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Formulation Evaluation and Optimization of Fast Dissolving Oral Strips of Isosorbide Mononitrate

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ABSTRACT

Fast dissolving oral films (FDOFs) are the most advanced form of oral solid dosage form due to more flexibility and comfort. Fast dissolving film is a dosage form which when placed in the oral cavity, quickly gets hydrated, sticks onto the site of application and then disintegrates to release the drug. Fast dissolving oral films of isosorbide mononitrate were prepared by solvent casting method. Optimization was carried out to study the effect of independent variables (different polymer and plasticizer concentration) such as HPMC E5 and HPMC E50 as polymer and PEG 400 as a plasticizer on the dependent variables like T90% (sec), *in-vitro* disintegration time (sec) & % moisture absorption (%). Design expert software (version 8.0.1.6) was used to optimize the formulation. Prepared films were subjected to different evaluation parameters such as surface pH, weight uniformity, thickness of strip, % moisture absorption, % moisture loss, swelling index, drug content, *in-vitro* disintegration time, *in-vitro* drug release, stability studies and mechanical properties like folding endurance, tensile strength.

Keywords: Fast dissolving oral films, Optimization, Isosorbide mononitrate, Anova, PEG, HPMC.

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INTRODUCTION

The oral route of drug administration is the most important method of administration of drug for systemic effect, despite of tremendous advancement in drug delivery system. Its ease of administration, pain avoidance and various advantages over other routes is the reason that the oral route achieved such popularity[1]. Oral drug delivery systems still need some advancements to be made because of their some drawbacks related to particular class of patients which includes geriatric, paediatric and dysphasic patients associated with many medical conditions as they have difficulty in swallowing solid dosage forms. Many paediatric and geriatric patients are having difficulty to take solid dosage forms due to fear of choking. Even with fast dissolving tablets there is a fear of choking due to its tablet type appearance[2]. Many pharmaceutical companies have directed their research activity in reformulating existing drugs into new dosage forms. One such relatively new dosage form is the oral strip, a thin film that is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity[3]. The fast dissolving films has also a clear advantage over the fast dissolving tablets (FDTs). A large number of drugs can be formulated as fast dissolving films. This fast-dissolving action is primarily due to the large surface area of the film, which wets quickly when exposed to the moist oral environment. These additional, superior benefits allow patients to take their medication anytime and anyplace under all circumstances. Quick-Dis ^{TM} however, comprises a tough, solid, soft, flexible film and does not require special packaging. It is thin and can be carried in a patient's pocket, wallet, or pocket book[4].

Angina pectoris is a medical condition characterized by a severe chest pain that occurs due to ischemia of the heart muscle which requires quick management in order to avoid the risk of Cardiac arrest. Ischemia is a restriction in blood supply and therefore, a lack of oxygen supply, generally due to factors in the blood vessels, with resultant damage or dysfunction of tissues. The main cause of angina pectoris is the coronary artery disease that occurs as the result of accumulation of athermanous plaques on the walls of the coronary arteries[5]. Isosorbide-5-mononitrate is an organic nitrate vasodilator that acts by relaxing peripheral vascular muscles and thereby reduces systolic blood pressure[6].

Optimization, a new approach that uses concept of statistics to optimize the formulation and process pararmeters, is being increasing used in formulation designing. The purpose of carrying out optimization is to select the best possible formulation from pharmaceutical as well as consumer point of view. Optimization is considered as an economical method to understand the

relationship between dependent and independent variables.

Independent variables are factors which can be changed by the developer at will, e.g., mixing time. A developer can increase the time of mixing as per his/her will. The response of the independent variable is dependent variable. Response is mostly interpreted as the outcome of an experiment. It is the effect which we are going to evaluate i.e. disintegration time, rate constant etc[7,8].

MATERIALS AND METHODS

Isosorbide mononitrate was obtained as a gift sample from Wallace pharmaceuticals, Goa. HPMC E5 LV and HPMC E50 were procured from yarrow chem. Product, Mumbai, India. Propylene glycol was obtained from Loba chem, Mumbai, India. Citric acid and sucrose were procured from Himedia, Mumbai, India. All the chemicals were of analytical grade.

Drug and excipient compatibility studies

Excipients are integral part of almost Excipients are integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients, which are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation. FTIR can be used to investigate and predict any physiochemical interaction between different excipients. IR spectra matching approach was used for detection of any possible chemical interaction between the drug and polymer. IR is also one of the most powerful analytical techniques to identify functional group of a drug.

Method: - The pure drug and polymers were subjected to FTIR studies. In the present study, the potassium bromide pellet method was employed. It was scanned from 4000 to 400 cm^{-1} in FTIR spectrometer. The IR spectrum of the physical mixture was compared with those of pure drug and polymer, and peak matching was done to detect any appearance or disappearance of peaks.

Preparation of fast dissolving oral films of isosorbide mononitrate[16]

Fast dissolving oral films of isosorbide mononitrate was prepared by solvent casting method by using combination of two different water soluble polymers i.e HPMC E5 LV and HPMC E50 LV at varied concentration. In preparation of strips solvent system was water, citric acid was used as saliva stimulating agent, sucrose was used as a sweetening agent, PEG 400 was used as a plasticizer. Accurately weighed HPMC E5 LV and was transferred to the solvent system, followed by addition of HPMC E50 LV to the same solvent system, stirred well using magnetic stirrer to obtain a clear homogenous polymeric solution. Then to this polymeric solution

plasticizer i.e PEG 400, drug, sucrose and citric acid was added and stirred for 30 min. The solution was allowed to stand for 10 min for de-aeration. Solution was then casted into a petri dish having area of 63.58 cm^2. Petri dish was then kept in hot air oven at 40ºC for 24 h. The films were cut in to size of 2×2 cm^2 containing 5 mg of isosorbide mononitrate. Strips were packed in aluminium foil and stored in desiccators for further evaluation.

