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FORMULATION AND CHARACTERIZATION OF ORAL THIN FILM CONTAINING DOMPERIDONE HYDROCHLORIDE

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ABSTRACT
The aim of the present work was to formulate and characterise oral thin film containing domperidone hydrochloride. To prepare the film, Maltodextrin, Hydroxy propyl methyl cellulose E3LV, Hydroxy propyl methyl cellulose E5LV and Hydroxy propyl methyl cellulose E15LV were used as film-forming polymers by solvent casting method. Propylene Glycol and Glycerine was used as plasticizer, aspartame, and mannitol as sweetener. All prepared films were evaluated for its weight variation, disintegration time, thickness, drug content, pH, dissolution study, and folding endurance. The drug-excipients compatibility study was done using differential scanning calorimetry (DSC) and Fourier transform infrared (FTIR). Satisfactory results obtained when Hydroxy propyl methyl cellulose E5LV was used as film-forming polymer, and the drug was dispersed in the polymer solution using poloxamer 407 as a solubilizing agent. DSC and FTIR studies showed no interaction between drug and the polymers. It can be concluded from the study that the fast-dissolving film can be prepared for poorly water-soluble drug domperidone hydrochloride using Hydroxy propyl methyl cellulose E5LV as a suitable film-forming polymer.

KEYWORDS: Domperidone hydrochloride, Fast dissolving film, Hydroxypropyl methylcellulose E5, Solvent casting method.

INTRODUCTION
Despite so much of advancements in various delivery systems developed for the administration of various drugs through different routes such as oral, parenteral, transdermal, and nasal, the oral route is considered as the most convenient and the preferred route of administration.[1] The oral route of administration still continues to be widely used accepted route, contributing to 50–60% of total drug formulations due to ease of administration, self-medication, and pain avoidance as compared to parenteral.[2] Fast Drug Delivery Systems are rapidly gaining interest in the pharmaceutical industry. These systems either dissolve or disintegrate generally within a minute without needing water or chewing. Fast-dissolving oral thin film offer fast, accurate dosing in a safe, efficacious format that is convenient and portable. It can be placed on the 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 active ingredient.

Domperidone is a peripheral dopamine D_2 and D_3 receptor antagonist. It provides relief from nausea by blocking receptors at the chemoreceptor trigger zone (a location in the nervous system that mediates nausea) at the floor of the fourth ventricle (a location near the brain).[3] It increases motility in the upper gastrointestinal tract to a moderate degree and increases lower esophageal sphincter pressure by blocking dopamine receptors in the gastric antrum and the duodenum. It blocks dopamine receptors in the anterior pituitary gland increasing release of prolactin which in turn increases lactation.[4] It is administered orally, rectally, or intravenously. Domperidone is used to relieve nausea and vomiting; to increase the transit of food through the stomach and to promote lactation by release of prolactin. It is also used in scientific research to study the biological function of dopamine, an important neurotransmitter and hormone, in the body.[5,6] The main objective of the study was to formulate and characterize oral thin film containing domperidone hydrochloride using hydroxypropyl methylcellulose (HPMC E5 and HPMC E15) as film-forming polymers by solvent casting method.

MATERIALS AND METHODS

Materials

The drug Domperidone Hydrochloride was purchased from Ipca Laboratories Ltd., Mumbai, India. Different HPMC grades were purchased from Colorcon Asia Pvt. Ltd., Goa, India. Maltodextrin was purchased from Himedia Laboratories Pvt. Ltd., Mumbai, India.

Methods

Determination of λ_{max}

The standard solution of 100µg/ml was scanned between 400 nm and 200 nm in ultraviolet (UV) spectrophotometer against phosphate buffer solution pH 6.8 as blank after baseline correction.

Calibration curve of Domperidone HCl

Preparation of standard stock solution

100mg of Domperidone HCl was accurately weighed into 100ml volumetric flask and dissolved with phosphate buffer pH6.8. The volume was made up to100ml with the same solution to get a concentration of 1000g/ml (1mg/ml).

Scanning of drug

Ultraviolet spectrum was taken from the stock solution between the wavelengths 200-400nm. It gave a peak at 257.2nm and the same was selected as max. The absorption maxima of Domperidone hydrochloride in pH buffer 6.8 is shown in figure.

Preparation of calibration curve

The stock solution was diluted with pH buffer 6.8 to get a concentration range of 100 to 1000 g/ml. Absorbance of these solutions was measured against a blank at 257.2nm using UV visible spectrophotometer (Shimadzu Corporation, Japan), and the absorbance values are summarized in Table. Calibration curve which was plotted against absorbance versus drug concentrations is given in the figure.

Preparation of mouth dissolving film of Domperidone HCl[7,8]

Calculation of dose of Domperidone HCl

The dose to be incorporated in the film was calculated using the following mathematical equation.

Drug input = Css ×ke × vd

=133 gL-1×0.3465hr-1×2.7 L

=6872.399ghr-1=6.87mg

Here, Css =133 gL^{-}

[1]Vd=2.7L

Ke=0.3465

Where, Css is the concentration at a steady state.

Ke = elimination rate constant.

Vd = volume of distribution.

The dose of Domperidone HCl is 7.17mg. Therefore 7.17 mg dose of Domperidone HCl was required in film containing 4cm^2 areas. Total area of 9.4cm diameter Petri dish was 69.43cm^2 So, the amount of drug present in 69.43cm^2 of Petri dish was 124.42 mg for all formulations. Therefore, the amount of Domperidone HCl in each film (4cm^2) was 7.17 mg.

Preparation of Film by Solvent Casting Method[9,10]

Various methods have been used for film preparation. Among all the methods, solvent casting method was the used to get a good and smooth film. Mouth dissolving film of Domperidone HCl was prepared by the solvent-casting method. Aqueous solution was prepared by dissolving the selected polymers in 25 ml distilled water and was kept for 1hour to remove all the air bubble sent rapped. Then API and plasticizer were dissolved in this polymeric solution. Then the mixture solution was casted as a film on to aplastic petridish and it was dried in the oven at 50°C for 24 hour. The film was carefully removed from the petridish, checked for any imperfections. The samples were wrapped in butter paper and aluminium foil and stored in a desiccator until further analysis.

Experimental design

Simplex Centroid Design

The application of simplex centroid experimental design is well documented in pharmaceutical literature. They are particularly appropriate in formulation optimization procedures where the total quantity of ingredients under consideration must be constant. In the films, the total amount of polymer, if changed, can lead to a large extent change in the mechanical properties of film, so simplex centroid is the appropriate design to be applied to the film formulation. A polynomial first order linear inter active model may be evolved using the values of dependent and independent variables.[11]

$Y = B_1X_1 + B_2X_2 + B_3X_3 + B_{12}X_1X_2 + B_{23}X_2X_3 + B_{13}X_1X_3 + B_{123}X_1X_2X_3$

Where, Y is the response parameter and B is are estimated coefficients for the factors Xi. The main effects (X_1, X_2 and X_3) represent the average result so changing one factor at a time from it slow to high value. The interaction terms (X_1X_2, X_2X_3, X_1X_3, $X_1X_2X_3$) show how the response changes when two or more factors are simultaneously changed.

