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PALONOSETRON HCL LOADED MOUTH DISSOLVING FILM FOR EFFECTIVE TREATMENT OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING

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ABSTRACT

Aim of present work is to formulate a fast dissolving film of potent 5-HT3 specific receptor inhibitor Palonosetron HCL used in treatment of Chemotherapy induced nausea and vomiting. Fast dissolving films provide ease of administration for patient who is mentally ill, disabled and uncooperative; requires no water; have quick disintegration and dissolution of the dosage form. Formulation was prepared by the solvent casting method using Film Forming Polymer hydroxyl propyl methyl cellulose and propylene glycol, glycerin as plasticizer. Final formulation was optimized by 3^2 factorial design by taking concentration of polymer and plasticizer and independent variable. Film was evaluated for its stability studies, complete dissolving time, mechanical properties, tensile strength, % elongation at break, thickness of film, drug content uniformity, in vitro dissolution study, stability study, scanning electron microscopy. The studies indicate that the stable quick disintegrating and quick dissolving oral thin strip can efficiently be formulated for Palonosetron HCL.

KEYWORDS: Fast dissolving oral films, Oral mucosa, Permeability, Solvent casting and disintegration.

INTRODUCTION

The oral route of drug administration is the most common and convenient for patient use. Quick dispersing/dissolving oral drug delivery systems (QD) are defined as oral drug delivery systems that dissolve or disintegrate within a few seconds after placement in the mouth and do not require water to aid swallowing. The QD systems include tablets, caplets, wafers, films, granules and powders. When QD are placed in the mouth, the dosage form disintegrates instantaneously or within a few minutes releasing the drug, which dissolves or disperses in the saliva. The saliva containing the medicament is then swallowed and the drug is absorbed in the normal way. Some fraction of it absorbed from pregastric sites such as the mouth, pharynx, and esophagus, etc. In these cases, the bioavailability of drugs from QD may be greater compared to the standard oral dosage forms.[1-6]

Fast-Dissolve Film should be stiff, flat and should not curl on the edges, robust enough to be removed from the unit-dose packaging without breaking, dissolve readily in order to deliver the API rapidly, mechanical property of fast 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 filmstrip is required.[7-9]

Palonosetron (INN, trade name Aloxi) is a 5-HT3 antagonist used in the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV). It is used for the control of delayed CINV—nausea and vomiting and there are tentative data to suggest that it may be better than granisetron.[10]

Palonosetron is administered intravenously, as a single dose, 30 minutes before chemotherapy,[11] or as a single oral capsule one hour before chemotherapy.[8] The oral formulation was approved on August 22, 2008 for prevention of acute CINV alone, as a large clinical trial did not show oral administration to be as effective as intravenous use against delayed CINV.[12-20]

MATERIAL AND METHODS

Material

Palonosetron was received as gift sample from Themis Medicare, Crospovidone, Croscarmellose Sodium, Sodium Starch Glycollate, D-Mannitol, Microcrystalline Cellulose were procured from lobachamie laboratories.

Methods

Calibration curve of Palonosetron Hydrochloride in phosphate buffer pH 6.8

From the Standard stock solution further serial dilution were made with phosphate buffer pH 6.8 to obtain concentrations ranging from 2-20 µg/ml. The absorbance of the samples was recorded at 255nm (λmax of

Palonosetron HCl) using UV-Visible spectrophotometer against phosphate buffer pH 6.8 solution as blank. Calibration curve was obtained by plotting graph between concentration of sample solution and absorbance.[21-23]

Drug-Excipients Compatibility studies

Fourier transform infrared spectroscopy was carried out for solid samples to detect if any interactions were present between the drug and polymers. The samples were prepared by the potassium bromide disc method (3mg sample in 297mg KBr). Powders were triturated in a small size glass mortar and pestle until the powder mixture was fine and uniform. Pure KBr powder was used as background, and for baseline correction. Samples were placed in a sample holder. Afterwards, the sample was transferred to sample compartment. Samples were scanned in the region of 4000-400 cm^{-1} using a brucker FTIR spectrometer.[24-25]