Experimental design:

Central composite design is an experimental design technique, by which the factor involved and their relative importance can be assessed. In the present study the formulation, which is design, based on central composite design containing 3 factor and the experimental trials were, performed at all possible combinations. To study all possible combination of all levels, a three factor, two- level full factorial design was constructed and conducted in full order.

The three independent formulation variable evaluated include:

Factor A: Amount of HPMC E5 LV (X_1)

Factor B: Amount of HPMC E50 LV (X_2)

Factor C: Volume of PEG 400 (X_3)

The dependent variable measured were *in-vitro* disintegration time (sec), time for 90 % of drug release (sec) and percentage moisture absorption (%). High and low levels of each variable were coded as 1 and -1 respectively. The range of factor must be chosen in order to adequately measure is effects on response variables. The range of each factor was chosen from the preliminary studies. Stepwise regression analysis was used to find out the control factors that significantly affect response variables.

The amount of the two different polymers HPMC E5 LV and HPMC E50 LV and the volume of plasticizer PEG 400 were selected as independent variable factor A, factor B, and factor C respectively. As variant concentration of the polymer and plasticizer combination will affect the drug release pattern. The selection of HPMC two different grade because it having good film forming capacity. Amount of two different polymers HPMC E5 LV and HPMC E50 LV and plasticizer were coded values in table 1

Table 1: Actual level of independent variables

Coded values	Actual values		
	HPMC E5LV	**HPMC E50LV**	**PEG400**
-1	250mg	200mg	0.1ml
0	300mg	250mg	0.2ml
+1	350mg	300mg	0.3ml

Central composite design – design expert software (8.0.6.1 stat Ease Inc.) was considered.

According to the model total 15 experiments were conducted.

Calculation of dose for isosorbide mononitrate

Internal diameter of the petridish = 9cm

Radius of the petri dish = 4.5cm

Internal surface area of petridish = πr^2

= 22/7 x $(4.5)^2$

= 3.142 x (20.25)

= 63.58 cm^2

Surface area of strip = 2 x 2cm = $4cm^2$

$4cm^2$ contains 5mg

(63.58) cm^2 contains = 79.45 mg of isosorbide mononitrate

Table 2: formulation table of fast dissolving oral films of isosorbide mononitrate

Formulation	Isosorbide mononitrate (mg)	HPMC E5 LV (mg)	HPMC E50 LV (mg)	PEG 400 (ml)	Citric acid (mg)	Sucrose (mg)	Pineapple flavour (ml)	Water (ml)
F1	79.45	250	200	0.1	18	18	0.3	10
F2	79.45	350	200	0.1	22	22	0.3	10
F3	79.45	250	300	0.1	22	22	0.3	10
F4	79.45	350	300	0.1	26	26	0.3	10
F5	79.45	250	200	0.2	18	18	0.3	10
F6	79.45	350	200	0.3	22	22	0.3	10
F7	79.45	250	300	0.3	22	22	0.3	10
F8	79.45	350	300	0.3	26	26	0.3	10
F9	79.45	250	250	0.2	20	20	0.3	10
F10	79.45	350	250	0.2	24	24	0.3	10
F11	79.45	300	200	0.2	20	20	0.3	10
F12	79.45	300	300	0.2	24	24	0.3	10
F13	79.45	300	250	0.1	22	22	0.3	10
F14	79.45	300	250	0.3	22	22	0.3	10
F15	79.45	300	250	0.2	22	22	0.3	10

Evaluation of fast dissolving oral films films

Weight uniformity of the strip: [9]

Three fast dissolving oral films having size of $2cm^2 \times 2cm^2$ were weighed individually using digital balance and average weighed was calculated.

Strips thickness uniformity: [9]

The thickness of the strip was measured by using with help of screw gauge with a range of 1-10mm and resolution 0.01mm. Thickness of oral strip determines at five different place of the strip and standard deviation was also calculated.

Surface pH: [9]

The surface pH of fast dissolving oral films was investigate in order check the possibility of any side effect due to change in pH *in vivo*, in the alkaline or acidic pH condition chances of irritation to mucosa. The oral film was placed in a petri dish which contains 0.5 ml of phosphate buffer having pH 6.8 to moisten it and kept a side for 30 sec. The pH of film was noted down by using digital pH meter. The average of 3 investigations for each formulation was done. Standard deviation was also calculated.

Folding endurance: [9]

Folding endurance of the films determine the flexibility of the films. It was determined by repeatedly folding a small strip at the same place until it breaks. The number of times strips could be folded at the same place, without breaking gives the value of folding endurance. Folding endurance was measure by manually for flash release oral strip ($2\times2cm^2$). Standard deviation was also calculated.

Drug content uniformity: [10, 11]

Fast dissolving film of size 4 cm^2 was cut and transferred into a beaker containing 100ml phosphate buffer pH 6.8.The contents were stirred to dissolve the film. The contents were transferred to a volumetric flask (100ml). The absorbance of the solution was measured against the corresponding blank solution at 220nm.

Measurement of swelling index: [12]

Measurements of swelling index of flash release oral strips were conducted in phosphate buffer of pH 6.8. The oral strip sample (surface area $2\times2cm^2$) was weighed by using digital weight machine and placed in a pre-weighed wire sieve made of stainless steel of approximately 800 µm mesh. The wire sieve containing sample film was put into 10 ml of phosphate buffer pH 6.8 medium in a petridish. At definite time intervals, wire was removed. Increase in weight of the film was determined at each time interval until a constant weight was observed. The degree of swelling was calculated using the formula,

$$\textbf{Swelling index} = W_t - W_1 / W_1$$

Where, W_t is weight of the film at time t and

W_1 is weight of the film at time zero.

Tensile strength: [13]

Is performed using Tensile Testing Machine. The 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 = force (load to break)/ Width × thickness

Percentage of moisture absorption: [9]

The percentage of moisture absorption measurement was carried out for the purpose of to ensure the integrity or physical stability of the flash release oral strip at high humid condition. The strip were weighed and placed in a desiccator containing 100 ml of saturated solution of $Alcl_2$ and 75 ± 5% RH was maintained. After competitions of 72 hours the films were taken and final weight was measured. The percentage of moisture absorption was calculated using the following formula.

