the area of petri plate. The amount of drug was then used for the preparation of film by solvent casting method utilizing HPMC E3, HPMC E5, HPMC E15, and HPMC E50 as a film-forming polymers. The effect of plasticizers (PEG 200, PEG 400, PEG 600, glycerine, propylene glycol, triethyl citrate) and their concentration were tested for physicomechanical properties of casted films. Aspartame was used as a sweetener. The IR spectral studies showed no interaction between drug and polymer or with other additives. Using experimental design, the prepared formulations were evaluated for *in-vitro* dissolution characteristics, *in-vitro* disintegration time and their physicomechanical properties. The optimized formulation (batch F1) containing HPMC E15 and PEG 400 showed greater drug dissolution (more than 95% within 10 min), satisfactory *in vitro* disintegration time (18 sec) and physicomechanical properties that were suitable for mouth dissolving film. The stability study of optimized formulation for 1 month showed no appreciable change in drug content, *in-vitro* drug release and *in-vitro* disintegration time.

INTRODUCTION: Like the emerging trend worldwide, India is also undergoing rapid urbanization, leading to a significant increase in traveling. This has lead to health-related issues like motion sickness, traveler's diarrhea, migraine, *etc*. Motion sickness also known as travel sickness is a condition in which there exists a disagreement between visually perceived movement and the vestibular system's sense of movement.

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Nausea, vomiting, dizziness, fatigue, and headache are the most common symptoms of motion sickness [1, 2]. Promethazine hydrochloride is a first-generation anti-histamine of the phenothiazines family. It acts mainly as a strong antagonist of the H1 receptor (antihistamine) and a moderate mACh receptor antagonist; hence it blocks the action of acetylcholine on the receptors (anticholinergic effect), and this explains its benefit in reducing nausea experienced during motion sickness [3].

Promethazine hydrochloride is available in conventional dosage forms such as tablets and syrups, also administered rectally as suppositories, intramuscularly, and intravenously. The injection dosage forms are limited primarily to inpatient use, and there are also chances of necrosis at the

injection site [4-6]. These dosage forms have their own limitations for the outpatient setting. Oral tablets have a delayed onset of action which is undesirable for acute treatment of emesis in motion sickness. For the treatment of nausea and vomiting, tablets and syrups are inconsistent with the cornerstone of treatment, nothing by mouth in the initial treatment period [7]. In fact, ingestion of these dosage forms and the accompanying required liquids may worsen the condition, resulting in vomiting and expulsion of a portion or the entire dose administered. The amount remaining in the body is now uncertain, but further action may result in overdosing. In addition, syrups are currently available only in pediatric concentrations. Although suppositories circumvent some of these specific problems, this is a very undesirable dosage form for the majority of the patient population [8].

Other experimental promethazine dosage forms have been considered. An experimental chewing gum resulted in the loss of drug in gum base if not properly chewed [9]. Although topical promethazine is of interest in the area of compounding pharmacy, the potential for local irritation and systemic toxicity is a concern with transdermal delivery of any compound. This is especially true in children because of variability in skin thickness and dermal blood flow. In fact, systemic poisoning resulting from topical promethazine has been reported [10].

Thus a novel approach is required to design and develop an ideal dosage form for promethazine HCl. Among the delivery routes, the oral route is the most acceptable from patient compliance aspects. Now a day, many pharmaceutical industries are reformulating the existing drugs into new dosage forms by effective life cycle management. One such relatively new dosage form is the fast-dissolving film. Basically the fast dissolving film is formulated using hydrophilic polymers and other excipients that rapidly dissolve on the tongue or buccal cavity. Fast dissolving films offer fast, accurate dosing in a safe, efficacious approach that is both convenient and portable, without the need for water or measuring devices [11, 12]. These dosage devices offer many advantages like accurate dosing, no risk of choking, rapid release profile, enhanced stability, taste masking, and improved patient compliance and convenience.

In the present research work, an attempt was made to formulate and evaluate fast dissolving oral films of promethazine hydrochloride using different polymers and design of experiment (DOE) approach for optimization.

MATERIALS AND METHODS:

Materials: Promethazine HCl was purchased from Balaji Drug Suppliers, Ahmedabad, India. Different grades of Hydroxypropyl methylcellulose (HPMC) like HPMC E3, HPMC E5, HPMC E15, HPMC E50 and aspartame were supplied by Yarrow Chem. Products, Mumbai, India. Different grades of polyethylene glycol (PEG 200, PEG 400, PEG 600), propylene glycol, triethaycitrate, glycerin were procured from Finar Chemicals Ltd, Ahmedabad, India. All other materials used were of pharmaceutical or analytical grade.

Drug-Excipients Compatibility Study: During the studies, the possible interaction of drug with various ingredients proposed for use in final dosage form was checked. The drug-excipient compatibility study was carried out by using Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared (FTIR) spectroscopy. FTIR study was conducted using KBr powder mixing method on FTIR spectrophotometer (FTIR-1700, Shimadzu, Kyoto, Japan) and the spectrums were recorded in the wavelength region of 4000 - 400 cm^{-1}. DSC study of pure drug, HPMC E15 and optimized batch was performed using DSC instrument (DSC- 60, Shimadzu, Kyoto, Japan). In this process, samples (3-5mg) were weighed into the aluminum cell and scanned at 30 to 300 º C, at 100 ml/min nitrogen flow rate against blank DSC aluminum cell as a reference.

Analytical Method Development: Calibration curve of promethazine HCl was taken in phosphate buffer pH 6.8. Accurately weighed 10 mg of promethazine HCl was transferred to 100 ml volumetric flask and dissolved in pH 6.8 phosphate buffer. The volume was adjusted up to 100 ml with respective solution to get 100 µg/ml stock solution of drug. The stock solution (100 µg/ml) was further diluted to get a concentration of promethazine HCl in the range of 1-10 µg/ml. These solutions were scanned for the maximum absorbance using Shimadzu UV/Vis double beam spectrophotometer.

The absorbance of these drug solutions was estimated at λmax.

Preparation of Oral Dissolving Film (ODF): The oral dissolving film was prepared by solvent casting method. The weighed quantity of polymer was dissolved in the minimum quantity of distilled water and stirred to ensure the complete mixing of polymer. Then the drug was dissolved in that polymer solution with stirring. After that a sweetening agent was added to the solution and stirred properly. Finally, calculated quantity of plasticizer was added to the above mixture and kept for sonication (if required) till the solution became clear and free of bubbles. After sonication, the solution was cast on the glass plate. The glass plate was kept in a controlled temperature oven at 50 ºC for 12 h for drying of the film. After the drying of films, it was peeled and cut into 2 cm × 2 cm (4 cm^2) size and stored in aluminum foil. These films were further subjected to various evaluation tests.

Preliminary Screening: For the selection of polymer type and its quantity, preliminary batches were formulated using PEG 200 as a plasticizer at 20% w/w of polymer weight and aspartame as a sweetener at 4.5% w/w of total weight as per the composition is shown in **Table 1**. The evaluation results for batches are shown in **Table 2**.