Table: Independent variables and their respective levels.

Independent variables	0	0.33	0.5	1
HPMCE5 (X1)	217	250	267	317
HPMCE15 (X2)	150	183	200	250
Maltodextrin (X3)	300	333	350	400

Table: Simplex Centroid Design.

Formulations*	CODED VALUES			ACTUAL VALUES (mg)		
	X_1	X_2	X_3	X_1	X_2	X_3
F1	1	0	0	317	150	300
F2	0	1	0	217	250	300
F3	0	0	1	217	150	400
F4	0.5	0.5	0	267	200	300
F5	0.5	0	0.5	267	150	350
F6	0	0.5	0.5	217	200	350
F7	0.33	0.33	0.33	250	183	333

Other common ingredients used for each formulation

Other ingredients that have been used include propylene glycol, 0.5ml, as plasticizer and brilliant blue as color. Glycerin was used for the lubrication of petridish so as to facilitate smoother peeling of the film.

Evaluation Parameters for Prepared Films

Thickness Measurement

The thickness of the Mouth dissolving film(2×2cm2) was determined by using as crew gauge. The thickness of each film at three different places was determined and standard deviation was also calculated.[12,13]

Drug Content Uniformity

Mouth dissolving film of size 4cm2 was cut into small pieces and transferred in to a graduated glass stoppered flask containing 10mL of 6.8 pH phosphate buffer. The flask was kept for 24hrs. The solution from the flask was filtered through what man filter paper and the amount of drug present was determined by UV spectrophotometric method at 257.2nm wavelength.[14,15]

Weight Variation

Three films of size (2×2cm2) from all batches of mouth dissolving film were weighed on an electronic balance (CitizonCY220C, Mumbai, India) and the average weight and standard deviation was calculated.[16]

Tensile Strength

Mechanical properties of the polymeric mouth dissolving film were conveniently determined by measuring their tensile strength. The tensile strength of the mouth dissolving film was determined using handmade tensile strength instrument. The mouth dissolving film was fixed to the assembly, the weights required to break the film were noted. Tensile strength was calculated using the following formula.[12]

$$T.S. = break\ force / A \quad (1)$$

Where, A=cross sectional area of the film

Percentage Elongation

Percentage elongation was calculated by measuring the increase in length of the film after tensile strength measurement using the following formula. [13,14]

$$\text{Percentage elongation} = (L_F - L_O)/L_O \times 100 \quad (2)$$

Where, L_F = final length, L_O= initial length

Moisture Content (%)

This test was also carried to evaluate the integrity films at dry condition. Film of $4cm^2$ was cut out and weighed accurately and kept in a desiccator containing fused anhydrous calcium chloride. After 24h the film was removed and weighed. Percentage moisture content of film was determined as follows.[10,17]

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight} \times 100}{\text{Initial weight}} \quad (3)$$

% Moisture Uptake

Formulation was exposed to an atmosphere of 84% RH at 28°C for three days using a saturated solution of NaCl. After three days the films were removed, weighed and percentage moisture absorbed was calculated. Average percentage moisture absorption of each film was calculated using the following formula

$$\% \text{ Moisture uptake} = \frac{\text{Final weight} - \text{Initial weight} \times 100}{\text{Initial weight}} \quad (4)$$

***In-vitro* Disintegration Time**

The test was performed using the same method as mentioned by Setouhy *et al*. with slight modification. The film size required for dose delivery(2×2cm) was placed on glass petri dish containing 10mL of distilled water. The time required for breaking of film was noted as in-vitro disintegration time.[18,19,20]

In-vitro Dissolution study

The test was performed using the same method as mentioned by Dinge *et al*. with slight modification. A film of $4cm^2$ was placed in a glass petridish and 25mL of dissolution medium (phosphate-buffered saline pH6.8) was added. Stirring speed of 100rpm was selected for dissolution of all the batches. Aliquot of 2.5ml was withdrawn and replaced with equal volumes of pH buffer 6.8 at regular intervals of 1,2,3,4,5,7.5 and 10 minutes. The collected samples were filtered through Whatman filter and the concentration of the dissolved Domperidone HCl was determined at appropriate wavelength using the UV-Visible spectrophotometer.[21,22]

Folding Endurance

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

computed as the folding endurance value.[18,19,20]

Stability Study

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-life. ICH specifies the length of study and storage conditions.[23,24]

Method

The sample was wrapped in aluminium foil and subjected to stability studies as per the International Conference on Harmonization (ICH) guidelines. After that, they were held in a stability chamber at 40°C/75°F for 3 months and tested for their physical appearance, drug quality, in-vitro disintegration duration, and drug release at 1-month intervals, with the findings being released.

RESULT AND DISCUSSION

λ_{max} for pure Domperidone hydrochloride in phosphate buffer solution pH 6.8

The max of drug was determined by scanning1000g/ml concentration solution prepared with pH6.8 buffer in the range 200-400 nm using double beam UV visible spectrophotometer. Max was found to be 257.257nm (figure). So, further studies were carried out in UV spectrophotometer at 257.2 nm.

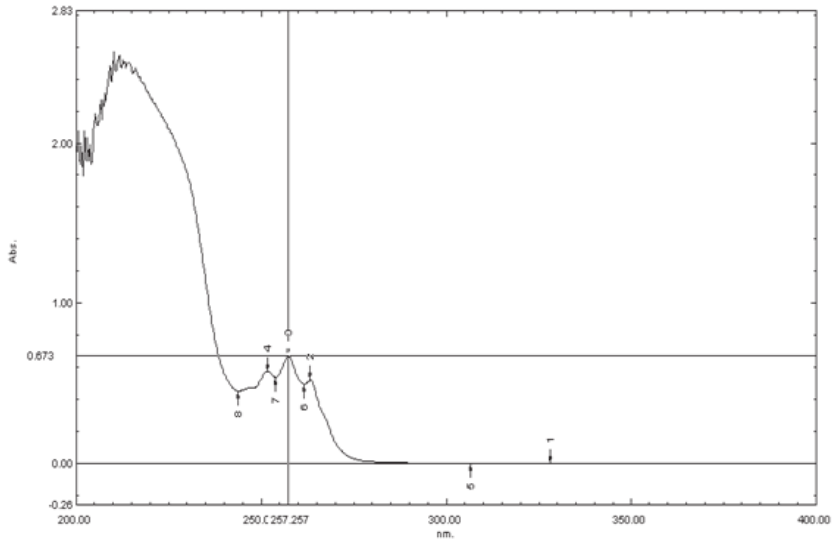


Figure: Absorption maxima of Domperidone HCl in pH 6.8 phosphate buffer.