%Moisture absorption= final weight- initial weight /Initial weight×100

Percentage of moisture loss: [14]

To check the integrity of films at dry atmosphere percentage of moisture loss was carried. It is found out by placing the prepared strip in desiccators containing anhydrous calcium chloride. After three days, the film was taken and reweighed. The percentage of loss was calculated using following formula.

%Moisture loss= Initial weight- Final weight/Initial weight ×100

***In-vitro* disintegration study:** [9]

The disintegration time is the time when a strip breaks or disintegrates. The test was performed using the same method as mentioned by setouhy *et al.*, with slight modification. The strip size required for dose delivery ($2\times2cm^2$) was placed on glass petri dish containing 10ml of phosphate buffer. The time required for breaking of strip was noted as *in-vitro* disintegration time.

***In-vitro* drug release:** [15]

The release rate isosorbide mononitrate from fast dissolving oral films was determined by using USP dissolution test Apparatus (Type I). The dissolution test was performed using 300 ml of Phosphate Buffer Solution (pH 6.8), at 37 ± 0.5°C with the paddle speed of 50 rpm. Aliquot (5 ml) of the solution was collected from the dissolution apparatus at time interval of 30, 60, 120, 180, 240, 300 seconds and were replaced with same amount of fresh dissolution medium. The aliquots were filtered through Whatman filter paper (0.45µm). Absorbance of the filtrates was measured at 230nm. Aliquots were withdrawn from a zone midway between the surface of dissolution medium and the top of rotating paddle not less than 1 cm apart from the vessel wall. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

Stability study: [9]

For any kind of dosage form for its evaluation stability is important, the stability of the API must be major criteria in determining the acceptance or rejection. Drug instability in particular dosage form is found by a change in the physical appearance such as colour, odour, taste or texture of the formulations, on other hand chemical changes may occur which can be identified by chemical analysis.

The stability studies of the fast dissolving oral films were carried out on formulated oral strip kept at temperature as per standard ICH guidelines. The film was packed in aluminium foil and stored in desiccators for stability studies at 40°C and 75% Relative Humidity (RH) for a period of 3months. The fast dissolving oral films were evaluated for drug content and other physical parameter at the end of every 1 month.

RESULTS AND DISCUSSION

The comparison of the IR spectrum revealed that there is no appreciable change in the positions of characteristic absorption bands of groups and bonds. The range of peak values were found to be the same indicating that there were no interaction of drug with different polymers confirming the stability of drug in the formulation. Results are shown in figure 1

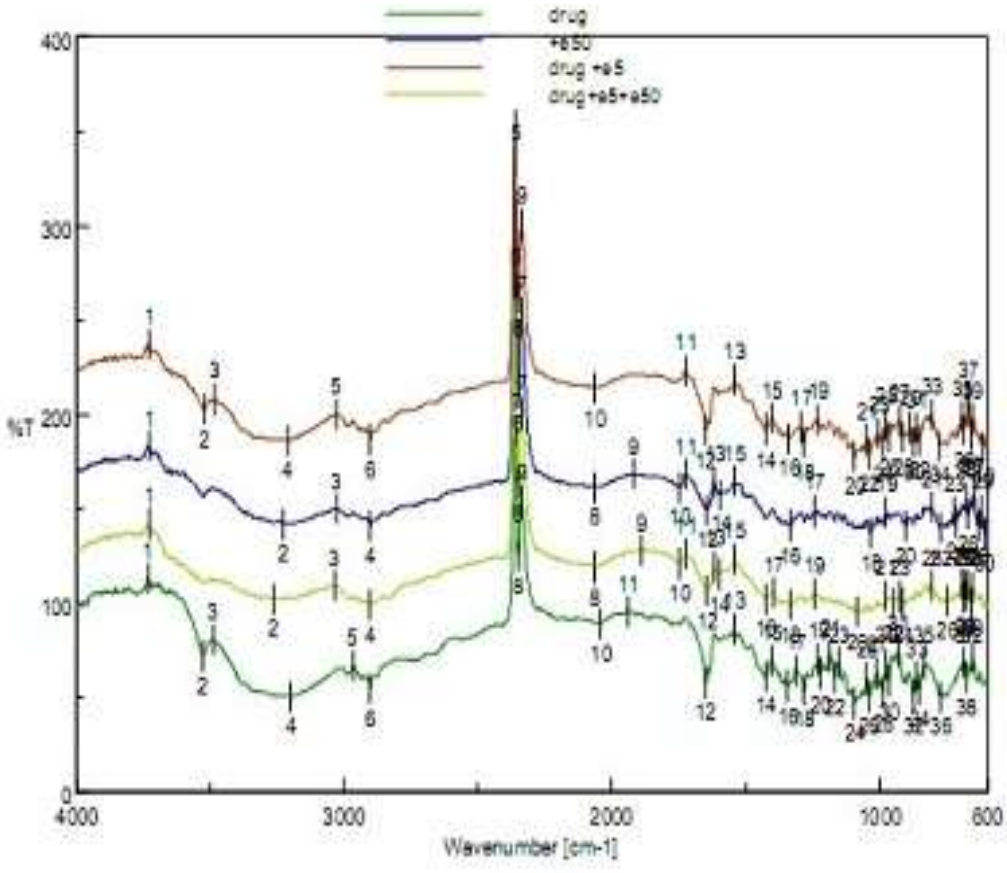

Figure 1: Comparison of IR spectra of drug with polymers

Table 3: uniformity of weight, surface pH, thickness.

