PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347 - 7881
Research Article

Formulation, Development and Optimization of Fast Dispersible Oral Films of Domperidone Maleate

Krupa Mehta*, Nitu Changoiwala, Sanjay Modi, Mukesh Gohel, Rajesh k. Parikh,
Department of Pharmaceutics,
L. M. College of Pharmacy,
Navrangpura, Ahmedabad, Gujarat, India
*krupa_mehta_21@yahoo.com

ABSTRACT

Objective: To Formulate, Develop and Optimize fast dispersible oral films of Domperidone maleate.
Materials and Methods: Fast dispersible films of Domperidone maleate were prepared using solvent casting method. Films were formulated using HydroxyPropylMethylCellulose (HPMC-E5) as a film forming agent, PEG-400 as a plasticizer. A 3^2 full factorial design was applied systematically to optimize the drug release and folding endurance. The concentration of HPMC-E5 (X1) and concentration of PEG-400 (X2) were selected as independent variables.
The Percentage Drug Release in 5 minutes (Y1) and Folding endurance (Y2) were selected as dependent variables. The prepared films were evaluated for Thickness, Folding endurance, Tensile Strength, Disintegration time, In vitro drug release and Drug content uniformity. DSC studies were conducted for drug-excipient interactions.
Results: Films prepared were found to be of good quality fulfilling all the requirements. Regression analysis and numerical optimization were performed to identify the best formulation. Formulations F10 prepared with 2.7% HPMC-E5 and 20% PEG-400 was found to be the best formulation with 96% Drug release in 5 minutes and folding endurance 24.
Discussion: X_1 and X_2 significantly affected the Percentage Drug Release in 5 minutes (Y1) and Folding endurance (Y2). Percentage Drug Release decreased as the concentration of HPMC-E5 and PEG-400 increased. Folding endurance increased as the concentration of HPMC-E5 and PEG-400 increased.
Conclusions: Fast dispersible films of Domperidone maleate were successfully formulated by Solvent casting technique with immediate onset of action & improved patient compliance

KEYWORDS: Solvent casting, 3^2 Factorial Design, HPMC-E5, PEG-400, Drug Release, Folding Endurance

INTRODUCTION

Fast dispersing film, a new drug delivery system for oral delivery of drugs consists of a very thin oral strip, which releases the active ingredient immediately after the uptake into the oral cavity. The delivery system is simply 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 oromucosal absorption or with formula modifications, will maintain the quick-dissolving aspects and allow for gastrointestinal absorption to be achieved when swallowed[1]. Fast Dispersing Films are a convenient way to deliver active pharmaceutical ingredients to the patient because they are easier to swallow. No water is

How to cite this article: Mehta K, Changoiwala N, Modi S, Gohel M, Parikh R, Formulation, Development and Optimization of Fast Dispersible Oral Films of Domperidone Maleate, PharmaTutor, 2013, 1(2), 75-87

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347 - 7881

needed for the filmstrips to dissolve, so it can be taken any time anywhere[2]. Such new drug delivery systems thus have been designed keeping in view the problems faced by pediatrics and geriatrics having difficulty in swallowing or chewing solid dosage forms[3].

It offers several advantages with respect to its administration without water, accurate dosing, easy manufacturing, ease of handling and administration and a pleasant taste.[4-5] "Quick Dissolving Film" for oral mucosal delivery overcomes the shortfalls of conventional fast-dissolving intraoral tablets. Films can be produced with manufacturing process that is competitive with the manufacturing costs of conventional tablets. Thus it allows children, elderly, and the general population to take their medications discretely wherever and whenever needed, satisfying an unmet need. Since the absorption is taking place directly from the mouth, so, bioavailability of the drug increases[6]. This type of drug delivery is becoming popular day by day due to its numerous advantages.

Fast dispersing films should be stiff, flat, and should not curl on the edges. For consumer acceptance, the water soluble film strip should be tough enough so that there won't be any damage while handling or during transportation[7]. The robustness of the strip depends on the type and concentration of polymer[8]. The strip must also dissolve readily in order to deliver the API rapidly when placed on the tongue, so that a gummy texture is avoided. Mechanical property of quick dissolve film is as important as its solubility rate. The most important component in the film matrix, which can achieve these characteristics, is to choose the correct polymer system. Careful balancing of the mechanical properties and solubility rate for the film strip is required which depends on the polymer matrix employed to design fast dispersing films.

HPMC forms transparent, tough and flexible films from aqueous solutions[9,10]. There is inverse relationship between mechanical properties and solubility rate for HPMC[11,12], therefore these two properties must be carefully balanced when designing, so that the stiff film strip can be efficiently cut to size, and filled into unit-dose packaging while still having rapid dissolution. By using optimum amount of water soluble film formers and plasticizer, it is possible to prepare fast dispersing films of Domperidone with acceptable mechanical strength and rapid disintegration.

Domperidone maleate is indicated for treatment of nausea and vomiting[13]. It is described as a first line treatment for nausea in Parkinson's disease. It is antiemetic of choice in acute migraine. It is also used in non ulcer dyspepsia. It is used in patients with dysmotility. Domperidone maleate is white solid with molecular weight of 542.0 g/mol[14]. It is very slightly soluble in water[14].