Calibration curve of Domperidone Hydrochloride

Calibration curve of Domperidone Hydrochloride was taken in 6.8 phosphate buffer at 257.2 nm. The absorbance values (mean of three determinations) with their standard deviation at different concentrations in the range of 100-1000g/ml is given in Table and their Calibration curve were given in Figure respectively. The Drug was found to obey Lambert Beer's law with regression coefficient (R2) values 0.9991 in 6.8 phosphate buffer. The regression equations for 6.8 phosphate buffer were y = 0.0007 x 0.0009, which can further be utilized for the calculation of amount of drug.

Table 6.1: Calibration data of drug in pH 6.8phosphate buffer at 257.2nm.

Concentration(µg/ml)	Absorbance			Mean absorbance*
	I	II	III	
0	0	0	0	0
100	0.056	0.084	0.068	0.0693±0.014
200	0.119	0.140	0.131	0.13±0.013
300	0.186	0.214	0.205	0.2017±0.014.
400	0.251	0.289	0.271	0.2703±0.019
500	0.327	0.369	0.349	0.3483±0.021
600	0.402	0.443	0.414	0.4197±0.021
700	0.456	0.485	0.471	0.4707±0.014
800	0.544	0.559	0.552	0.5517±0.017
900	0.602	0.649	0.623	0.6247±0.023
1000	0.664	0.682	0.673	0.673±0.014

*Results are shown in mean±S.D.(n=3)

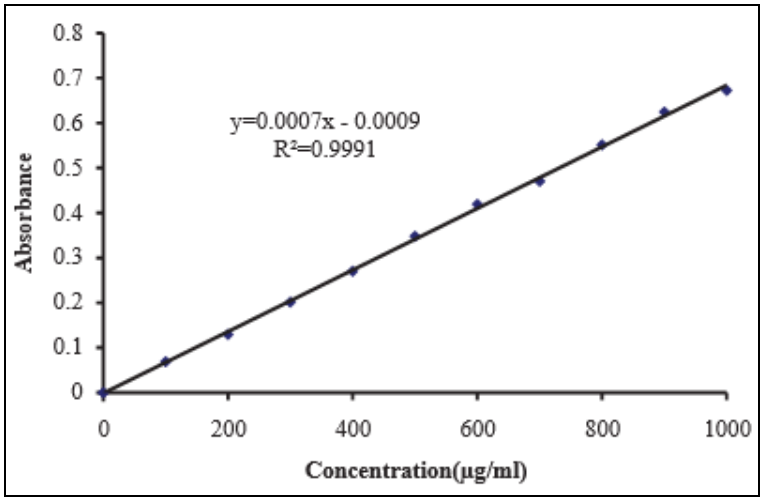


Figure: Standard Curve of Domperidone HCl in pH 6.8 phosphate buffer.

FTIR and DSC Study

Compatibility studies were performed using FTIR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied by making a KBr disc. The characteristic peaks of Domperidone Hydrochloride were obtained at different wave numbers in different samples.

The spectra for all formulations are shown below

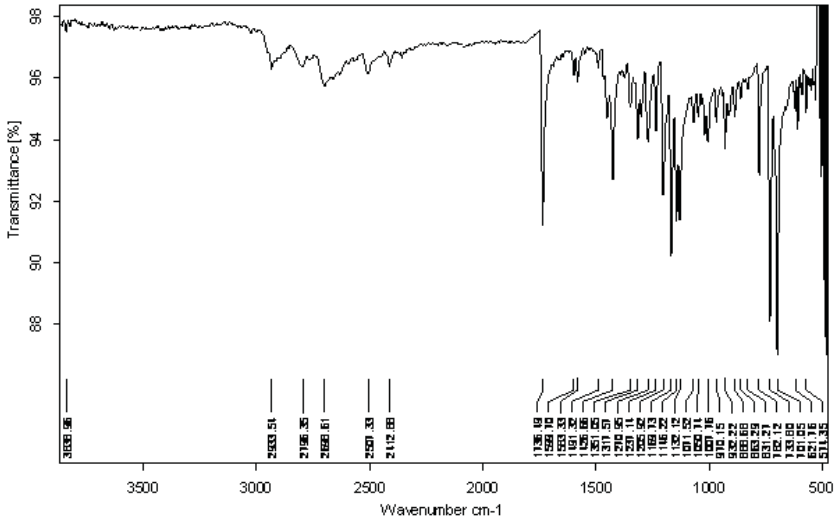


Figure: FTIR spectrum of pure Domperidone Hydrochloride.

In the above spectrum the characteristic (principal) peaks of Domperidone hydrochloride are seen which are as follows.

Table: FTIR characteristic (principal) spectral details.

Pure Domperidone Hydrochloride	Stretching
701733	Mono substituted Benzene
1599	Aromatic Stretch
2412-2698	Second Arty Amine Salt
1736	C=O Stretch
1146-1169	C-O Stretch

FTIR spectra of Domperidone Hydrochloride+ HPMCE5 exhibitedpeaksat711cm-1(Mono substituted Benzene), 1593cm-1presence of (Aromatic Stretch),2411-2681cm-1(Secondary Amine Salt),1756cm-1(C=O Stretch),1182-1201cm-1(C-O Stretch). Here, all the principal peaks exhibited din range. FTIR spectra of Domperidone Hydrochloride+ HPMCE 15 (Figure5.5) exhibited peaks at 699cm-1(Mono substituted Benzene), 1592cm-1 presence of (Aromatic Stretch), 2411-2588 cm -1(Secondary Amine Salt), 1745cm -1(C=O

Stretch),1110-1210 cm^{-1}

All the characteristic peaks are present in the spectrum of drug-polymer mixture and the formulation. This indicates that the drug is compatible with the formulation components.