Formulation code	Uniformity of weight (mg)±SD, n=3	Surface pH ±SD, n=3	Thickness (mm)±SD, n=3
F1	21.03±0.9	6.73±0.05	0.063±0.005
F2	31.16±0.65	6.83±0.05	0.126± 0.005
F3	31.53±0.503	6.7±0.1	0.136±0.005
F4	46.1±0.9	6.83±0.05	0.176±0.005
F5	21.63±1.37	6.63±0.05	0.066±.0005
F6	33.1±0.9	6.76±0.05	0.13±0.01
F7	33±1.60	6.7±0.1	0.136±0.005
F8	46.2±1.1	6.63±0.15	0.183±0.005
F9	27.36±0.55	6.7±0.1	0.093±0.005
F10	35.1±0.65	6.60±0.1	0.143±0.005
F11	26.9±0.60	6.76±0.05	0.103±0.015
F12	35.6±1.26	6.73±0.11	0.146±0.005
F13	33.1±0.95	6.76±0.05	0.133±0.005
F14	32.2±0.95	6.66±0.15	0.14±0.01
F15	32.4±0.86	6.83±0.05	0.133±0.015

The physical evaluation of fast dissolving oral films has been given in table 3. The thickness of oral strips was found in the range of 0.063± 0.005mm to 0.183±0.005mm. The weight of all oral films was in the range of 21.03±0.9mg to 46.2±1.1mg. The thickness and the weight of films were affected by the concentration of the polymer proportionally. The surface pH of the oral strips was found in between the 6.60±0.1 to 6.83±0.05 which indicate pH of the prepared oral films almost near to the buccal pH.

Table 4: Folding endurance, %moisture absorption, Swelling index

Formulation code	Folding endurance ±SD, n=3	% Moisture Absorption ±SD, n=3	Swelling index ±SD, n=3
F1	>100	2.58±0.11	0.0586±0.0005
F2	>100	4.8±0.05	0.0986±0.0005
F3	>100	5.34±0.14	0.099±0.0005
F4	>100	7.15±0.04	0.126±0.001
F5	>200	3.17±0.09	0.06±0.001
F6	>200	4.88±0.06	0.0998±0.0001
F7	>200	5.65±0.05	0.103±0.001
F8	>200	7.21±0.08	0.131±0.001
F9	>150	4.11±0.11	0.08±0.001
F10	>150	6.29±0.09	0.114±0.0005
F11	>150	3.91±0.06	0.080±0.001
F12	>150	6.16±0.08	0.121±0.001
F13	>100	4.90±0.05	0.101±0.001
F14	>200	5.42±0.12	0.103±0.001
F15	>150	5.11±0.07	0.102±0.001

Considering the fact that acidic or alkaline pH may cause irritation to the oral mucosa and influence the degree of hydration of polymer, the surface pH of the flash release oral strips determine the drug permeation. Attempts were made to keep the surface pH as close to salivary pH as possible, by the proper selection of polymer for designing the flash release oral strips. The surface pH of all the strips was within the range of salivary pH. No significant difference was found in surface pH of different oral strips. The standard deviation value calculated for all the strips are very low which conclude that the surface pH of all the strips was uniform and within the range.

Folding endurance study of the oral films concluded that the two independent variables (i.e HPMC E5 and HPMC E50) showed positive effect on the folding endurance, but the third independent variable (i.e PEG 400) had some effect. As the plasticizer concentration increases the folding endurance also increases. Folding endurance values are in the range of 100 to 200, which shows good nature of elasticity of the films.

Percentage of moisture absorbed was found in the range of 2.58±0.11 to 7.21±0.08.

Swelling index of films was in the range of 0.0586 to 0.13. It was seen that as the polymer concentration increases swelling index increases. It also affects the drug release from the strips, higher the swelling index minimum the drug release from the oral films. Results are shown in table 4.

Table 5: *In-vitro* disintegration time, tensile strength, % moisture loss, drug content

Formulation code	*In-vitro* disintegration time (sec) ±SD, n=3	Tensile strength (N/cm^2) ±SD, n=3	%Moisture loss (%)±SD, n=3	Drug content (%)±SD, n=3
F1	17.03±0.66	1.27±0.02	1.08±0.01	97.76±0.015
F2	21.94± 0.20	2.75±0.02	1.87±0.01	98.84±0.015
F3	38.66±0.51	2.84±0.02	1.96±0.025	98.27± 0.01
F4	45.64±0.49	3.48±0.02	3.35±0.01	99.65±0.068
F5	17.18±0.84	1.073±0.01	1.14±0.01	99.42±0.070
F6	25.20±0.43	2.12±0.03	2.45±0.01	97.38±0.035
F7	41.60±0.45	2.26±0.01	2.76±0.01	98.52±0.056
F8	52.71±0.49	3.34±0.02	3.63±0.01	99.71±0.065
F9	19.75±0.39	1.77±0.02	1.63±0.01	97.49±0.065
F10	43.14±0.87	2.94±0.03	3.14±0.01	98.34±0.077
F11	18.33±0.67	1.57±0.02	1.53±0.01	97.70±0.055
F12	45.29±0.85	3.04±0.03	3.20±0.02	97.23±0.081
F13	28.57±0.56	2.80±0.01	1.90±0.005	98.79±0.055
F14	32.79±0.70	2.23±0.03	2.62±0.02	99.50±0.055
F15	30.35±0.61	2.63±0.05	2.34±0.03	98.32±0.045

The *in-vitro* disintegration time of fast dissolving oral films was found be in the range of 17.03±0.66sec to 52.71±0.49sec.

The tensile strength was in the range of 1.07±0.01 N/cm^2 to 3.488±0.02 N/cm^2. The % moisture loss was found to be in the range of 1.08±0.01% to 2.63±0.01%. Isosorbide mononitrate oral films prepared with two different polymers subjected to the uniform dispersion of drug throughout the oral strip. In each evaluation three films were used and average drug content was calculated. The drug content was in the range of 97.23±0.081% to 99.71±0.065%. The results are shown in table 5.