The objective of the present study was to develop fast dispersible taste masked oral films of Domperidone maleate. Films were formulated using HPMC E5 as a film forming agent, PEG-400 as a plasticizer, Polysorbate 80 as surfactant, menthol as flavoring agent and Neotame as sweetening agent.

MATERIALS AND METHODS

Materials:

Domperidone maleate was obtained from Cadila Pharmaceuticals, India. HPMC E5 was obtained from Signet Chemicals, Mumbai. PEG-400 was obtained from Burgoyne Urbidges & co. Menthol was obtained from Raj Shah Pharmaceuticals. Neotame was obtained from Kawarlal & Co., Chennai and Polysorbate 80 from SD'S Chem Lab, Mumbai. All other solvents and reagents used were of analytical grade.

Method:

Spectroscopic Analysis of Domperidone maleate:

In the present investigation, Domperidone maleate has been estimated by UV/Visible Spectrophotometry. The drug release study was

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347 - 7881

carried out using simulated saliva (pH 6.8) as the dissolution medium.

Preparation of Standard Curve:

- For preparation of stock solution, the drug Domperidone maleate (100 mg) was dissolved in 100 ml of simulated saliva to obtain a solution 'A' (1000 µg/ml). The 10 ml of solution 'A' was diluted to 100 ml with simulated saliva to get solution 'B' (100 µg/ml).
- The 1 ml of the stock solution was diluted to 20 ml using simulated saliva (5 µg/ml).
- Aliquots of 2, 3, 4, 5, 6, 8, 10, 15, 20 ml of the stock solution were serially diluted with simulated saliva to 20 ml to get 10, 15, 20, 25, 30, 40, 50, 75, 100 µg/ml concentrations respectively.
- The absorbance of each solution was measured at 287 nm against simulated saliva as a blank. λmax of Domperidone maleate in simulated saliva is found to be at 287nm.
- The assay was performed in triplicate and average absorbance was considered.

Formulation of Domperidone maleate Fast Dispersible films:

Preliminary studies were carried out to optimize a suitable polymer and plasticizer system and to obtain films of desirable mechanical property and dissolution characteristics.

In order to investigate the effect of formulation variables on the response variables, and to predict an optimized formulation, a 3^2 factorial design was adopted. List of Independent variables and Dependent variables are mentioned in Table1.

Selection of levels for independent variables:

3 levels selected: High, Medium and Low for both the independent variables, summarised in Table 2. The concentration of HPMC E5 (X_1) and PEG-400 (X_2) were selected for different levels, on the basis of the preliminary work done on the formulation of fast dispersing films of Domperidone maleate. Nine batches were prepared as per the design layout shown in the Table 3.

Procedure for preparation of films:

Films of single polymer and their combinations were prepared by solvent casting method. The polymer (HPMC E5), optimized amount of plasticizer (PEG-400), optimized amount of sweetener (Neotame), flavor (Menthol) and surfactant (Tween80) were dissolved in 20ml distilled water.

The aqueous solution was stirred for 5min using magnetic stirrer and was kept undisturbed till the entrapped air bubbles were removed. Drug was dissolved in optimum amount of ethanol. The drug solution was added to the aqueous solution.

The final solution was casted in a petridish having 63.59 cm^2 surface area and was dried at controlled room temperature. The film took approximately 48 hr to dry at controlled room temperature. The dried film was carefully removed from the petridish and was cut into size required for testing. The films were stored in airtight plastic bags till further use.

RESULT

Spectroscopic Analysis of Domperidone maleate:

Equation of the regression line from (Figure 1 & Table 4 & 5):

Absorbance= (0.011*Concentration) + 0.0408

R^2 = 0.9999021

Slope of the Regression Line = 0.011

Intercept of the Regression Line = 0.0408

Drug-Excipient Compatibility Studies:

Differential scanning calorimeter (DSC) allows the fast evaluation of possible incompatibilities, because it shows changes in the appearance, shift or disappearance of melting endotherms and exotherms, and/or variations in the corresponding enthalpies of reaction. The DSC

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347 - 7881

thermograms of pure drug and drug with polymer were recorded. The samples were separately sealed in aluminum cells and set in Perkin Elmer (Pyris 1) DSC (Waltham, MA). The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10°C/min over a temperature range of 50°C to 300°C.

Domperidone maleate showed a sharp endothermic peak that corresponds to its melting range as shown in Figure 2. The DSC of the blend of Domperidone maleate- HPMC E5 is shown in Figure 3.

Measurement of *in vitro* disintegration time[15]

The *in vitro* dissolving time was measured (n=3) for film of each batch in 20 ml of simulated saliva (pH 6.8). Film sample (2 cm x 2 cm) was placed in 20 ml of simulated saliva. The medium was kept mildly agitated using a magnetic stirrer. The time for complete dissolution of the film was recorded as dissolving time. The average of three measurements was taken into consideration.

Result of disintegration time of prepared films is shown in Table 6.