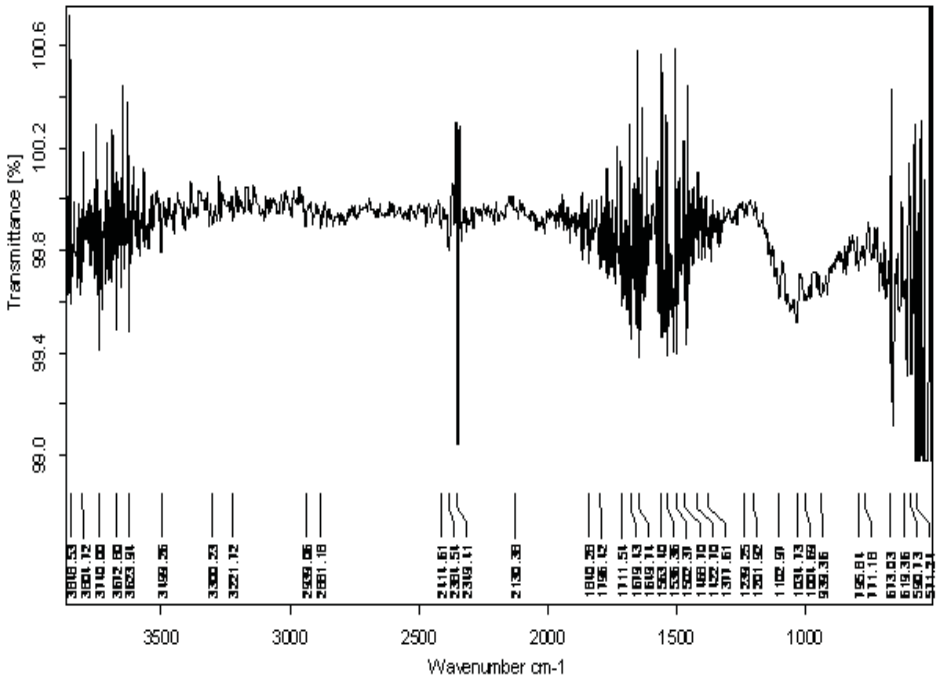


Figure: FTIR Spectrum of Domperidone HCl + HPMC E5.

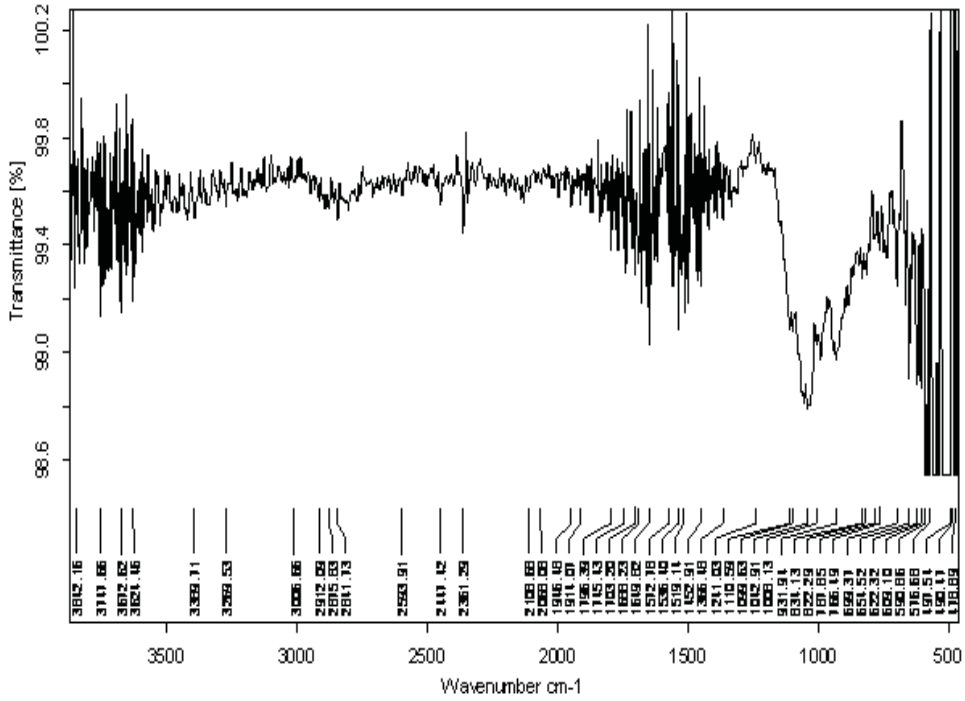


Figure: FTIR spectrum of Domperidone HCl + HPMC E15.

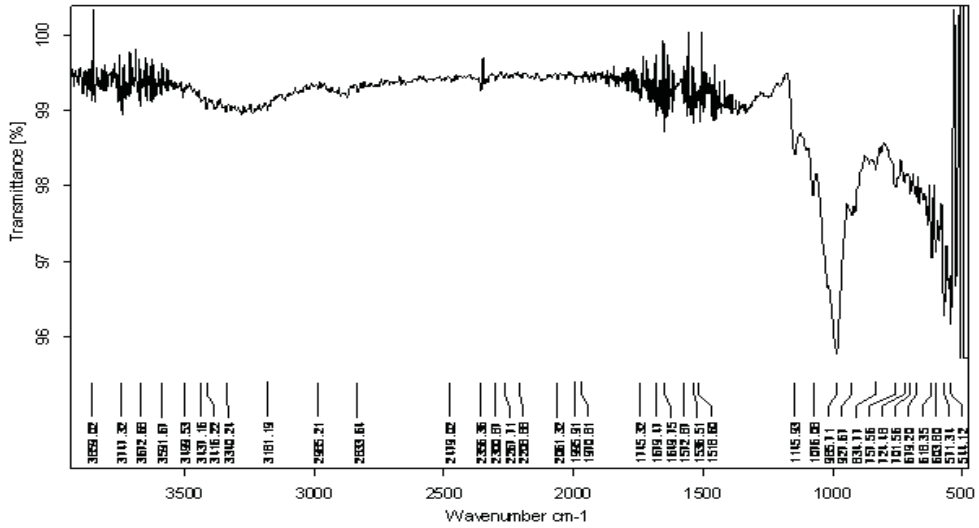


Figure: FTIR Spectrum of Domperidone HCl+ Malt dextrin

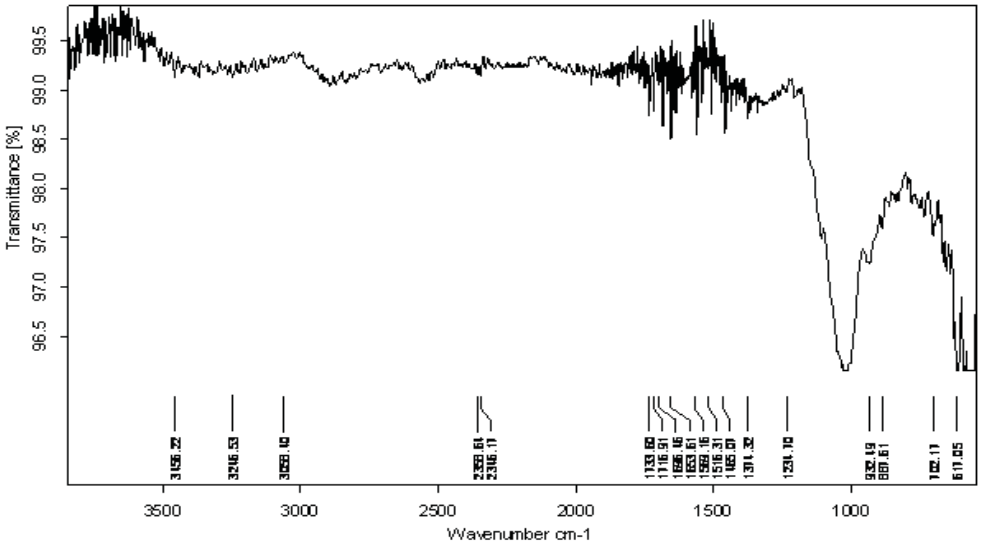


Figure: FTIR of Mouth Dissolving Film Formulation

Differential Scanning Calorimetry (DSC)