***In-vitro* drug release studies**

Table 6: *In-vitro* drug release profile of F1, F2, F3, F4, F5, F6, F7, F8

Time (sec)	Percentage Cumulative Drug Release							
	F1	F2	F3	F4	F5	F6	F7	F8
0	--	--	--	--	--	--	---	--
15	14.42	11.42	7.84	5.16	13.33	10.89	8.93	5.93
30	27.78	19.18	19.04	13.62	26.19	17.78	17.11	10.99
60	49.58	45.46	27.63	19.07	47	42.82	26.1	16.75
90	71.03	61.28	43.24	35.67	67.33	58.07	39.68	30.35
120	97.62	79.6	57.61	52.37	96.6	76.86	57.48	47.83
150	--	99.35	80.58	69.07	--	97.43	77.92	64.46
180	--	--	96.15	75.06	--	--	91.62	71
240	--	--	--	86.63	--	--	--	84.37
300	--	--	--	99.91	--	--	--	93.44
T90%	110.63 sec	135.88 sec	168.48 sec	270.24 sec	111.80 sec	138.56 sec	176.81 sec	288.89 sec

Table 7: *In-vitro* drug release profile of F9, F10, F11, F12, F13, F14, F15

Time (sec)	Percentage Cumulative Drug Release						
	F9	F10	F11	F12	F13	F14	F15
0	--	--	--	--	--	--	---
15	11.5	6.97	12.46	7.41	12.11	8.71	10.37
30	21.97	13.32	24.43	17.11	24.77	20.97	23
60	44.64	19.07	46.61	23.49	34.24	30.64	34.18
90	63.92	37.77	65.06	43.99	49.34	45.6	45.71
120	90.31	54.67	92.16	57.51	64.51	60.44	62.98
150	--	72.63	--	75.51	93.6	81.62	90.84
180	--	85.46	--	82.29	--	99.82	--
240	--	96.13	---	99.87	--	--	--
T90%	119.58 sec	224.69 sec	117.19 sec	216.28 sec	144.23 sec	162.29 sec	148.61 sec

In-vitro dissolution studies were carried out of fast dissolving oral films of isosorbide mononitrate by using phosphate buffer pH6.8 which is same as buccal pH. The *in-vitro* dissolution study was carried up to 300 seconds and the values are shown in table 6 & 7.

From the *in-vitro* dissolution data, it was found that the drug release studies of prepared strips with lower concentration of polymer which shows good release of drug and higher concentration shows slower drug release, This might be due to the increase in the concentration

of polymer, results in the formation of strong matrix layer caused by more intimate contact between the particles of HPMC results in decreased in mobility of drug particles in swollen matrices, which leads to decrease in drug release. It was also seen that as the plasticizer concentration increases drug release decreases and vice versa.

In the formulation F1, F4, F5 and F8 having total and individual polymer concentration was same but plasticizer concentration was different. $T_{90\%}$ data were 110.63 sec, 270.24 sec, 111.80 sec and 288.89 sec respectively. F9, F10, F11 and F12 having total polymer concentration same but individual polymer concentration was different and showed T90% as 119.58 sec, 224.69sec, 117.19 sec and 216.28 sec respectively.F2, F3, F6, F7, F13, F14 and F15 having total polymer concentration same but individual polymer concentration was different and plasticizer concentration was different, but shows T90% as 135.88 sec, 168.48 sec, 138.56 sec, 176.81 sec, 144.23 sec, 162.29 sec and 148.61 sec respectively. This shows the effectiveness of the polymers and plasticizer in the formulation. Nature of the polymer also affects the drug release pattern, higher molecular weight polymer affect the drug release from the formulation.

Data Analysis by ANOVA

The response was recorded and analysis of data was carried out using ANOVA in DESIGN EXPERT Software version 8.0.6.1(State Ease Inc.).The individual parameters were evaluated using F test and polynominal equation. Design summary and response data are in table

Table 8: Design summary and response data

Standard Run	Type	Factor A	Factor B	Factor C	Responses		
					T90% (sec)	Disintegration time (sec)	%Moisture absorption(%)
1	Factorial	-1	-1	-1	110.63	17.03±0.66	2.58±0.11
2	Factorial	+1	-1	-1	135.88	21.94± 0.20	4.8±0.05
3	Factorial	-1	+1	-1	168.48	38.66±0.51	5.34±0.14
4	Factorial	+1	+1	-1	270.24	45.64±0.49	7.15±0.04
5	Factorial	-1	-1	+1	111.80	17.18±0.84	3.17±0.09
6	Factorial	+1	-1	+1	138.56	25.20±0.43	4.88±0.06
7	Factorial	-1	1	+1	176.81	41.60±0.45	5.65±0.05
8	Factorial	+1	+1	+1	288.89	52.71±0.49	7.21±0.08
9	Axial	-1	0	0	119.58	19.75±0.39	4.11±0.11
10	Axial	+1	0	0	224.69	43.14±0.87	6.29±0.09
11	Axial	0	-1	0	117.19	18.33±0.67	3.91±0.06
12	Axial	0	1	0	216.28	45.29±0.85	6.16±0.08
13	Axial	0	0	-1	144.23	28.57±0.56	4.90±0.05
14	Axial	0	0	1	162.29	32.79±0.70	5.42±0.12
15	Center	0	0	0	148.61	30.35±0.61	5.11±0.07

RESPONSE 1: T90% (second)

Table 9: Model summary statistics

Source	Std Dev.	R-Squared	Adjusted R-Squared	Predicted R-Squared	PRESS
Linear	21.86	0.8830	0.8511	0.7450	11455.41
2FI	15.40	0.9578	0.9261	0.8069	8675.13(suggested)
Quadratic	12.02	0.9839	0.9550	0.8620	6200.23
cubic	8.33	0.9985	0.9784	-3.6555	2.091E+005(aliased)

Table 10: ANOVA for Response Surface 2FI Model

Source	Sum of square	DF	Mean square	F value	P value Prob>F	
Model	43026.55	6	7171.09	30.23	<0.0001	Significant
A-E5	13761.13	1	13761.13	58.00	<0.0001	
B-E50	25668.41	1	25668.41	108.19	<0.0001	
C-PEG	239.02	1	239.02	1.01	0.3449	
AB	3273.62	1	3273.62	13.80	0.0059	
AC	17.49	1	17.49	0.074	0.7928	
BC	66.87	1	66.87	0.28	0.6099	
Residual	1897.96	8	237.24	-	-	
Cor total	44924.51	14	-	-	-	

The model F value 30.23 implies the model is significant.