Measurement of Mechanical Properties[16,17]

The measurement of mechanical properties gives an indication of the strength and elasticity of the film. A suitable film should have a relatively moderate tensile strength, high % elongation at break but a low elastic modulus. The polymer should give soft but tough film.

Tensile strength is the maximum stress applied to a point at which the film specimen breaks. The tensile strength (TS) can be calculated by dividing the maximum load by the original cross-sectional area of the specimen and it is expressed in force per unit area (kg/cm^2).

$$\text{Tensile Strength (kg/cm}^2\text{)} = \frac{\text{Force at break (kg)}}{\text{Initial cross sectional area of the sample (cm}^2\text{)}}$$

Mechanical properties of film were evaluated using universal testing machine (Instrument: Shimadzu AG-100kNG and Software: Winsoft Tensile and Compression Testing). Film strip with dimension 10 mm x 10 mm and free from air bubbles or physical imperfections was held between two clamps positioned at a distance of 10 mm. During measurement, the strip was pulled at a speed of 5 mm/min. The values of mechanical properties were recorded when the film broke. Results from film samples, which broke at and not between the clamps, were not included in calculations. Measurements were run in triplicate for each film. Three mechanical properties namely tensile strength, % strain and elastic modulus of films were evaluated.

Result of mechanical properties of prepared films is shown in Table 6.

Measurement of Folding endurance[18]

Folding endurance was determined by repeatedly folding the film at the same place till it break. The numbers of times the film can be folded at the same place without breaking give the value of folding endurance.

Result of folding endurance of prepared films is shown in Table 6.

Thickness of film

The thickness of each sample was measured using calibrated ocular stage micrometer slide and microscope. Three film samples (2cm×2cm) were cut from three different locations of 63.58cm^2 films and the mean thickness calculated. The film was placed in vertical position supported by two clamps below the lens.

Result of thickness of prepared films is shown in Table 6.

Drug content uniformity

Five film units (2 cm× 2 cm) were cut from the four corners and the central part of the film (n=3). Each film unit was placed in 100 ml of distilled water. The solutions were filtered and

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347 - 7881

analyzed at 287 nm using UV-Visible Spectrophotometer (Model UV-1700, Pharmaspec, UV-Visible Spectroph0tometer, Shimadzu, Japan). The average of five films was taken as the content of drug in one film unit.
Result of Drug Content uniformity of prepared films is shown in Table 6.

***In Vitro* Dissolution Study**[19]

The dissolution study was carried out using USP XXIII paddle apparatus (Model TDT-00T, Electrolab, Mumbai, India), at 37˚C ± 0.5˚C using 250 ml of simulated saliva (pH 6.8) as a dissolution medium. The agitation rate of paddle was 50 rpm. The drug loaded film (2cm× 2cm) was hanged in the dissolution media after fixing one side of the film on 5g weight using two sided adhesive tape. Five ml samples were withdrawn at 1,2,3,4,5 minute time and were filtered through whatman filter paper and analyzed spectrophotometrically at 287nm (Model UV-1700, Pharmaspec, UV-Visible Spectrophotometer, Shimadzu, Japan). An equal volume of the fresh dissolution media, maintained at the same temperature, was added after withdrawing the sample to maintain the volume.
The dissolution profile of all the batches is shown in Table 7.

Short Term Stability Study[20]

Stability study was carried out on optimized formula. All the films were suitably packed in aluminum foil. The films to be tested at room conditions were kept outside in a petridish. At the end of every week the sealed films were opened and evaluated for different parameters.
For films to be studied at room temp. With 75 %RH, clean and dry desiccators were taken and saturated sodium chloride solution was poured inside the desiccators. The holding plate was placed inside and the desiccators were closed properly. The desiccators were allowed to get saturated for 1-2 hrs. This gave the humidity chamber of 75%RH. Then the desiccators were reopened and the aluminum foil sealed fast dispersible films were placed inside and the desiccators were closed. At the end of every week the sealed films were opened and evaluated for different parameters.
The results of stability study are shown in Table 12.

Statistical Analysis:

The mean ± standard deviation of the experiment results were analyzed using one-way analysis of variance by using Sigma Plot software, the results were subjected to multiple regression analysis and the equations were evolved.
Data transformation of a 3^2 Factorial Design is given in Table 8.

Summary output of regression analysis for effect of X1 and X2 on Y1 is shown in Table 9.
Three-Dimensional Response Surface Curve (Contour Plot) for % Drug Release in 5min. Figure4 shows the effect of the concentration of HPMC E5 (X_1) and PEG-400 (X_2) on %Drug Release in 5min. (Y1)
Summary output of regression analysis for effect of X1 and X2 on Y2 is shown in Table 10.
Three-Dimensional Response Surface Curve (Contour Plot) for Folding endurance in Figure5 shows the effect of concentration of the concentration of HPMC E5 (X_1) and PEG-400 (X_2) on Folding endurance (Y2).