The DSC thermogram of Domperidone Hydrochloride exhibited an endothermic peak at 229.41°C corresponding to its melting point. The DSC thermograms of Domperidone Hydrochloride with other excipients does not show profound shift in peaks (229.41°C) which indicates compatibility. The DSC thermogram of the individual drug and final formulation show in figures.

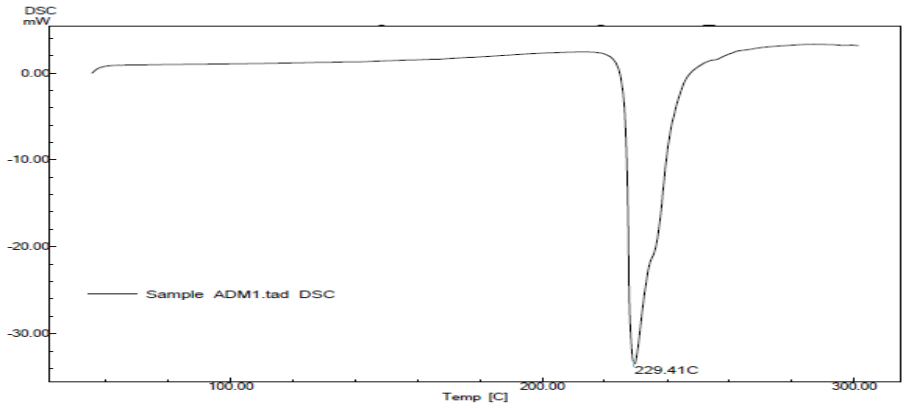


Figure: DSC of pure drug.

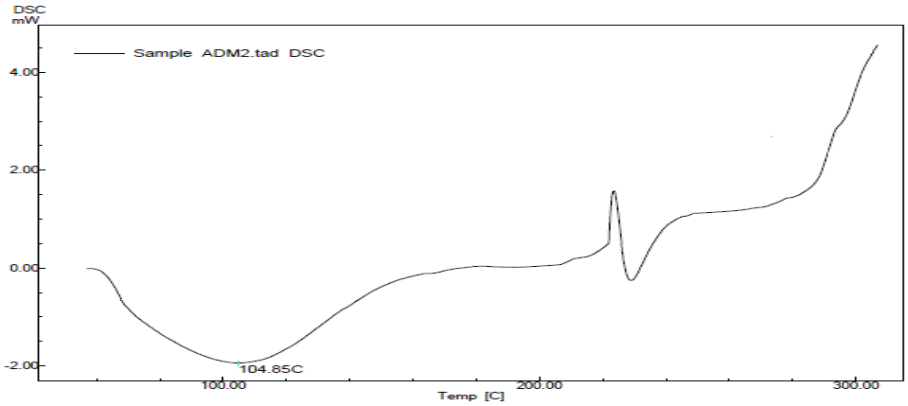


Figure: DSC of formulation.

Experimental Design

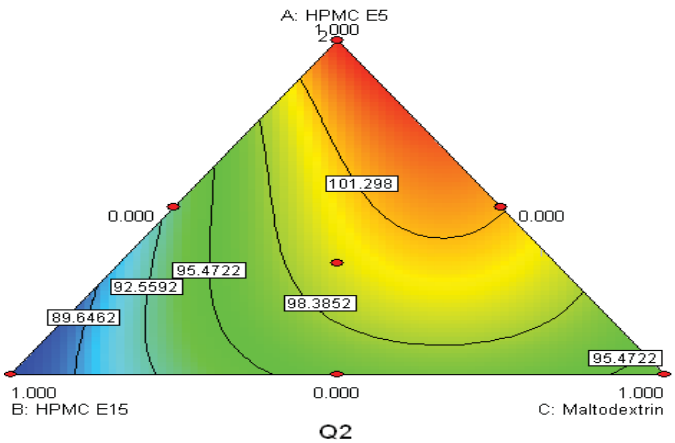
Simplex Centroid design is a mixture design, often been applied to optimize the formulation variable switch basic requirement of understanding interaction of independent variables. Preliminary investigations of the process parameters revealed that factors like amount of HPMC E5(X1), amount of HPMC E15(X2) and amount of Maltodextrin (X3) showed significant in flounce on amount of drug dissolve in 2min (CPRQ2; R1), disintegration time (R2) and tensile strength (R3) of the drug added fast dissolving film. Hence, they were utilized for further studies. For all 7 batches, all three of the selected dependent variables (X1, X2 and X3) showed a wide variation in disintegration time, amount of drug release in 2 min and tensile strength (Table5.6). The data clearly indicated strong influence of X1, X2 and X3 on selected responses (R1, R2and R3). The polynomial equations can be used to draw conclusions after Considering magnitude of coefficients and mathematical sign it conveys either positive or negative. Results for design batches and its ANOVA are shown below.

Table: Design Summary.

Formulation Code	R1	R2	R3
	Q2 min*	Disintegration time(sec)*	Tensile strength(N/cm^2) *
F1	104.44±2.91	38±0.57	2.7±0.02
F2	97.08±2.89	78±1.15	3.43±0.06
F3	99.80±0.80	35±2.01	2.39±0.03
F4	98.12±1.62	52±2.64	3.1±0.07
F5	101.41±1.89	46±1.73	2.52±0.01
F6	98.86±3.18	63±2.31	2.94±0.04
F7	99.73±1.78	46±2.64	2.84±0.02
F1(R)	103.94±0.27	39±1.52	2.72±0.02

*Results are shown in mean ±S.D. (n=3)
R1:Response1, R2: Response2, R3: Response3

Statistical analysis was carried out in Design Expert software (7.1.5), which suggested that special cubic mode l (SCM) was followed for % drug release at 2 minutes with P-value of 0.0385, this indicated that model was highly significant.