Values of "Prob > F" less than 0.0500 indicate model terms are significant.

The "Pred R-Squared" of 0.8069 is in reasonable agreement with the "Adj R-Squared" of 0.9261.

Final equation in terms of coded factors

T90%= +168.94+37.10*A+50.66*B+4.89*C+20.23*A*B+1.48*A*C+2.89*B*C

Final equation in terms of actual factors

T90%= +336.79000-1.34011*Hpmc E5-1.52982*Hpmc E50-184.39750*PEG+8.09150E-003*HpmcE5*Hpmc E50+0.29575*HpmcE5*PEG+0.57825*HpmcE50*PEG

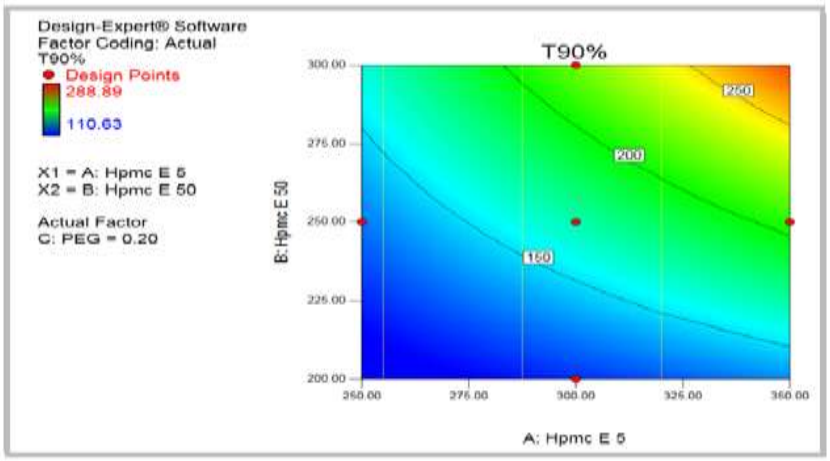

Figure 2: Contour plot for T90%

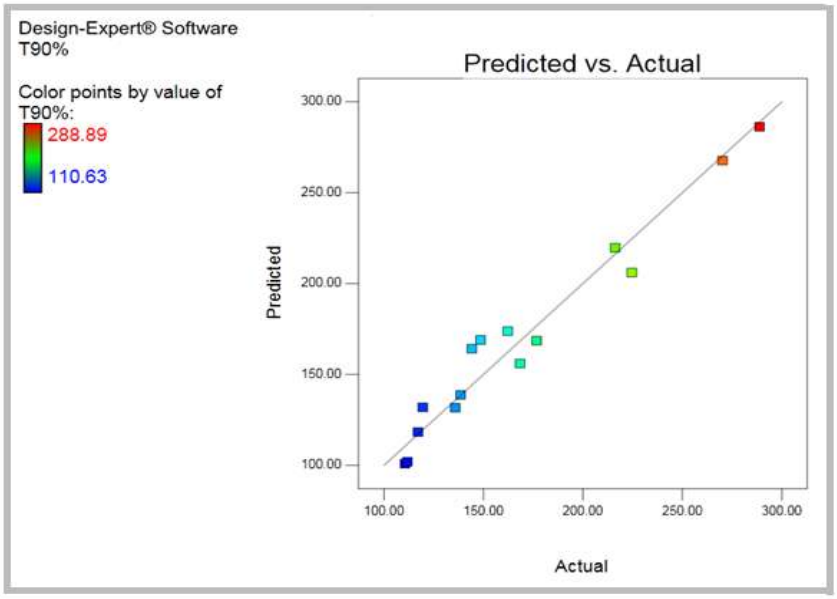

Figure 3: Predicted v/s Actual plot for T90%

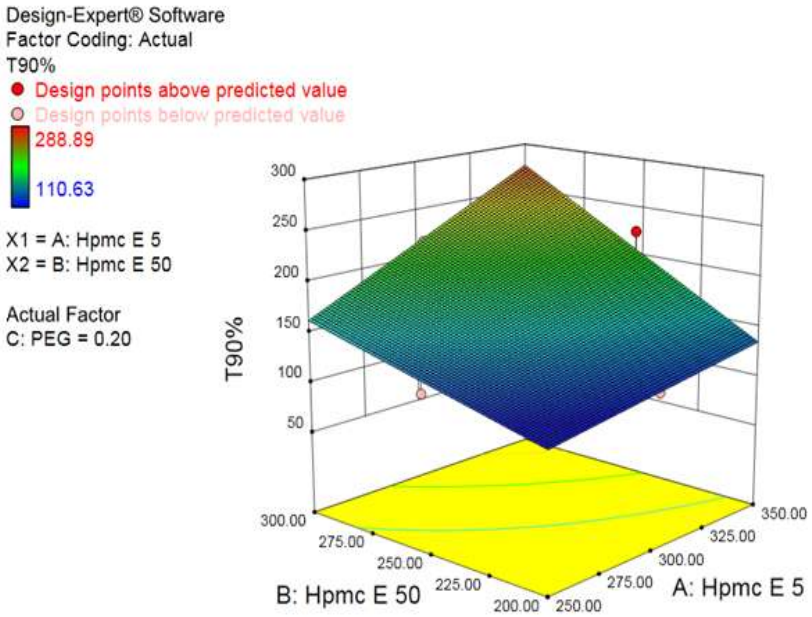

Figure 4: Response surface plot (3D) for T90%

RESPONSE 2: *in-vitro* disintegration time (sec)