DISCUSSION

Drug-Excipient Interaction Studies:

Domperidone maleate showed a sharp endothermic peak that corresponds to its melting range as shown in Figure 2. The DSC of the blend of Domperidone maleate- HPMC E5 as shown in Figure 3 showed a similar characteristic peak with decreased intensity showing drug in combination with the excipient. The results of DSC thermo grams indicate that there was no interaction between Domperidone maleate and HPMC E5 and

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347 - 7881

confirmed the drug-excipient compatibility. Hence, DSC studies did not reveal any significant drug-polymer interaction. Domperidone maleate was found to be compatible with HPMC E5.

Evaluation parameters:

All the prepared films showed acceptable pharmaceutical properties as shown in Table 6.

In –Vitro Drug Release:

From the dissolution profile of all the batches it was found that there was fast drug release at initial state of dissolution as shown in Table 7.

Statistical Analysis:

Data transformation of a 3^2 Factorial Design is given in Table 8. The data transformation simplifies the calculations for model development. The data generated by the experimental design was utilized for drawing contour plot, to obtain an optimized region within the factorial space, and thereby produce an optimized formulation.

Summary output of regression analysis for effect of X1 and X2 on Y1 is shown in Table 9. Coefficients with one factor represent the effect of that particular factor on responses while the coefficients with more than one factor and those with second order terms represent the interaction between those factors and the quadratic nature of the phenomena, respectively. Positive sign in front of the terms indicates synergistic effect while negative sign indicates antagonistic effect upon the responses. For response Y1 reduced mathematical model was evolved omitting the insignificant terms ($p>0.05$) by adopting multiple regression analysis. The main effect X_1, X_2 & polynomial term X_1^2 and were found significant as P value was less than 0.05.

From the eq. of the reduced model as shown, it can be qualitatively concluded that X_1 had the largest antagonistic effect on the response of Y_1, which indicated that X_1 was a more important parameter to regulate percentage drug release, while the antagonistic effect of the X_2 and quadratic term of X_1 was comparatively smaller.

Summary output of regression analysis for effect of X1 and X2 on Y2 is shown in Table 10. For response Y_2 (Folding endurance) reduced mathematical model was evolved omitting the insignificant terms ($p>0.05$) by adopting multiple regression analysis. The main effect X_1 and X_2, were found significant as P value was less than 0.05. The interaction term X_1X_2 and polynomial terms $X_1^2 X_2^2$ was found insignificant as P value was more than 0.05.

Three-Dimensional Response Surface Curve (Contour Plot) for % Drug Release in 5min. in Figure4 shows the effect of the concentration of HPMC E5 (X_1) and PEG-400 (X_2) on %Drug Release in 5min. (Y1). As concentration of X1 and X2 increases, the value of response Y1 decreases and Three-Dimensional Response Surface Curve (Contour Plot) for Folding endurance in Figure 5 shows the effect of concentration of the concentration of HPMC E5 (X_1) and PEG-400 (X_2) on Folding endurance (Y2). As concentration of X1 and X2 increases, the value of response Y2 also increases.

Optimization of the Formulation:

The optimization was performed by superimposing the contour plots of the response Y_1 and Y_2 and locating the region of optimal surface common to both the plots as shown in Figure 6.

The overlay plot of the responses is shown in Figure 7, generates an optimized area, as per the desired criteria. The %Drug release (X1) was set to 95 and the folding endurance (X2) values was set to 25. These specifications satisfy the requirements of fast dispersible films for rapid dissolution and sufficient mechanical strength. Based on these requirements a checkpoint batch was formulated and evaluated (Table 11).

It can be concluded that by adopting a systemic formulation approach, one can reach to an

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347 - 7881

optimum point in the shortest time with minimum efforts.

Short term Stability Studies:

The results of stability study as shown in Table 12, indicates no significant change in the film properties except a slight increase in in-vitro disintegration time. At the end of the one month the film became slightly soft and sticky. The results of stability study indicate the film requires protection from humidity and proper package to prevent water uptake. Hence it can be concluded that the formulated fast dispersible films require the moisture proof packaging.

CONCLUSION

The research work was started with the aim to formulate taste masked fast dissolving oral films of Domperidone maleate for treatment of nausea and vomiting. The need has driven the development of fast dissolving film dosage form to overcome the shortfalls of the conventional as well as the fast dissolving tablets.

Domperidone maleate was selected as a model drug which is an anti dopaminergic drug and widely used orally, rectally or intravenously, generally to suppress nausea and vomiting. Fast dispersible films were prepared with the aim of reducing the lag time and providing faster onset of action.

There is inverse relationship between mechanical properties and solubility rate so by using optimum amount of water soluble film formers and plasticizer; it is possible to prepare fast dispersing films of Domperidone with acceptable mechanical strength and rapid disintegration.

In the preliminary studies, selection and optimization of film forming polymer, plasticizers and sweeteners was done. Films were prepared by Solvent casting technique using HPMC E5 (Polymer), PEG-400 (Plasticizer), Neotame (Sweetener) and Polysorbate 80 (Surfactant). HPMC E5 gave film with required dissolving time and physical characteristics.