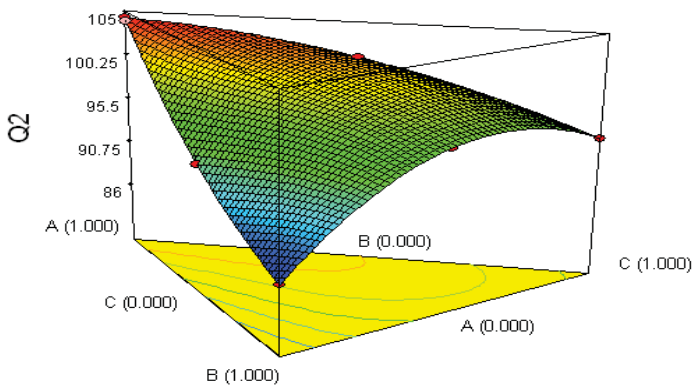


Figure: Contour plot and 3D Surface Plot of CPRQ2 (%) against amounts of HPMCE5, HPMCE15 and Mal to dextrin.

Polynomial equation

R1(CPRQ2) =+104.21*A+86.83*B+94.30*C
9.16*A*B+8.62*A*C+23.53*B*C+55.72*A*B*C

In order to find out contribution of each component and their interaction, Analysis of Variance (ANOVA) for SCM was carried out.

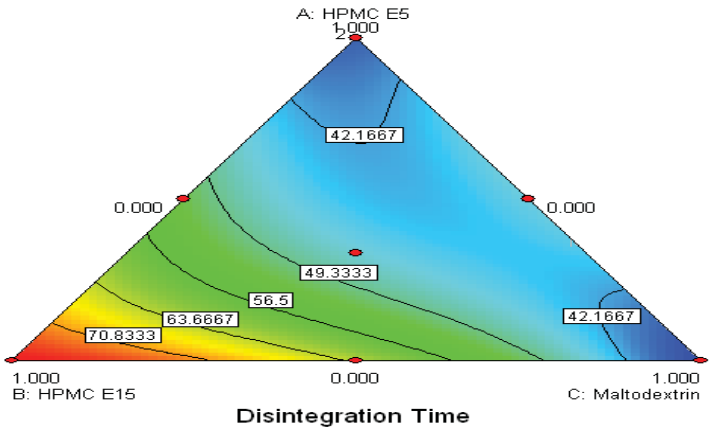
The ANOVA results (Table5.7), contour plot and 3D surface plot for the CPRQ2 (Figure5.15) showed the strong effect of the three factors (amounts of HPMCE5, HPMCE 15 and Mal to dextrin). Polynomial equation of Q2 indicates that the all the three-polymer amount has positive effect on the Q2. In vitro dissolution of the films was found to increase with increase in the amount of the polymer. It was observed that when the amounts of polymer were selected within the limits of the design, in vitro dissolution rate increased to a greater extent with amount of HPMCE5 and increased to a lesser extent in case of Maltodextrin followed by HPMCE15. As per the equation, better release can be achieved with the combination of all the three polymers, rather than combining any two of them.

Response 2: Disintegration Time (R2)

Table: ANOVA for special cubic model (Disintegration time).

Source	Sum of squares	DF	Mean square	F value	Prob>F
Model	1477.38	6	246.23	492.46	0.0345
Linear mixture	1320.95	2	660.48	1320.95	0.0195
AB	28.41	1	28.41	56.82	0.0840
AC	62.23	1	62.23	124.45	0.0569
BC	28.17	1	28.17	56.33	0.0843
ABC	46.86	1	46.86	93.72	0.0655
Pure error	0.50	1	0.50		
Core total	1477.88	7			

Statistical analysis was carried out in Design Experts of two are (7.1.5), which suggested that special cubic model (SCM) was followed for release at T2min with P-value of 0.0385.this indicated that model was highly significant.



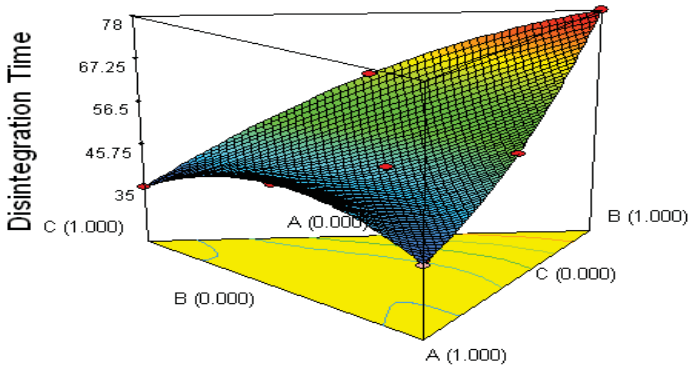


Figure: Contour plot and 3D Surface Plot of disintegration time (seconds) against amounts of HPMCE5, HPMCE 15 and Maltodextrin.

Polynomial equation

R2 (Disintegration Time) =+38.50*A+ 78.00*B + 35.00*C - 25.00*A*B+37.00*A*C+26.00*B*C-235.50*A*B*C

In order to find out contribution of each component and their interaction, Analysis of Variance (ANOVA) for SCM was carried out.

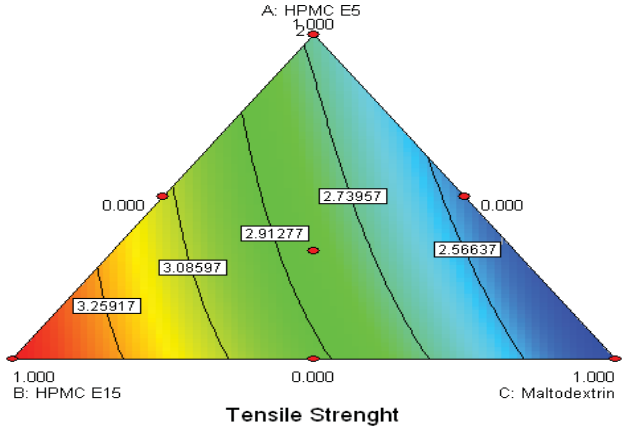
The ANOVA results (Table5.8), contour plot and 3D surface plot for the disintegration time (Figure5.15) showed the strong effect of the three factors (amounts of HPMCE5, HPMCE 15 and Maltodextrin). Polynomial equation of Disintegration time indicates that the all the three-polymer amount has positive effect on the Disintegration time. In vitro disintegration time of the films was found to increase with increase in the amount of the polymer. It was observed that when the amounts of polymer were selected within the lim its of the design, in vitro dissolution ate was decreased the most when more amount of mal to dextrin was used in the formulation and it increase gradually with HPMCE5 followed by HPMCE15. As per the equation, shorter disintegration time can be achieved with the combination of all the three polymers, rather than the single polymer or with the combination of any two of them.

Response 3: Tensile Strength (R3)

Table: ANOVA for special cubic model (Tensile Strength).