TABLE 1: COMPOSITION OF BATCHES FOR POLYMER SCREENING

	Quantity for 38.46 cm^2 in mg				
Ingredients	**OP1**	**OP2**	**OP3**	**OP4**	**OP5**
Promethazine HCl	240	240	240	240	240
HPMC E3		240			
HPMC E5			240		
HPMC E15	480			240	
HPMC E50					240
PEG 200	96	48	48	48	48
Aspartame	37	24	24	24	24
Distilled Water (ml)	10	10	10	10	10

TABLE 2: EVALUATION RESULTS FOR POLYMER SCREENING

Parameters	**OP1**	**OP2**	**OP3**	**OP4**	**OP5**
Tensile Strength (Kg/cm^2)	0.400	Not formed	0.200	0.150	0.300
Disintegration Time (sec.)	96	Not formed	55	20	67
Surface Texture	Rough	Not formed	Smooth	Smooth	Smooth
Transparency	Bad	Not formed	Good	Good	Good

Once the polymer and its quantity were finalized, the type of plasticizer was screened. Six plasticizers were screened for the selection at the same concentration (20% w/w). The batches are shown in **Table 3**. The evaluation results for batches are shown in **Table 4**.

TABLE 3: COMPOSITION OF BATCHES FOR PLASTICIZER SCREENING

	Quantity for 38.46 cm^2 in mg					
Ingredients	**P1**	**P2**	**P3**	**P4**	**P5**	**P6**
Promethazine HCl	240	240	240	240	240	240
HPMC E15	240	240	240	240	240	240
PEG 200	48					
PEG 400		48				
PEG 600			48			
Glycerin				48		
Propylene glycol					48	
Triethylcitrate						48
Aspartame	24	24	24	24	24	24
Distilled Water (ml)	10	10	10	10	10	10

TABLE 4: EVALUATION RESULTS FOR PLASTICIZER SCREENING

Parameters	**P1**	**P2**	**P3**	**P4**	**P5**	**P6**
Tensile Strength (Kg/cm^2)	0.207	0.130	0.195	0.240	Not formed	0.135
Folding Endurance	>300	>300	>300	191	Not formed	77
Surface Texture	Rough	Smooth	Smooth	Smooth	Not formed	Rough
Transparency	Medium	Good	Good	Good	Not formed	Bad

Optimization of Oral Dissolving Film Formulation Using 3^2 Full Factorial Design: From the results of preliminary screening studies, the optimization was carried out using the design of expert (DOE) approach. To study the effect of 2 independent variables, *i.e.* the amount of HPMC E15 (X_1) and amount of PEG 400 on responses 3^2 full factorial design was used. In this design HPMC E15 and PEG 400 were used as independent variables while disintegration time, tensile strength and % drug release at 4 min. were selected as response variables. Trials were taken at all possible combinations. The detailed layout of factorial batches is shown in **Table 5**. The equations relating independent variables and responses were obtained by subjecting the results to statistical evaluation. Design Expert 9.0.0.7 was used to perform multiple linear regressions to determine the control factors that significantly affect the responses.

Polynomial equation for 3^2 full factorial design: $Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1^2 + b_{22}X_2^2 + b_{12}X_1X_2$ was used. In this equation, Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and bi is the estimated coefficient for the factor Xi. The significant factors in the equations were selected using a stepwise forward and backward elimination for the calculation of regression analysis. The terms of the full model having non-significant p-value ($p > 0.05$) have negligible contribution hence they were neglected.

TABLE 5: DETAILED LAYOUT OF DIFFERENT FACTORIAL BATCHES

Ingredients	Formulation Code								
	F_1	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**
Promethazine HCl	240	240	240	240	240	240	240	240	240
HPMC E15	180	180	180	240	240	240	300	300	300
PEG 400 (% of Polymer)	10%	15%	20%	10%	15%	20%	10%	15%	20%
Aspartame	24	24	24	24	24	24	24	24	24
Mango flavor	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Distilled water q.s (ml)	10	10	10	10	10	10	10	10	10

Independent Variable	Coded Value			Actual Value		
HPMC E15 (mg)	-1	0	+1	180	240	300
PEG 400 (%)	-1	0	+1	10	15	20

Evaluation of Oral Dissolving Films: The prepared films were evaluated for thickness, folding endurance, surface pH, tensile strength, assay, *in-vitro* disintegration, and dissolution studies. A thickness of the film was measured by using micrometer screw gauge. The film was measured at three positions, *i.e.,* central and the two corners and the mean thickness was calculated [13]. Folding endurance of the film was measured by folding the film at the same point until it breaks. The number of folds before the film breaks is the folding endurance of the film [14].

The surface pH of the oral dissolving film was determined in order to investigate the possibility of any side effect *in-vivo*. As an acidic or alkaline pH may cause irritation of the oral mucosa, it was decided to keep the surface pH as close to neutral as possible. A combined pH electrode was used for this purpose. The 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 [15].

The tensile strength of the film was evaluated by using the push-pull instrument. It consists of two load cell grip, the lower one was fixed, and upper one was movable. Film strips with dimensions of 2×2 cm^2 were fixed between these cell grips and force was gradually applied till the film brake.[16] The breaking force was taken directly from the dial reading in gm. It is calculated by the equation: Tensile strength = Break force/Area of film in cm^2. The assay was determined by dissolving one film of dimension 2 cm × 2 cm containing 25 mg of promethazine HCl by homogenization in 100 ml of phosphate buffer pH 6.8 for 30 min with continuous shaking. From this, 10 ml was diluted to 50 ml with phosphate buffer pH 6.8. The absorbance was measured at 250 nm using a UV spectrometer.[17]

The experiments were carried out in triplicate for the films of all formulations and average values were recorded. The *in-vitro* disintegration time is the time at which the film starts to break. The disintegration time was measured in a beaker

containing 20 ml phosphate buffer pH 6.8. The timing film starts to break was measured as a disintegration time of film. The time at which the film completely dissolves is considered as dissolution time or solution time [18, 19].

For *in-vitro* dissolution studies, each film was placed with the help of forceps in a 50 ml glass beaker containing 20 ml of phosphate buffer pH 6.8. The beaker was put on a constant temperature magnetic stirrer and agitation was provided by the magnetic stirrer at 100 rpm. The temperature of the dissolution media was maintained at 37 ± 0.5 °C. During the study, 4 ml of aliquots were withdrawn at 2, 4, 6, 8 and 10 min and were replaced by the fresh buffer. The amount of promethazine HCl released in the media was determined by a UV-visible spectrophotometer at 250 nm.

Stability study was conducted at the accelerated condition of 75 ± 5% relative humidity and 40 ± 2 ºC temperature in the stability chamber for 1 month. After 1 month, films were evaluated for the drug content, disintegration time and physical appearance as well as change *in-vitro* drug release pattern [20].