Table 11: Model summary statistics

Source	Std Dev.	R-Squared	Adjusted R-Squared	Predicted R-Squared	PRESS
Linear	3.37	0.9374	0.9203	0.8897	220.00(suggested)
2FI	3.70	0.9450	0.9038	0.7627	473.40
Quadratic	4.50	0.9493	0.8581	0.5476	902.71
Cubic	0.31	1.0000	0.9993	0.8528	293.65(aliased)

Table 12: ANOVA for Response Surface Linear Model

Source	Sum of square	DF	Mean square	F value	P value	
Model	1870.22	3	623.41	54.87	<0.0001	Significant
A-E5	296.04	1	296.04	26.06	0.0003	
B-E50	1543.06	1	1543.06	135.82	<0.0001	
C-PEG	31.12	1	31.12	2.74	0.1261	
Residual	124.97	11	11.36	-	-	
Cor total	1995.19	14	-	-	-	

The Model F-value of 54.87 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms, model reduction may improve your model

Final equation in terms of coded factors *in-vitro* disintegration time= **+31.88+5.44*A+12.42*B+1.76*C**

Final equation in terms of actual factors *in-vitro*disintegration time = **66.40533+0.10882*HpmcE5+0.24844*HpmcE50+17.64000*PEG**

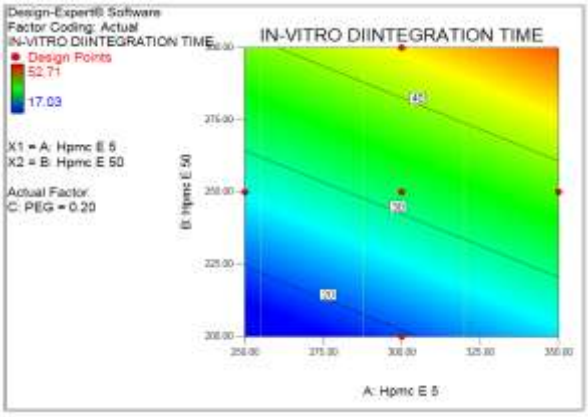

Figure 5: Contour plot for *in-vitro* disintegration time

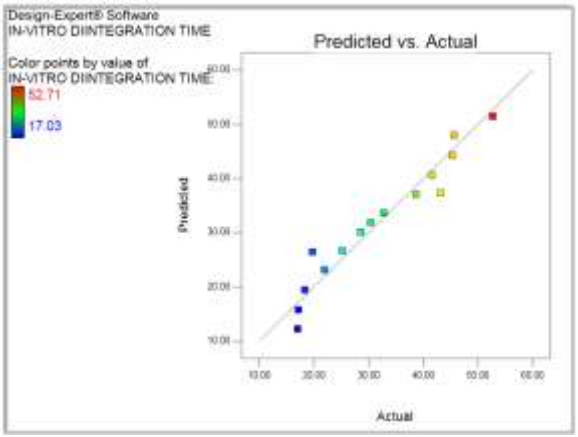

Figure 6: Predicted v/s Actual plot for *in-vitro* disintegration time

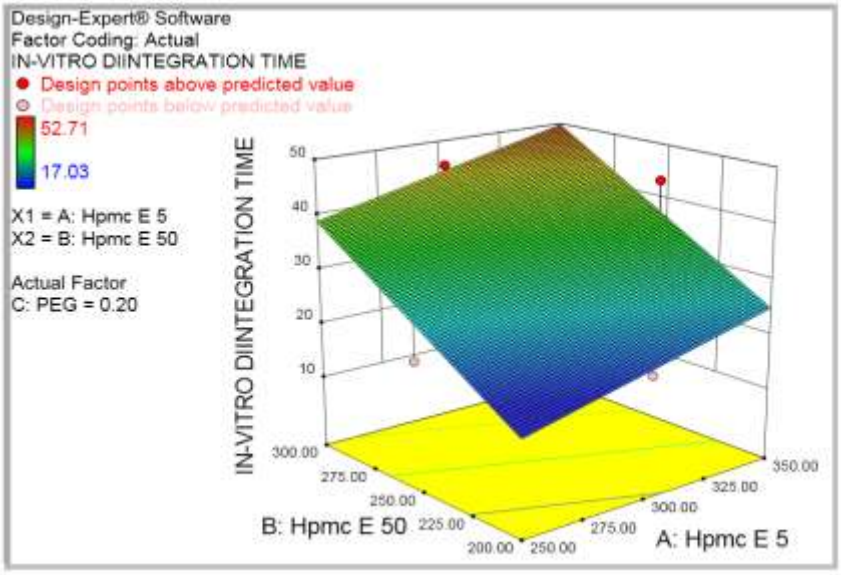

Figure 7: Response surface plot (3D) for *in-vitro* disintegration time

RESPONSE 3: %Moisture absorption (%)

Table 13: Model summary statistics

Source	Std Dev.	R-Squared	Adjusted R-Squared	Predicted R-Squared	PRESS
Linear	0.15	0.9892	0.9862	0.9778	0.54(suggested)
2FI	0.13	0.9942	0.9899	0.9750	0.61
Quadratic	0.15	0.9956	0.9875	0.9552	1.09
Cubic	0.033	1.0000	0.9994	0.8675	3.22(aliased)

Table 14: ANOVA for Response Surface Linear Model

Source	Sum of square	DF	Mean square	F value	P value	
Model	24.04	3	8.01	334.73	<0.0001	Significant
A-E5	8.99	1	8.99	375.38	<0.0001	
B-E50	14.81	1	14.81	618.64	<0.0001	
C-PEG	0.24	1	0.24	10.17	0.0086	
Residual	0.26	11	0.024	-	-	
Cor total	24.30	14	-	-	-	

The Model F-value of 334.73 implies the model is significant. Values of "Prob > F" less than 0.0500 indicate model terms are significant The "Pred R-Squared" of 0.9778 is in reasonable agreement with the "Adj R-Squared" of 0.9862. Final equation in terms of coded factors %Moisture absorption = **+5.11+0.95*A+1.22*B+0.16*C**

Final equation in terms of actual factors % Moisture absorption=-**6.97300+0.018960*HpmcE5+0.024340*HpmcE50+1.56000*PEG**