Source	Sum of squares	DF	Mean square	F value	Prob>F
Model	0.77	6	0.13	450.86	0.0360
Linear mixture	0.76	2	0.38	1348.51	0.0193
AB	9.924E-004	1	9.924E-004	3.51	0.3122
AC	5.767E-004	1	5.767E-004	2.04	0.3889
BC	5.709E-004	1	5.709E-004	2.02	0.3905
ABC	1.690E-004	1	1.690E-004	0.60	0.5811
Pure error	2.828E-004	1	2.828E-004		
Core total	0.77	7			

Statistical analysis was carried out in Design Expert software (7.1.5), which suggested that special cubic model (SCM) was followed for release at T2min with P-value of 0.0385. this indicated that model was highly significant.



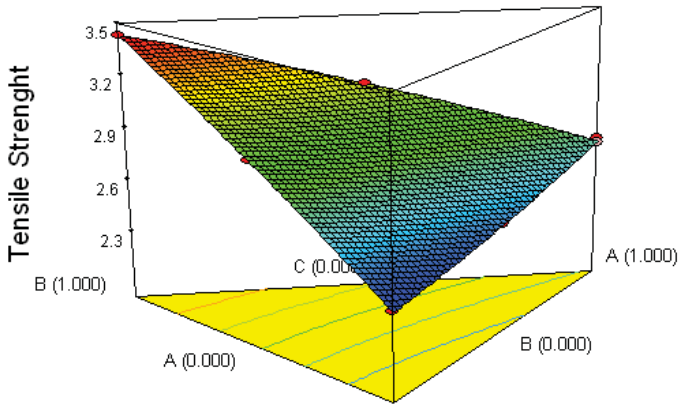


Figure 5.12: Contour plot and 3D Surface Plot of Tensile strength (N/cm2) against amounts of HPMC E5, HPMC E15 and Maltodextrin.

Polynomial equation

R3 (Tensile Strength) = +2.71*A + 3.43*B+2.39*C + 0.15*A*B-0.11*A*C +0.12*B*C-0.45*A*B*C

In order to find out contribution of each component and their interaction, Analysis of Variance (ANOVA) for SCM was carried out.

The ANOVA results (Table5.9), contour plot and 3D surface plot for the tensile strength (Figure5.15) showed the strong effect of the three factors(amounts of HPMCE5, HPMCE 15 and Mal to dextrin). Polynomial equation of Tensile strength indicates that the all the three polymer amount as positive effect on the Tensile strength. It was observed that when the amounts of polymer were selected within the limits of the design, tensile strength was increased when more amount of HPMCE 15 was used in the formulation and it increased to a less exerting in HPMCE5 followed by Mal to dextrin. As per the equation, values of tensile strength were decreased with the combination of all the three polymers.

Evaluation Parameters of film formulation

Weight variation test

The percentage weight variation for all the formulation is tabulated in Table5.10. All the films passed weight variation test as the % weight variation was wit in the pharmacopoeia limits of±7.5%. It was found to be in range of 37±2.081 to 81.67±2.081mg. Films having more amount of Mal to dextrin exhibited higher weight whereas films having HPMCE5 were lighter in weight. The weight of all the films was uniform.

Thickness

The thicknesses of formulated films were found to be in range of 0.103±0.015 to 0.207±0.02mm. The mean values are tabulated in Table 5.10. The values are almost uniform in all formulations. Films containing Mal to dextrin resulted in increased thickness which was required for com for table handling of the film.

Folding Endurance

Folding endurance measures the ability of film to with stand rupture. The folding endurance of the films was determined by repeated l y folding a small strip of the films at the same place till it broke and the average folding endurance of all films was given in Table 5.10. Folding endurance of all the batch estranges from 101±2.645to177.67±3.51. Increase in concentration of polymer increases folding endurance.

Drug content

The drug content and content uniformity test was performed to ensure uniform and accurate distribution of drug. The content uniformity was per formed for all the nine formulations and results are tabulated in Table 5.10. Three trials from each formulation were analyzed on spectrophotometer. The mean value and standard deviation of all the formulations were calculated. The results indicated that in all the formulations the drug content was uniform. The cumulative percentage drug released by each film to the in vitro release studies was based on the mean content of the drug present in the respective film. The ranges of drug content in all the formulations were 95.218% to 98.00%.

Table: Evaluation parameters of experimental design batches.

Batches	Weight Variation	Thickness	Folding Endurance	Drug Content
F1	37.33±2.081	0.117±0.011	108±3.51	95.21±0.52
F2	72.66±1.527	0.167±0.005	101±2.645	95.41±0.63
F3	81.67±2.081	0.207±0.02	116±3.05	96.41±0.46
F4	54.33±1.527	0.137±0.011	103±2.0	98.00±0.87
F5	80.33±2.081	0.17±0.02	117.67±4.15	95.41±0.56
F6	76.33±2.301	0.103±0.015	109±5.03	97.40±0.58
F7	62.66±1.527	0.133±0.011	115±5.291	96.01±0.48
F1(R)	37.66±2.31	0.17±0.10	108±3.60	95.41±0.52

*All results are shown in mean±S.D. (n=3)

In-vitro dissolution study

In-*vitro* release studies of Domperidone hydro chloride films were carried out in phosphate buffer (pH6.8). Cumulative drug release was calculated on the basis of drug content of Domperidone.

Drug dissolution was observed in F1, F5, which release 104.44% and 101.41% respectively, at end of 2 min. Comparatively slow drug dissolution was observed in F6, F7 with release 96.45% and 99.73% respectively at end of 2 min. This might be due to the higher viscosity of polymer, results in formation of strong matrix layer resulting in decreased in mobility of drug particles in swollen matrices, which leads to delay in drug release.

Table: Cumulative percentage drug release from film formulations

Time(min)	0	1	2	3	4
F1	0.0±0.0	75.19±2.30	104.44±2.91	-	-
F2	0.0±0.0	73.34±1.04	86.83±1.00	89.64±3.40	97.08±2.89
F3	0.0±0.0	72.62±3.88	94.30±2.04	99.80±0.80	-
F4	0.0±0.0	78.60±2.98	93.23±2.02	98.12±1.62	-
F5	0.0±0.0	80.12±2.27	101.41±1.89	-	-
F6	0.0±0.0	81.40±2.53	96.45±2.81	98.86±3.18	-
F7	0.0±0.0	77.46±1.42	99.73±1.78	-	-
F1(R)	0.0±0.0	75.74±0.378	103.94±0.27	-	-

*All results are shown in mean±S.D. (n=3)

The table shows the data of the dissolution of the prepared design batches. The figure shows the graph of cumulative percentage release versus time in minutes. The data shown shows the data up to two minutes only so that we can easily compare the dissolution and percentage drug release within our desired time limit. So, to get quicker release, lower viscosity grade polymers are desirable.