RESULTS AND DISCUSSION:

Drug- Excipients Compatibility Study: FTIR spectrums of drug and drug in combination with excipients are shown in **Fig. 1** and **Fig. 2**, respectively. It was observed that there were no changes in main peaks in the FTIR spectra of a mixture of drug and excipients. The FTIR study demonstrates that no physical or chemical interactions of promethazine with the polymeric system.

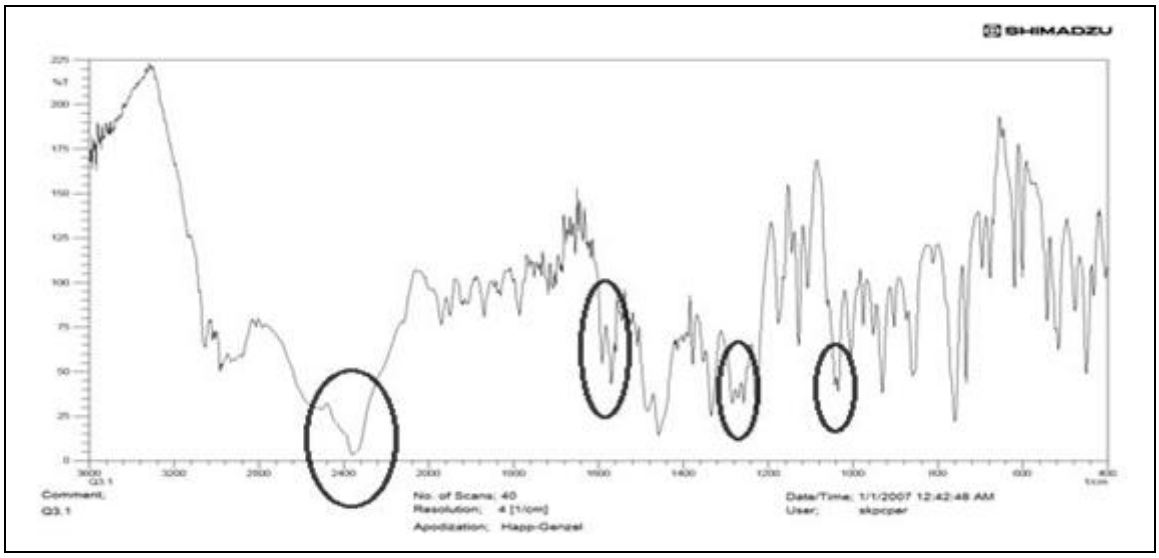

FIG. 1: FT-IR SPECTRA OF PROMETHAZINE HCl

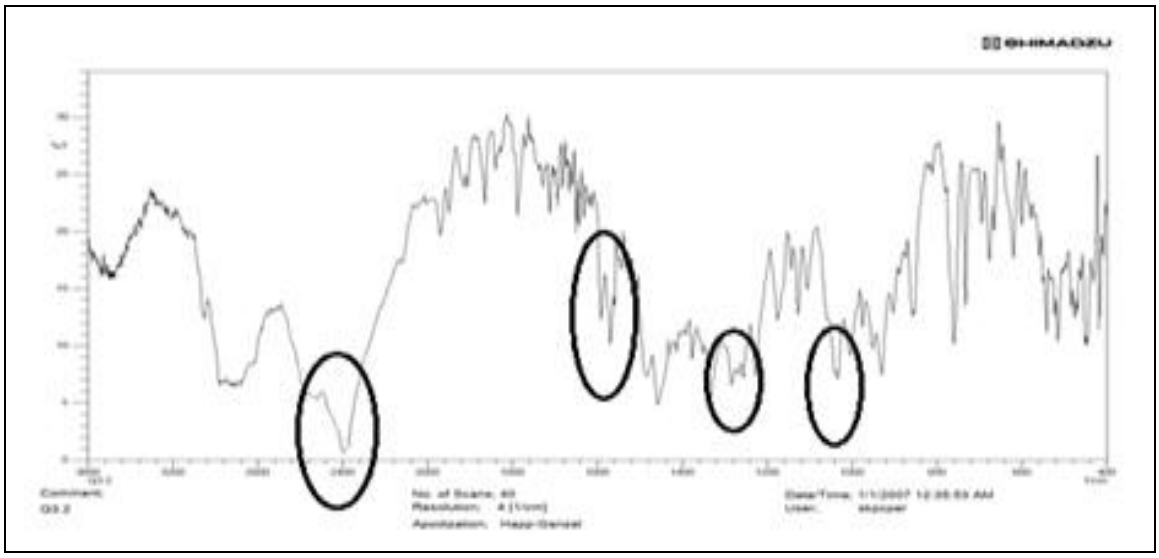

FIG. 2: FT-IR SPECTRA OF DRUG AND EXCIPIENTS

DSC thermogram of promethazine HCl and drug excipients mixture are shown in **Fig. 3** and **Fig. 4**, respectively. It is evident from DSC thermograms that sharp endothermic peak obtained in pure drug was retained without any measure shift in the composite mixture, indicating the absence of any physical incompatibility of drug with excipients used in film formulation.

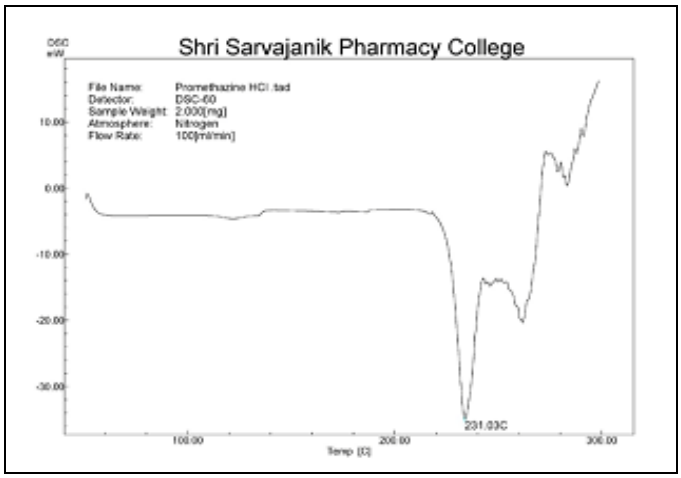

FIG. 3: DSC OF PROMETHAZINE HCl

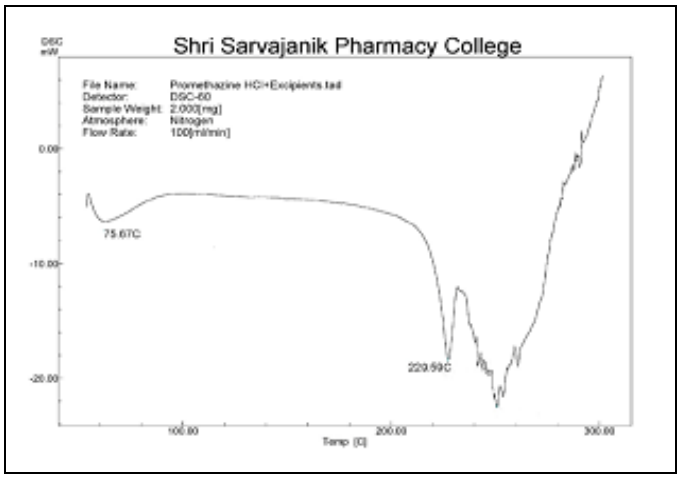

FIG. 4: DSC OF DRUG AND EXCIPIENTS

Analytical Method Development: The drug was analyzed using UV visible spectrophotometer. The UV spectrum of drug solution in phosphate buffer pH 6.8 is shown in **Fig. 5.** The drug exhibited λmax at 250 nm. The calibration curve was generated using different concentration (1-10 µg/ml) of drug solutions in the Beer-Lambert law. The data for the calibration curve are shown in **Table 6** and the calibration curve is shown in **Fig. 6.**