A 3^2 full factorial design was applied to investigate the combined effect of the two independent formulation variables (i.e. concentration of HPMC E5 (X_1) and concentration of PEG-400(X_2)) on the dependent variables (%Drug Release in 5minutes (Y1) and Folding endurance (Y2)). Results of the multiple regression analysis revealed that the independent variables significantly affected the dependent variables. Then optimum batch was identified.

Then a Check point batch was formulated using 2.7%w/v HPMC E5 and 20% (of polymer concentration) PEG-400 and 1%w/v Neotame. It gave desired results in terms of 96% Drug Release in 5minutes and Folding endurance 24.

DSC study was done to estimate whether any chemical interaction occurs between drug and polymer. DSC curve of optimized batch retained the characteristic peak of the drug which is an indication of absence of incompatibility between drug and excipient.

The stability study of optimized batch was carried out at room temperature and 75% RH for one month. It showed no statistically significant difference in disintegration time, folding endurance and drug content profile before and after stability study. Study indicated the need of moisture proof packaging for the prepared fast dissolving film.

In conclusion the present study underlines the importance of formulation and processing variables. By using optimum amount of film forming polymers and plasticizers, it is possible to prepare fast dispersible films of Domperidone maleate with acceptable mechanical strength and rapid disintegration, to provide desired drug release property and pleasant mouth feel.