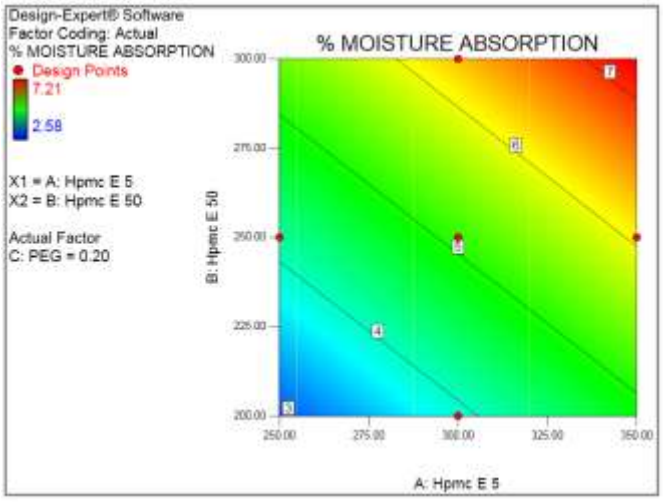

Figure 8 : Contour polt for %Moisture absorption

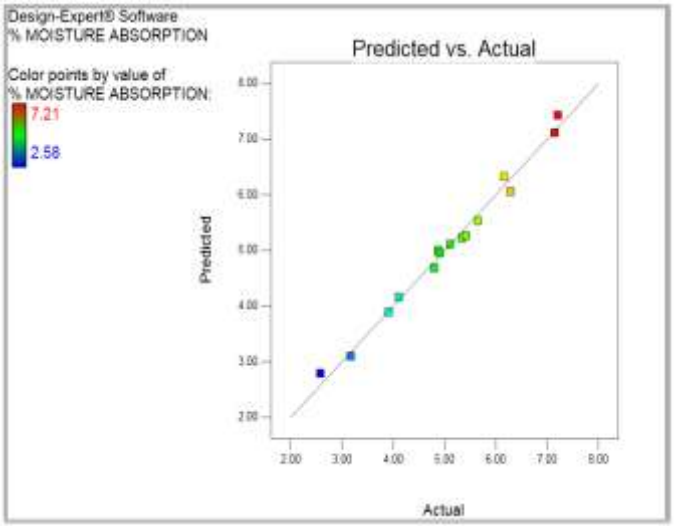

Figure 9: Predicted v/s Actual plot for %Moisture absorption

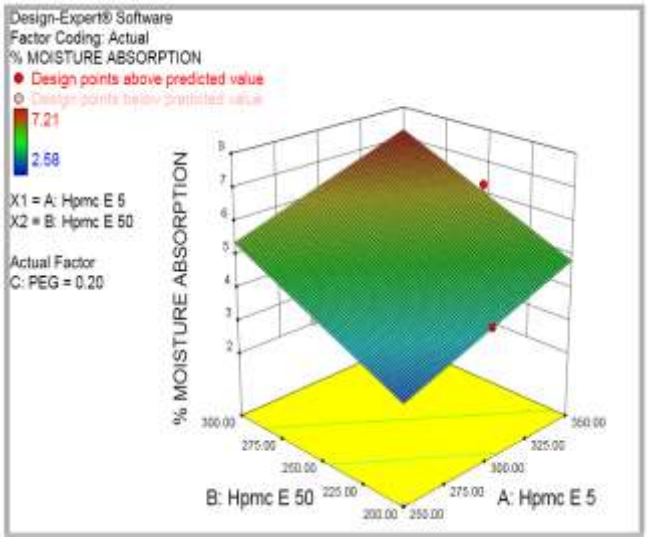

Figure 10: Response surface plot (3D) for %Moisture absorption

OPTIMIZED FORMULATION

Usign the polynominal equations, the optimized formulation were obtained for the response parameters. In the trial runs the optimized formulation were arrived using numerical optimization in Design Expert Software version 8.0.6.1 (Stat Ease Inc.)

The data for the formulation variable, the response parameter and the constraints placed on them are as follows.

Table 15: Constraints for optimized formula

Constrains	Goal	Lower limit	Upper limit	Predicted solution
HPMC E5 LV	Is in range	-1	+1	250mg
HPMC E50 LV	Is in range	-1	+1	207.99mg
PEG400	Is in range	-1	+1	0.26ml
Citric acid	-	-	-	18.31mg
Sucrose	-	-	-	18.31mg
Pineapple flavour	-	-	-	0.3ml
Water	-	-	-	10ml
T90%	Is in range	90	120	106.832sec
In-vitro disintegration	Is in range	17	30	17 sec
% Moisture absorption	Minimize	2	4	3.22%

***In-vitro* disintegration**

The average of *in-vitro* disintegration time of the optimized formulation was found to be 17.23 ±0.08 sec %Moisture absorption: The % moisture absorption of the optimized formula found on average of three trials is 3.14% ±0.07

***In-vitro* dissolution profile for optimized formula**

Table 16: Dissolution profile for the optimized formulation

Time (sec)	**0**	**15**	**30**	**60**	**90**	**120**
%CDR	**0**	**16.30**	**33.03**	**45.33**	**78.66**	**99.53**

T90% of the formulation is **108.50 sec**

CONCLUSION

Fast dissolving oral films of isosorbide mononitrate were prepared using different polymers like HPMC E5 and HPMC E50 and PEG as a plasticizer by using Design Expert Software 8.0.6.1. Prepared films were subjected to various evaluation parameters such as surface pH, weight uniformity, thickness of strip, % moisture absorption, % moisture loss, swelling index, drug content, *in-vitro* disintegration time, *in-vitro* drug release, stability studies and mechanical properties like folding endurance, tensile strength. By considering parameters (dependent variables) such as T90%, in-vitro disintegration time, % moisture absorption by using aid of

software we get the optimized formula by which we can predict the concentration of polymer and plasticizer by keeping the desirability constant. The films were found to be stable during the testing condition.

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