TABLE 6: CALIBRATION CURVE DATA OF DRUG IN PHOSPHATE BUFFER pH 6.8

Concentration (µg/ml)	Absorbance			Average Absorbance ± SD (n=3)
	I	II	III	
1	0.140	0.140	0.138	0.139 ± 0.001
2	0.203	0.203	0.205	0.204 ± 0.001
3	0.272	0.274	0.273	0.273 ± 0.001
4	0.345	0.349	0.347	0.347 ± 0.002
5	0.417	0.419	0.419	0.418 ± 0.001
6	0.483	0.481	0.485	0.483 ± 0.002
7	0.561	0.559	0.561	0.560 ± 0.001
8	0.634	0.640	0.637	0.637 ± 0.003
9	0.703	0.702	0.704	0.703 ± 0.001
10	0.791	0.795	0.793	0.793 ± 0.002

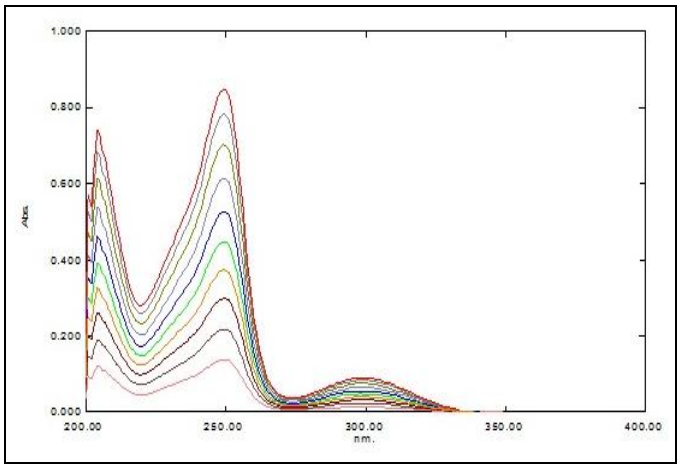

FIG. 5: UV SPECTRUM OF DIFFERENT SOLUTIONS

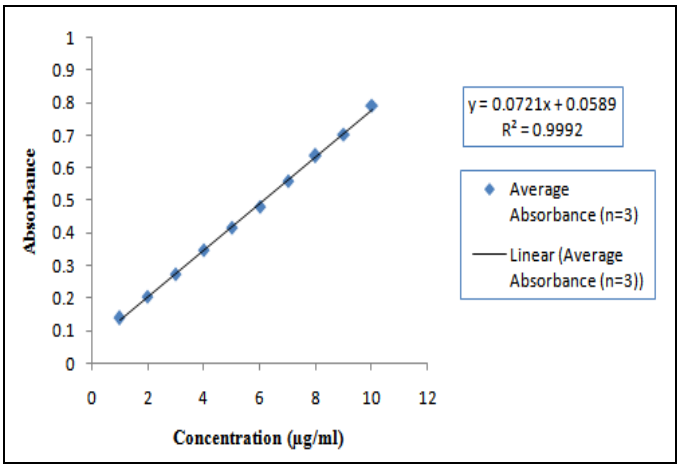

FIG. 6: CALIBRATION CURVE OF PROMETHAZINE HCl

Preliminary Trials: Various preliminary trials were carried out to choose a suitable polymer-plasticizer system, capable of producing films of desirable physicomechanical property and good disintegration time. Preliminary batches were prepared using different polymers at 1:2 and 1:1 drug to polymer ratio. The films (batches OP2-OP5) with 1:1 ratio of drug to HPMC E15 showed good physical characteristics and disintegration time. Plasticizers were screened and evaluated based on physical properties and disintegration time. PEG 400 showed good results. As a result, an attempt was made to prepare films using a combination of HPMC E15 and PEG 400 for the further studies, using DOE approach.

Evaluation of Factorial Batches F1 to F9: The factorial batches were evaluated for various parameters by the methods described in the methodology section. The evaluation results are shown in **Table 7**.

TABLE 7: EVALUATION PARAMETERS OF FACTORIAL BATCHES

Batch code	Thickness (mm)	Folding endurance	Surface pH	T.S (Kg/cm^2)	C.U (%)	*In-vitro* D.T (sec.)	Dissolution time (min.)
F1	0.05	180	6.85	0.185	99.10	17.86	1.36
	±0.02	±2.00	±0.02	±0.001	±0.36	±2.00	±0.57
F2	0.05	245	6.73	0.197	97.93	18.07	2.16
	±0.01	±3.00	±0.04	±0.001	±0.45	±1.00	±0.94
F3	0.04	300	6.64	0.205	98.87	19.38	2.33
	±0.01	±2.00	±0.01	±0.001	±0.90	±2.00	±0.57
F4	0.04	253	7.00	0.202	96.08	21.54	1.95
	±0.01	±4.00	±0.03	±0.002	±1.01	±3.51	±1.00
F5	0.05	191	6.69	0.220	94.03	26.64	2.43
	±0.01	±5.00	±0.03	±0.004	±1.00	±2.83	±1.40
F6	0.07	300	6.97	0.230	99.10	28.58	2.61
	±0.02	±3.00	±0.04	±0.001	±0.96	±2.09	±0.53
F7	0.06	159	6.82	0.230	100.03	26.88	3.31
	±0.01	±2.00	±0.08	±0.003	±0.12	±1.03	±0.59
F8	0.05	177	6.64	0.240	97.03	37.85	4.31
	±0.04	±3.00	±0.06	±0.002	±1.05	±3.06	±0.59
F9	0.07	300	6.95	0.255	99.47	38.29	4.00
	±0.03	±3.00	±0.05	±0.005	±0.93	±1.66	±1.00

T.S: tensile strength, C.U: content uniformity, D.T: disintegration time. Values are mean ± S.D for 3 determinations

Thickness was found in the range of 0.05 to 0.07 mm, the uneven surface of the plate could be the reason for the variable thickness of the films. Folding endurance gives an indication of the brittleness of the film. A result showed as the concentration of plasticizer increases, folding endurance of film increases. Surface pH of all the films prepared was found to be in the range 6.64 to 7, which was close to the neutral pH. Thus, films may have less potential to irritate the oral mucosa. Tensile strength was found in range of 0.185 ± 0.001 to 0.255 ± 0.005 kg/cm^2.