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347 - 7881

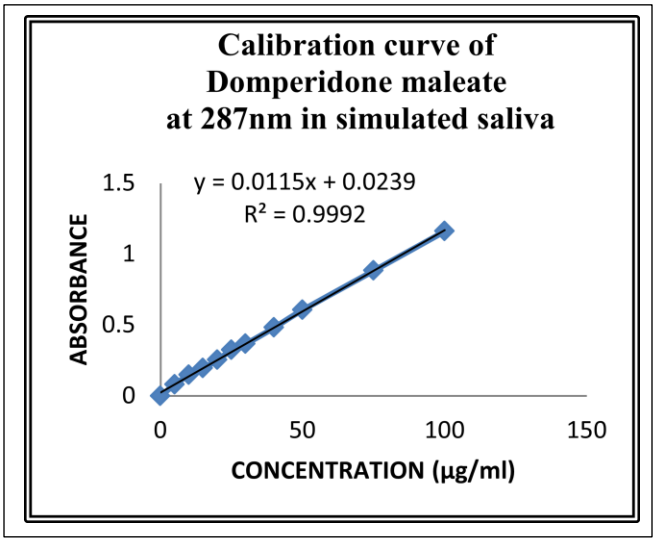


Figure 1: Standard curve of the UV analysis of Domperidone maleate

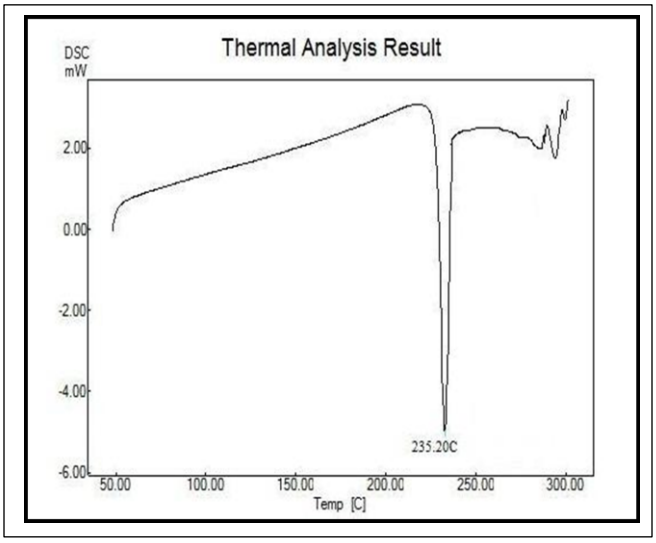


Figure 2: DSC thermogram of Domperidone maleate

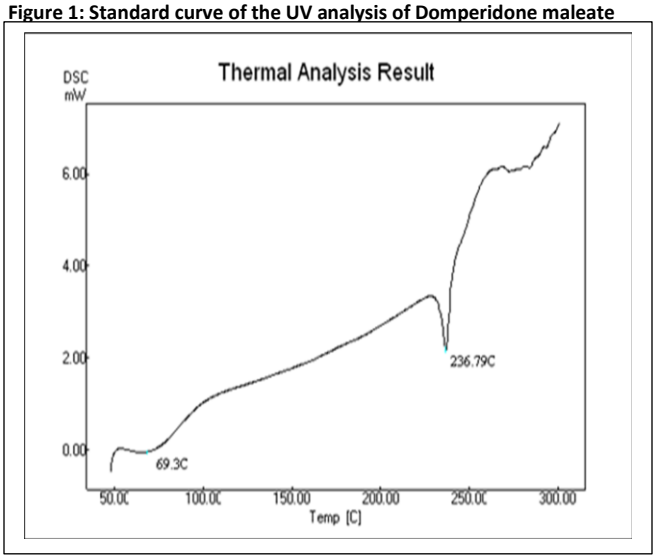


Figure 3: DSC thermogram of a mixture of Domperidone maleate and HPMC E5

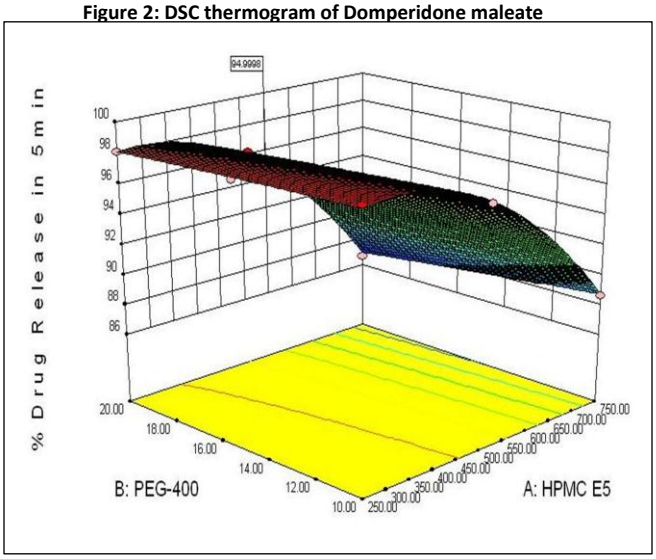


Figure 4: Three-Dimensional Response Surface Curve (Contour Plot) %Drug Release in 5minutes

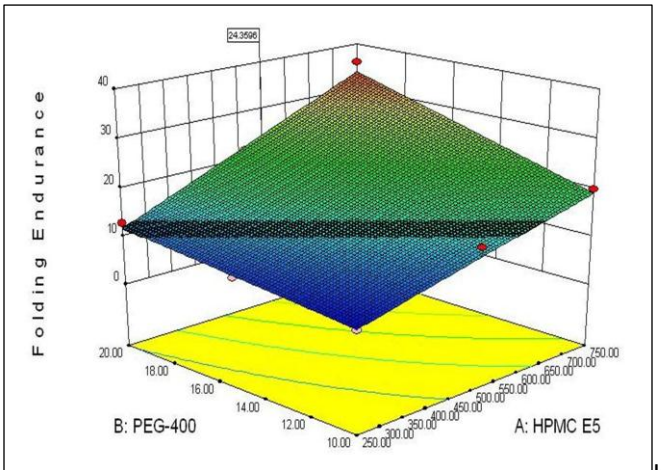


Figure 5: Three-Dimensional Response Surface Curve (Contour Plot) for Folding endurance

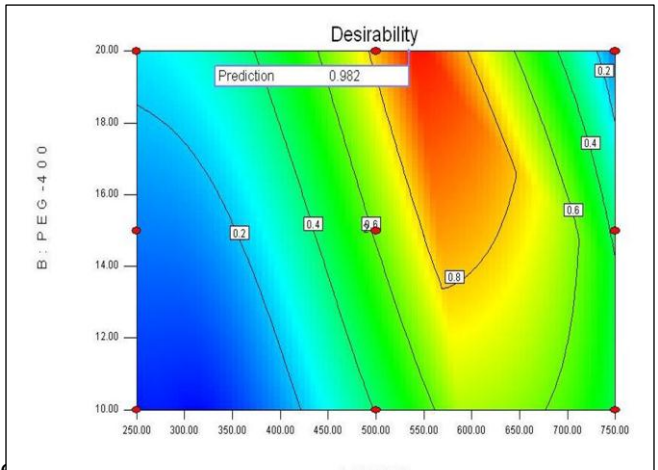
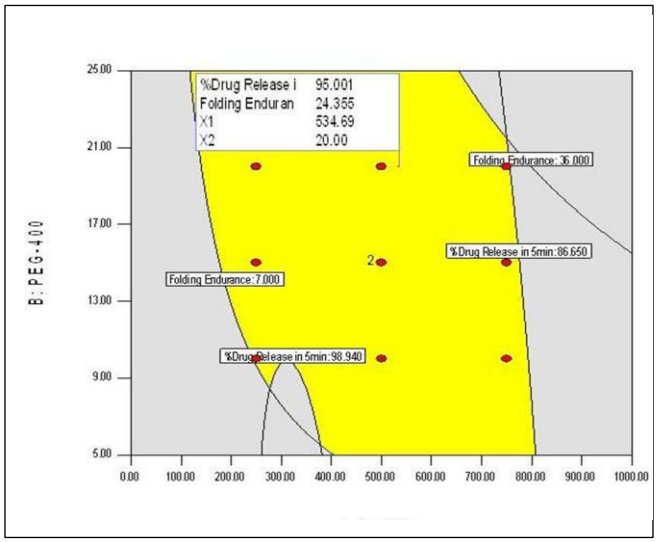


Figure 6: Desirability Plot of Response Variables

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347 - 7881



TABLES:

Table 1: Selection of Independent variables and Dependent variables

3^2 full factorial design			
Independent variables		**Dependent variables**	
X1	X2	Y1	Y2
Concentration of HPMC E5 (mg)	Concentration of PEG-400 (%of Polymer)	%Drug release in 5minutes	Folding endurance