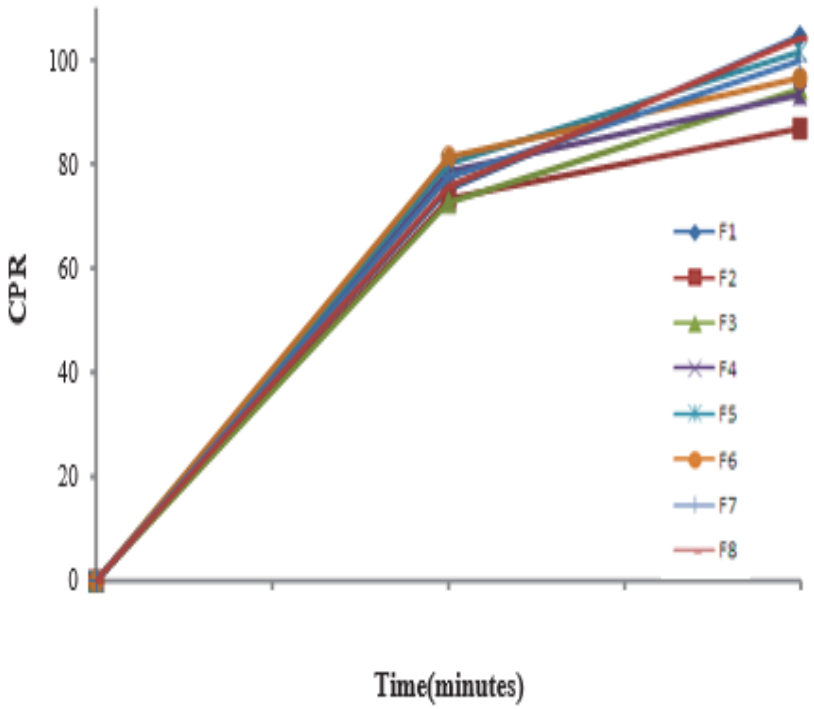


Figure: *In-vitro* release of Domperidone hydrochloride in phosphate buffer (pH 6.8) from film formulation.

Optimized Batch Analysis

The optimized formulation was selected based on criteria, higher amount of drug release at 2 minutes, shortest disintegration time and a medium value of tensile strength. The overlay plot was constructed to obtain optimized batch using Design Expert (7.1.5) (figure 5.14).

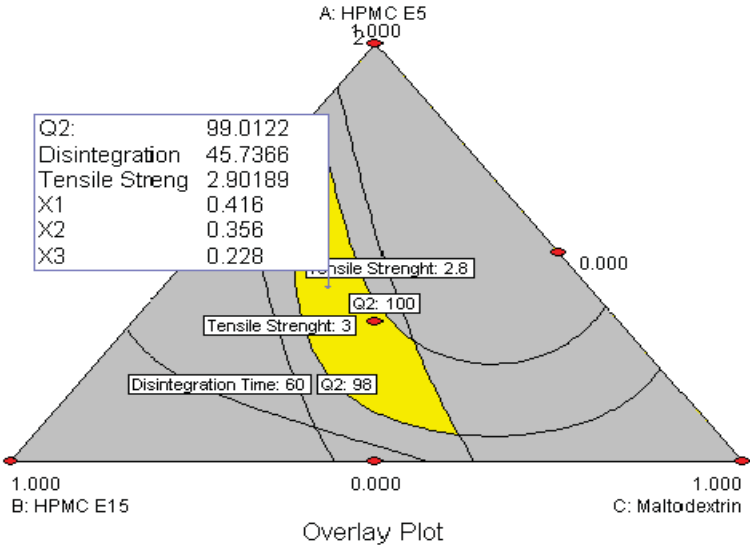


Figure: Overlay Plot.

Optimized batch of the film was prepared experimentally using the same procedure/ the results of stated parameters were compared with the computed values from the regression equations. When the experimental and theoretical values were compared and % error was found to be less than 8% for all the responses.

Table: Evaluation of Optimized Batch.

Responses	Predicted Value	Experimental value*	Relative error (%)
Q2 min	99.01	98.45 ± 0.99	-0.5+6
Disintegration time	45.73	49 ± 3	7.15
Tensile Strength (N/mm^2)	2.90	2.98 ± 0.14	2.75

Stability Studies

Stability study has been performed according to ICH guidelines for short period of time. The optimized formulations were evaluated for stability studies which was stored at 400C at 75%RH tested for 1 month and was analyzed for their tensile strength, disintegration time, in vitro drug release on intervals of 7, 15 and 30 days. Results of formulations were found to be within the permissible limits and the results are shown in the Table5.13. There was no significance difference seen in the Observable Parameters. So, the formulation was found to be stable for tested period.

Table: Results of accelerated stability studies.

Evaluation parameters	Time period for sampling*			
	Initial	After 7 days	After 15 days	After 30 days
CPR at 2 min (%)	98.45±0.99	98.06±5.44	98.15±4.78	98.42±2.35
Disintegration time (sec)	49±3	47±1	48±0.57	49±0.57
Tensile strength (N/cm2)	2.98±0.14	2.95±0.081	3.01±0.07	2.99±0.14

*All results are shown in mean±S.D.(n=3)

CONCLUSION

In the present research work, an attempt has been made to prepare mouth dissolving films of Domperidone Hydrochloride which is NSAID, water-insoluble with bitter taste. The fast-dissolving films of Domperidone Hydrochloride were prepared by solvent casting method using film-forming polymer Maltodextrin, Hydroxy propyl methyl cellulose E3LV, Hydroxy propyl methyl cellulose E5LV, Hydroxy propyl methyl cellulose E15LV and Propylene Glycol and Glycerin as plasticizer. The mouth dissolving film of Domperidone Hydrochloride obtained by the solvent casting method showed desired % drug release, disintegration time and tensile strength. The prepared film was having very smooth surface because of Maltodextrin and without any interactions between drug and polymer. The optimization of MDF was done by simplex centroid design. The multiple regression analysis of the results led to equations that describe adequately the influence of the selected variables on the responses understudy. Formulations with % drug release of more than 95 % within 2 minutes were found in a specific region containing having more amount of HPMCE5 resulting in quicker drug release. Formulations with in-vitro disintegration time<60 sec were found in a specific region containing high levels HPMCE5 and Maltodextrin and low levels of HPMCE15. A desired level of Tensile strength was achieved when optimum amount of HPMCE15 was present in the film. The high % drug release of the film in simulated saliva (pHbuffer6.8)

indicated that it could be helpful for the treatment of acute attention deficit hyperactivity disorder and Narcolepsy where quick bioavailability of the drug is desired.

So, all the designed batches were prepared and their evaluations were carried out which shown acceptable results. On the bases of the results, we may conclude that project aim was fulfilled successfully.

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