It was seen with the result that with the higher concentration of the polymer, the thickness of the film increases which leads to higher tensile strength. Content uniformity of formulations F1, F3, F6, F7, and F9 showed better drug content of above 98%. Hence, it can be concluded that the drug was distributed uniformly throughout the film. The reason for the slight variation in the drug content of the prepared film was attributed to the difference in the thickness of the film. No significant difference in the drug content among the films indicated good content uniformity.

In-vitro disintegration time and dissolution time for fast dissolving film were in the range from 17.86 ± 2.00 to 38.29 ± 1.66 and 1.36 ± 0.57 to 4.31 ± 0.59, respectively. Results showed that as the polymer concentration increases, disintegration time increases. *In-vitro* dissolution study in phosphate buffer pH 6.8 was conducted as per the method described earlier. The data for *in-vitro* release are shown in **Table 8** and are compared in **Fig. 7**.

TABLE 8: *IN-VITRO* DRUG RELEASE STUDY IN PHOSPHATE BUFFER pH 6.8

Time (min)	%CPR*								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	57.62 ±1.50	50.37 ±1.15	53.81 ±2.19	51.61 ±1.57	48.51 ±0.54	50.97 ±1.40	19.32 ±2.03	15.61 ±0.82	11.79 ±0.49
4	91.87 ±0.77	85.20 ±1.53	83.49 ±1.44	57.99 ±1.29	77.49 ±0.61	81.66 ±1.61	32.44 ±2.96	28.63 ±1.40	25.84 ±0.79
6	97.39 ±1.19	96.11 ±0.85	97.31 ±1.27	85.01 ±1.26	88.56 ±0.67	86.20 ±0.97	59.29 ±1.58	51.33 ±0.96	42.66 ±0.66
8	97.84 ±1.28	99.81 ±1.31	99.93 ±1.17	91.45 ±1.97	99.85 ±0.49	93.59 ±0.21	70.51 ±1.10	74.75 ±0.40	63.76 ±0.40
10	98.44 ±0.97	100.2 ±0.85	100.3 ±1.25	93.74 ±1.72	100.1 ±0.89	98.36 ±0.70	97.73 ±2.48	79.68 ±1.34	71.10 ±1.03

* Values are expressed as mean ± S.D for three determinations

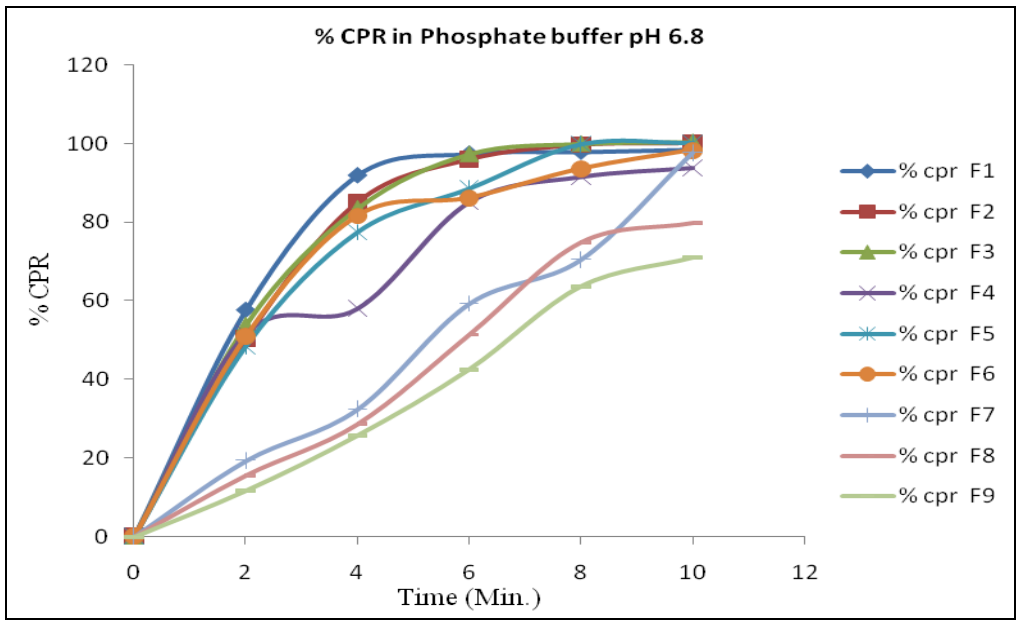

FIG. 7: DRUG RELEASE COMPARISON OF BATCHES F1 TO F9

Statistical Analysis of Factorial Design Batches Full and Reduced Model for Disintegration Time: The summary of regression analysis and ANOVA for disintegration time is shown in **Table 9**. The contour plot and 3D surface plot are shown in **Fig. 8** and **Fig. 9**, respectively. From the equation of full model, the reduced model is drawn by rejecting insignificant factors on the basis of p-value. From the model, it was found that concentration of HPMC E15 showed positive effect on the disintegration time. As its concentration increases, disintegration time of film increases. The concentration of PEG 400 also showed positive effect on the disintegration time. It was concluded that X_1 and X_2 both had significant effect on the disintegration time.

TABLE 9: SUMMARY OUTPUT OF REGRESSION ANALYSIS AND ANOVA FOR DISINTEGRATION TIME

	DF	SS	MS	F	P-value Prob > F
Regression	5	480.39	96.08	24.74	0.0121
Residual	3	11.65	3.88		
Total	8	492.04			Significant
Coefficient	**b_0**	**b_1**	**b_2**	**b_{11}**	**b_{22}**	**b_{12}**
Coefficient value	26.99	7.95	3.33	2.47	0.80	-2.10
P-value	0.0121	0.0022	0.0256	0.6054	0.2292	0.0870

Full Model: $Y_1 = 26.99 + 7.95\ X_1 + 3.33\ X_2 + 2.47\ X_1^2 + 0.80\ X_2^2 - 2.10\ X_1X_2$