Table 2: Selection of levels for independent variables

Independent Variables	**Levels**		
	Low	**Intermediate**	**High**
	-1	**0**	**1**
X1	250	500	750
X2	10	15	20

Table 3: Design Layout of factorial design batches

FORMULATION INGREDIENTS	**FORMULATION BATCH CODE**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Domperidone maleate(mg)	101	101	101	101	101	101	101	101	101
HPMC E5(mg)	**250**	**250**	**250**	**500**	**500**	**500**	**750**	**750**	**750**
PEG-400(% of polymer)	**10**	**15**	**20**	**10**	**15**	**20**	**10**	**15**	**20**
Polysorbate 80(%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Neotame(mg)	20	20	20	20	20	20	20	20	20
Mint flavour (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Distilled water	20	20	20	20	20	20	20	20	20

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347 - 7881

Table 4: Results of spectrophotometric analysis of Domperidone maleate in Simulated Saliva

Sr. No.	Concentration (µg/ml)	Absorbance			Average Absorbance
		Set 1	Set 2	Set 3	
1	0	0	0	0	0
2	5	0.079	0.081	0.083	0.081
3	10	0.148	0.147	0.149	0.148
4	15	0.195	0.196	0.196	0.196
5	20	0.249	0.253	0.257	0.253
6	25	0.325	0.327	0.323	0.325
7	30	0.368	0.368	0.367	0.368

Table 5: Results of Weighted Regression

Summary Output	
Multiple R	0.999951
R Square	0.9999021
Standard Error	0.00536808
Observations	7
Slope	0.011228
Intercept	0.0407666

Table 6: Evaluation Parameters

TEST PARAMETERS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Thickness(mm) (±0.003)	0.12	0.12	0.14	0.13	0.15	0.15	0.17	0.17	0.18
Folding Endurance	7	9	13	15	17	22	20	24	36
Tensile Strength (kg/cm^2)	0.45	0.51	0.6	4.23	5.67	5.79	8.88	8.74	9.09
Disintegration time (sec)	19	23	24	53	55	59	72	80	85
%Drug release in 5min	98.9	98.3	98.1	96.9	96.4	96.1	88.7	88.3	86.7
Drug content(mg) (±0.005)	4.92	4.94	4.90	4.96	4.99	4.98	4.92	4.94	4.98

Table 7: In - Vitro Dissolution

Batch Code	Time	Absorbance	conc. (µg/ml)	conc. (µg/5ml)	conc. (µg/250ml)	% drug released after 5min
F1	5min	0.240	18.825	94.13	4706.34	98.94
F2	5min	0.239	18.734	93.67	4683.44	98.34
F3	5min	0.238	18.711	93.56	4677.76	98.10
F4	5min	0.236	18.511	92.56	4627.80	96.93
F5	5min	0.235	18.406	92.03	4601.62	96.38
F6	5min	0.235	18.378	91.89	4594.42	96.18
F7	5min	0.218	16.936	84.68	4234.01	88.65
F8	5min	0.217	16.867	84.34	4216.77	88.31
F9	5min	0.213	16.531	82.66	4132.78	86.65

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347 - 7881

Table 8: Data transformation of a 3^2 Factorial Design

BATCH	REAL VALUES		TRANSFORMED VALUES		RESPONSE	
	HPMC E5 (mg)	PEG-400 (% of polymer)	X1	X2	%Drug release in 5min	Folding Endurance
F1	250	10	-1	-1	98.94	7
F2	250	15	-1	0	98.34	9
F3	250	20	-1	1	98.10	13
F4	500	10	0	-1	96.93	15
F5	500	15	0	0	96.38	17
F6	500	20	0	1	96.18	22
F7	750	10	1	-1	88.65	20
F8	750	15	1	0	88.31	24
F9	750	20	1	1	86.65	36

Table 9: Summary output of regression analysis for effect of X1 and X2 on Y1

Regression statistics		
Multiple R	0.998806	
R Square	0.997614	
Adjusted R square	0.993638	
Standard error	0.392164	
Observations	9	
Coefficients		
Coefficient	**Coefficient value**	**P-value**
b_0	96.54	6.12E-08
b_1	-5.295	6.08E-05
b_2	-0.59833	0.033408
b_{12}	-0.29	0.235692
b_{11}	-3.33167	0.001241
b_{22}	-0.10167	0.738229
Equation		
Full Model $Y_1 = 96.54 – 5.295X_1 - 0.59833\ X_2 - 3.33167X_1^{\ 2} - 0.10167X_2^{\ 2} - 0.29X_1X_2$ **(R^2=0.997614)**		
Reduced Model $Y_1 = 96.54 – 5.295X_1 - 0.59833\ X_2 - 3.33167X_1^{\ 2}$		