Reduced Model: $Y_1 = 26.99 + 7.95\ X_1 + 3.33\ X_2$

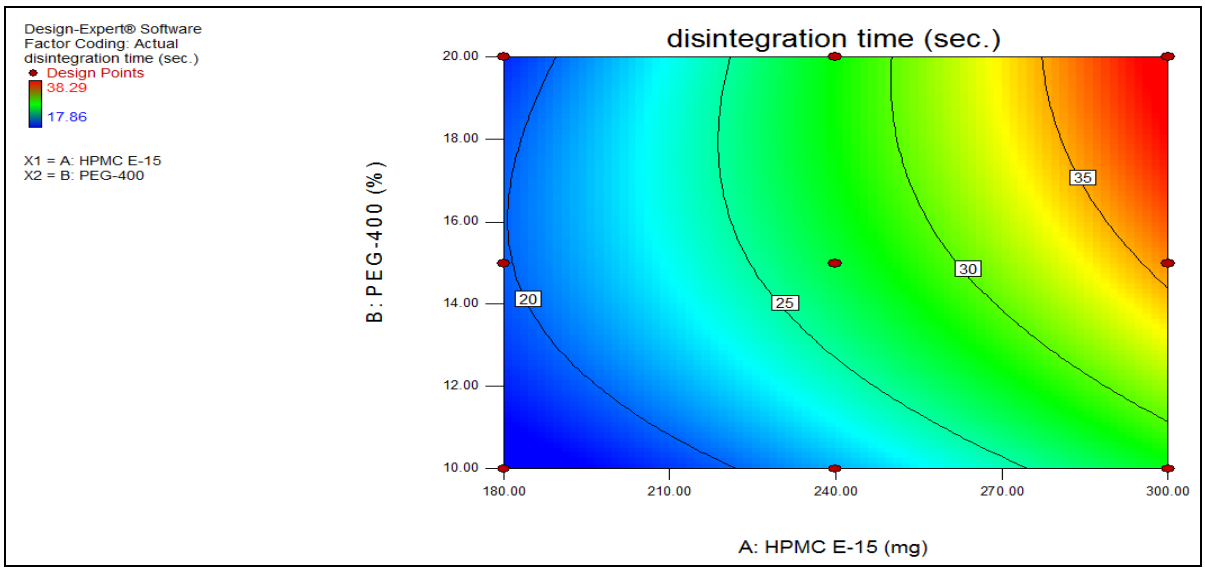

FIG. 8: CONTOUR PLOT OF DISINTEGRATION TIME

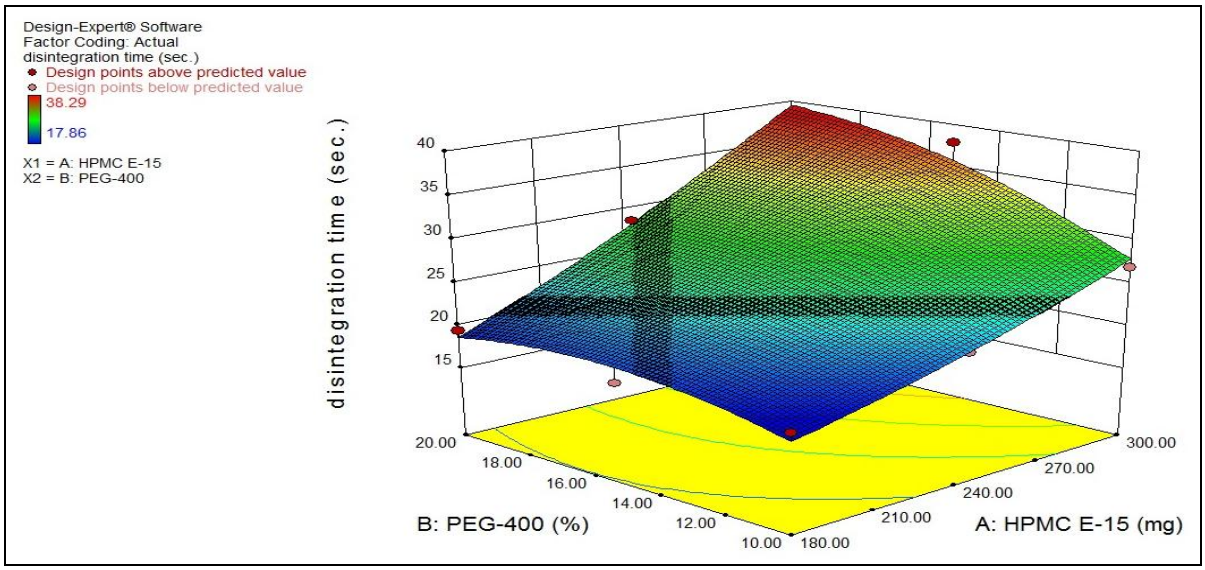

FIG. 9: 3D SURFACE PLOT OF DISINTEGRATION TIME

Full and Reduced Model for *in-vitro* Drug Release at 4 min: The summary of regression analysis and ANOVA for *in-vitro* drug release at 4 min is shown in Table 10. The contour plot and 3D surface plot are shown in **Fig. 10** and **Fig. 11**, respectively. From the equation of full model, reduced model is drawn by rejecting insignificant factors on the basis of p-value. From the model, it was found that the concentration of HPMC E15 shows negative effect on the *in-vitro* drug release. As its concentration increases, *in-vitro* drug release of film decreases. It was concluded that X_1 had the largest effect on the drug release at 4 min, which indicated that HPMC E15 was important factor to regulate drug release.

TABLE 10: SUMMARY OUTPUT OF REGRESSION ANALYSIS AND ANOVA FOR *IN-VITRO* DRUG RELEASE AT 4 min

	DF	**SS**	**MS**	**F**	**P-value Prob > F**
Regression	5	5462.62	1092.52	9.05	0.0497
Residual	3	362.23	120.74		
Total	8	5824.85			Significant
Coefficient	**b_0**	**b_1**	**b_2**	**b_{11}**	**b_{22}**	**b_{12}**
Coefficient value	73.42	-28.94	1.45	-14.47	-1.56	0.45
P-value	0.0497	0.0076	0.7680	0.1595	0.8539	0.9405

Full Model: $Y_2 = 73.42 - 28.94\ X_1 + 1.45\ X_2 - 14.47\ X_1^2 - 1.56\ X_2^2 + 0.45\ X_1X_2$

Reduced Model: $Y_2 = 73.42 - 28.94\ X_1$

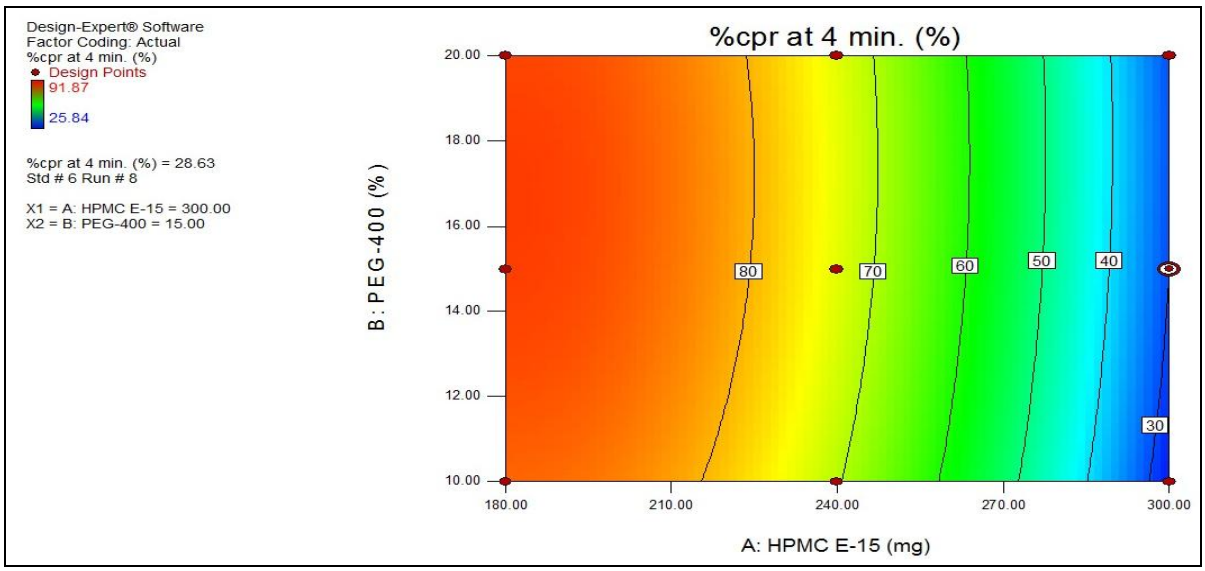

FIG. 10: CONTOUR PLOT OF *IN-VITRO* DRUG RELEASE AT 4 min

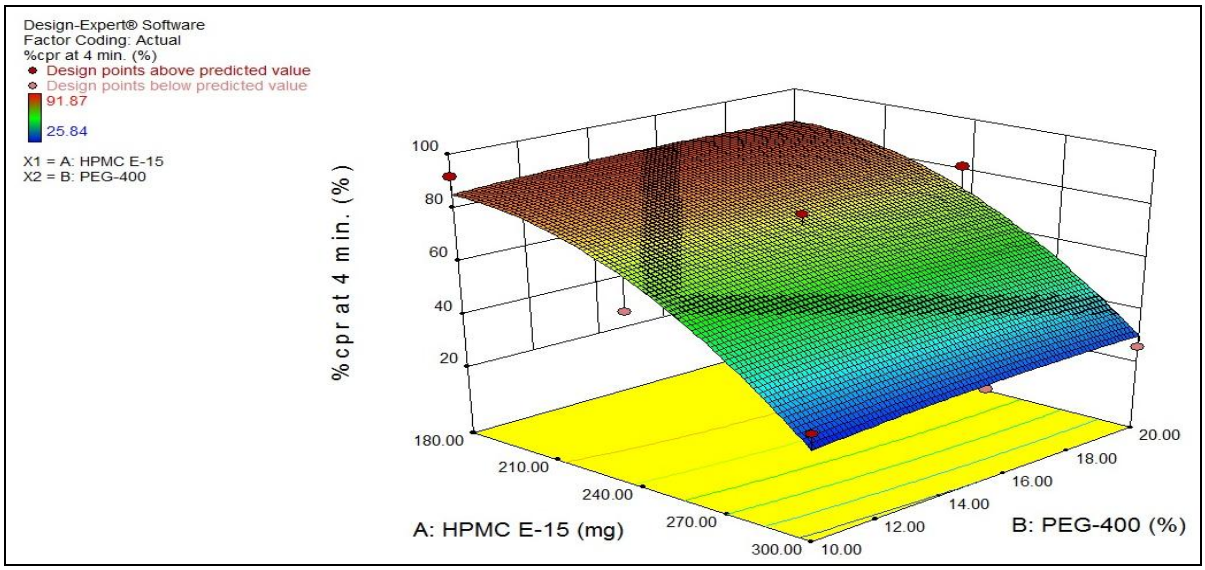

FIG. 11: 3D SURFACE PLOT OF *IN-VITRO* DRUG RELEASE AT 4 min

Full and Reduced Model for Tensile Strength: The summary of regression analysis and ANOVA for tensile strength is shown in **Table 11**. The contour plot and 3D surface plot are shown in **Fig. 12** and **Fig. 13**, respectively. From the equation of full model, the reduced model is drawn by rejecting insignificant factors on the basis of p-value.

From the model, it was found that the concentration of HPMC E15 shows positive effect on the tensile strength. As its concentration increases, tensile strength of film increases. The concentration of PEG 400 also shows positive effect on the tensile strength. It was concluded that X_1 and X_2 both had significant effect on tensile strength.

TABLE 12: SUMMARY OUTPUT OF REGRESSION ANALYSIS AND ANOVA FOR TENSILE STRENGTH

	DF	**SS**	**MS**	**F**	**P-value Prob > F**
Regression	5	4.088E-003	8.176E-004	63.12	0.0031
Residual	3	3.886E-005	1.295E-005		
Total	8	4.127E-003			Significant

Coefficient	**b_0**	**b_1**	**b_2**	**b_{11}**	**b_{22}**	**b_{12}**
Coefficient value	0.2200	0.0230	0.0130	0.0012	0.0021	- 0.0018
P-value	0.0031	0.0006	0.0034	0.4571	0.5233	0.5373

Full Model: $Y_3 = 0.22 + 0.0230\ X_1 + 0.0130\ X_2 + 0.0012\ X_1^2 + 0.0021\ X_2^2 - 0.0018\ X_1X_2$