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347 - 7881

Table 10: Summary output of regression analysis for effect of X1 and X2 on Y2

Regression statistics		
Multiple R	0.99286	
R Square	0.985771	
Adjusted R square	0.962056	
Standard error	1.710534	
Observations	9	
Coefficients		
Coefficient	**Coefficient value**	**P-value**
b_0	16.55556	0.000986
b_1	8.5	0.001194
b_2	4.833333	0.006183
b_{12}	2.5	0.061344
b_{11}	0.166667	0.899131
b_{22}	2.166667	0.171161
Equation		
Full Model $Y_2 = 16.55556+8.5X_1 +4.833X_2 +0.167X_1^2 +2.167\ X_2^2 + 2.5X_1X_2$ **(R^2=0.98577)**		
Reduced Model $Y_2 = 16.55556+8.5X_1 +4.833X_2$		

Table 11: Formulation and Evaluation of checkpoint batch F10

FORMULATION INGREDIENT	**FORMULATION BATCH F10**
Domperidone (mg)	5
HPMC E5 (%w/v)	2.7
PEG- 400 (% of polymer)	20
Polysorbate 80 (%)	0.5
Neotame (%w/v)	1
Mint Flavour (mg)	1.5
Water (ml)	q.s.
EVALUATION	
Thickness (mm) (±0.003)	0.156
Folding Endurance	24
Tensile Strength(kg/cm^2)	5.67
Elastic modulus (kg/cm^2)	52
%Strain	13.6
Disintegration time (sec)	55
In-vitro drug release	99.84% at 1Hr

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347 - 7881

Table 12: Results of short term stability study

No. of weeks	Physical Appearance	Folding Endurance	Disintegration time (sec)	% Drug Content
0	Stable	23	55	97.10
1	No change	23	55	97.10
2	No change	23	57	96.60
3	No change	22	58	96.60
4	Slightly sticky	22	58	96.60

↓ REFERENCES

1. ArunArya et al., Fast Dissolving Oral Films: An Innovative Drug Delivery System and Dosage Form, International Journal of ChemTech Research, CODEN(USA): IJCRGG ISSN : 0974-4290,Jan-Mar 2010, 2(1), pp 576-583
2.Frey.Film Strips and Pharmaceuticals. PharmaMfg&PackagSourcer. 2006:92–93.
3.Slowson M, Slowson S., What to do when patients cannot swallow their medications. PharmTimes.1985;51:90-96
4.Habib W, Khankari RK, Hontz J. Fast dissolve drug delivery systems. Crit Rev Ther Drug Carrier Syst.2000;17:61-72
5.Seager H. Drug delivery products and Zydis fast-dissolving forms. J Pharm Pharmacol. 1998; 50:375–82
6.Behnke K, Sogaard J, Martin S, Bauml J, Ravindran AV, Agren H. Mitrazapine orally disintegrating tablet versus sertraline: A prospective onset of action study. J ClinPsychopharmacol. 2003; 23:358–64.
7.RathiVarun et al. A Brief Review on oral film Technology/ IJRAP 2011, 2(4) 1138-1147
8.Corniello C. Quick dissolving strips: from concept to commercialization. Drug Del Technol 2006, 6(2): 68-71
9.McGinity, J. W., Felton, L. A. An aqueous polymeric coating for pharmaceutical dosage forms , 3rd Ed., New York: Informa Healthcare, 2008
10.Priyanka Nagar, et al. : Insights into Polymers: Film Formers in Mouth Dissolving Films Drug Invention Today ,ISSN: 0975-7619, Review Article , ditonline.info
11.elementoorganika.ru/files/metolose_sr.pdf
12.JafarAkbari et al. "Influence of Hydroxypropyl Methylcellulose Molecular Weight Grade on Water Uptake, Erosion and Drug Release Properties of Diclofenac Sodium Matrix Tablets", Tropical Journal of Pharmaceutical Research, October 2011; 10 (5): 535-541
13.Sweetman S. Martindale "The complete drug reference". 2007,35th ed. Pharmaceu press; 1726-1727
14.Raymond C Rowe, Paul J Sheskey,Sian C Owen; Handbook Of Excipients, 5th Edition, Pharmaceutical Press and American Pharmacists Association, 2006
15.L. Huges and A. Gehris. "A New Method of Characterizing the Buccal Dissolution of Drugs", Rohm and Haas Research Laboratories- Spring House, PA, USA.
16.K.K. Peh, C.F. Wong. "Polymeric Films as Vehicle for Buccal Delivery: Swelling, Mechanical, and Bioadhesive Properties"; Journal Of Pharmacy and Pharmaceutical Sciences, 1999, 2(2), pp 53-61
17.Materials Testing Solutions, instron.com
18.A. Semalty et al., " Design and Evaluation of MucoadhesiveBuccal Films of Diltiazem Hydrochloride", Indian Journal of Pharmaceutical Sciences, 2005, 67(5), pp 548-552
19.H.Okamoto et al., "Development of Polymer Film Dosage Forms of Lidocaine for Buccal Administration: II, Comparison of Preparation Methods", Journal of Pharmaceutical Sciences, 2002, 91(11), pp 2424-2432
20.ICH Harmonised Tripartite Guideline. Stability Testing of New Drug Substances and Products Q1A (R2). Current step 4 version. 2003; 3: 8.