Reduced Model: $Y_3 = 0.22 + 0.02300\ X_1 + 0.01300\ X_2$

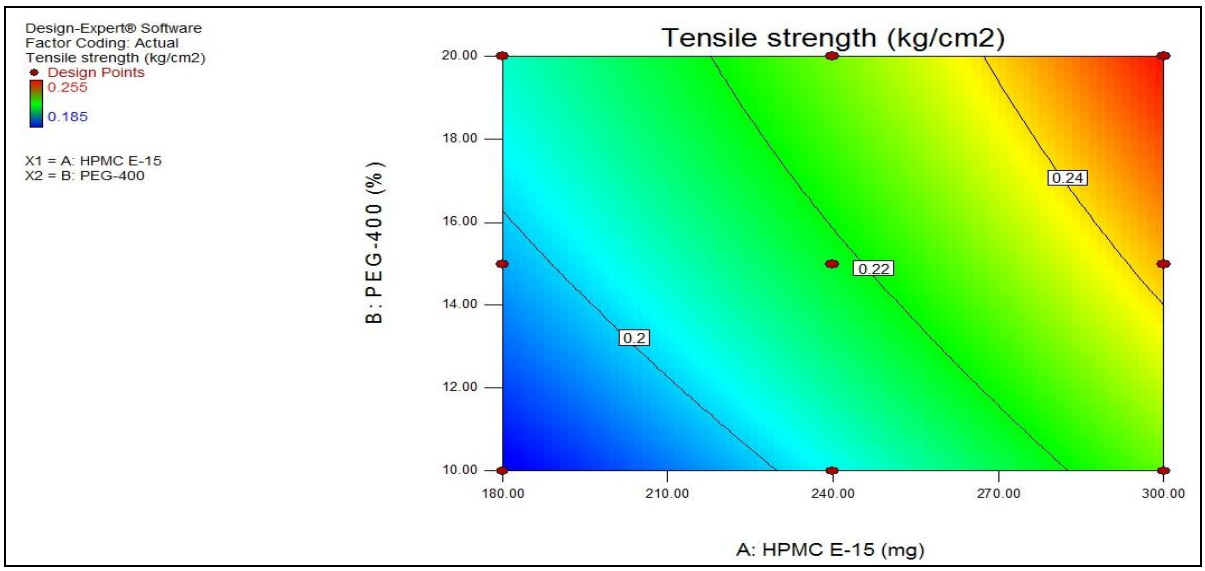

FIG. 12: CONTOUR PLOT OF TENSILE STRENGTH

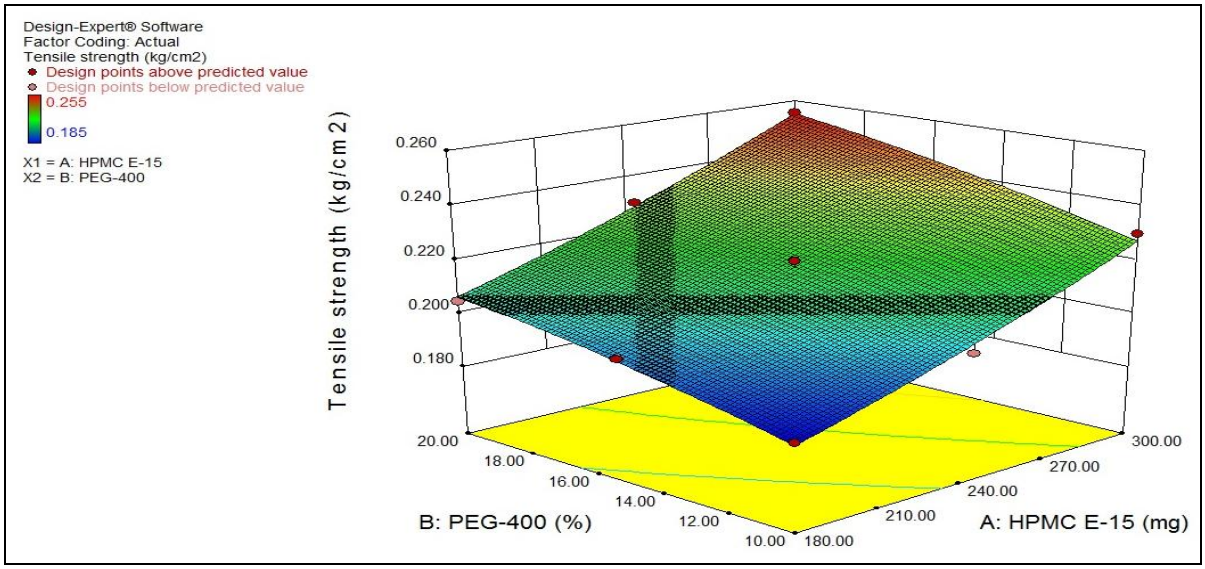

FIG. 13: 3D SURFACE PLOT OF TENSILE STRENGTH

Validation of Model by Check Point Batch: Checkpoint batches C1 and C2 were selected from the overlay plot of responses. The amount of HPMC E15 and PEG 400 were selected from overlay plot and predicted responses were calculated and are given in **Table 13**. The actual response of C1 and C2 batch were measured and compared with the predicted response of checkpoint batches. All the values of responses were within the upper and lower predicted interval. Hence, this model is valid, and an optimized batch can be selected from the overlay plot of this model.

TABLE 13: PREDICTED AND ACTUAL RESPONSES OF CHECKPOINT BATCHES

Batches	Predicted Response			Actual Response		
	D.T. (sec)	% CPR	Tensile Strength (kg/cm^2)	D.T. (sec)	% CPR	Tensile Strength (kg/cm^2)
C1	17.42	85.00	0.187	21	81.23	0.200
C2	17.67	85.67	0.188	20	82.55	0.198

Optimization of Batch from Overlay Plot: From the overlay plot it was seen that batches F1, F2, F3, and F4 fall under the optimized area. So, the batch with the minimum amount of both the factors, *i.e.* HPMC E15 and PEG 400 was selected as the optimized batch. Thus batch F1 was selected as the optimized batch.

Stability Study of Optimized Batch: After one month of accelerated stability study (40ºC ± 2ºC and 75 ± 5% RH) of optimized batch F1, all evaluation parameters and dissolution test were performed. The results are shown in **Table 14** and the comparison profile in **Fig. 14**. Results of the accelerated stability study had shown no remarkable change in the release profile of the promethazine HCl fast dissolving oral film after one month accelerated stability study.

TABLE 14: EVALUATION OF OPTIMIZED BATCH F1

After accelerated stability study 40 ± 2 ºC and 75 ± 5% RH		
Evaluation parameters	0 days	30 days
Tensile strength(Kg/cm^2)	0.185	0.182
Folding endurance	180	177
In vitro disintegration time (sec)	17.86	19.37
% drug content	99.10	98.21
% Drug release (after 10 min)	99.64	96.75

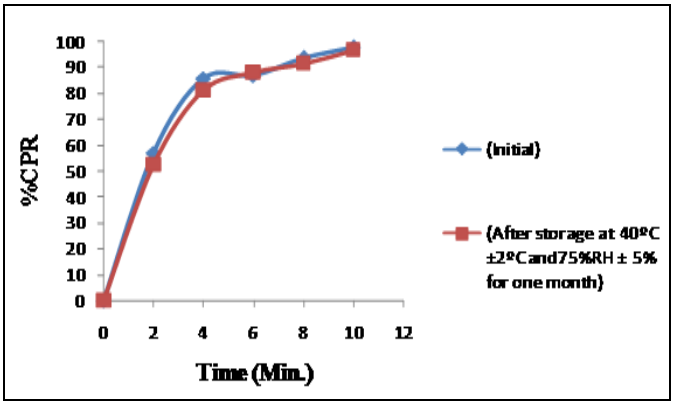

FIG. 14: COMPARATIVE DISSOLUTION PROFILE OF BATCH F1 INITIALLY AND AFTER ONE MONTH STABILITY

CONCLUSION: The quality of film was affected by type and concentration of polymer and plasticizer. The development of oral film drug delivery of promethazine HCl is one of the alternative routes to provide immediate action. Also, this formulation enhances patient compliance, especially for an outpatient setting. The results of present study indicated that HPMC E15 could be used as a film-forming polymer for formulation of fast dissolving film containing promethazine HCl. Based on data obtained from *in-vitro* dissolution studies, it was concluded that F1 is promising formulation suitable for the immediate release of promethazine HCl.

The formulation batch F1 was found to be stable for a period of one month at 40 ºC/ 75% RH. Fast dissolving film can be a potential novel drug dosage form for pediatric, geriatric and also for the general population.

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CONFLICT OF INTEREST: Nil

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