Preparation of film

Polymeric solution of HPMC E 5 of different concentration shown in table 1, were prepared in 10ml of distilled water with constant stirring for 15 mins. 20 ml of polymeric solution were divided into two parts 10 ml each. In first part Drug was dispersed. In second part different concentration of plasticizer according to table 1 and other excipients were dissolved. Both the solution were thoroughly mixed and homogenized by using on magnetic stirret for 15 mins. Processed liquid mixture casted into petridish and dried at room temperature for 48 hours.[26-27]

Table 1: Optimization of formulation of fast dissolving film

Batch	F1	F2	F3	F4	F5	F6	F7	F8	F9
Palonosetron HCl	10	10	10	10	10	10	10	10	10
HPMC E 5 LV (mg)	100	150	200	100	150	200	100	150	200
PEG 400 (% W/W of polymer)	15	15	15	20	20	20	25	25	25
Aspartame (mg)	1	1	1	1	1	1	1	1	1
Water (ml)	20	20	20	20	20	20	20	20	20

Evaluation resulting Dosage form[28-33]

Weight variation

Film was cut in to five different strips from casted petridish. Weight of each film was taken and variation was calculated.

Film thickness

The thickness of 3 film was measured by screw gauge micrometer at different position of film and average thickness was calculated.

Folding endurance

A film of 2 x 2 cm^2 was repeatedly folded and unfolded at the same place till it brakes. The number of times, the film could be folded at same place, without breaking was recorded as the value of folding endurance. This gives an indication of brittleness of the film.

Surface pH

The film to be tested was placed in a petridish; 1 ml of distilled water was added and kept for 30 seconds. The pH was noted after by electrode of the pH meter allowing contact time of 1 min. the average of three measurements for each formulation was carried out.

Disintegration time

In-vitro Disintegration tine was determined visually in petridish containing 25 ml of simulated salivary fluid pH 6.8.

Drug Content

Determined by dissolving one film of dimension of 2 x 2 cm^2 in 100 ml of pH 6.8 simulated salivary fluid for 30 minutes. From this, 1 ml was diluted to 10 ml and absorbance was measured at 285.0 nm using UV spectrophotometer.

In vitro dissolution study

Dissolution profile of formulation was carried out using USP type II (paddle apparatus) with 300ml of pH 6.8 simulated salivary fluid as dissolution medium maintained at 37± 0.5°C. Dissolution medium was stirres at 50 rpm. Samples were withdrawn at every 30 second interval, replacing the same amount with fresh medium. Absorbance was determined by UV spectrophotometer at 285.00 nm.

Ex-vivo permeation studies

Ex vivo permeation studies through porcine oral mucosa (ventral surface of tongue) was carried out using the Franz diffusion cell. The buccal mucosa was excised and trimmed evenly from the sides, washed in SSF of pH 6.8 and used immediately. The mucosa was mounted between the donor and receptor compartments. The receptor compartment was filled with 25 ml of SSF of pH 6.8 which was maintained at 37± 0.2^0C and hydrodynamics were maintained using magnetic stirrer. One film of dimension 2 cm × 2 cm was previously moistened with a few drops of pH 6.8 phosphate buffer and placed in donor compartment. The donor compartment was filled with 1 ml of pH 6.8 SSF. 1 ml samples from receptor compartment were withdrawn at suitable time interval which was then replaced with 1 ml of pH 6.8 phosphate buffer. The percentage of domperidone permeated was determined by measuring the absorbance in UV-Visible spectrophotometer at (λ_{max}) 285 nm.

Tensile strength

Tensile testing was conducted using a texture analyzer. The film was cut into 60 × 20 mm strips. Tensile tests were performed according to ASTM International Test Method for Thin Plastic Sheeting on the texture analyzer. Initial grip separation was 20 mm and crosshead speed was 1 inch/min. The test was considered concluded when the film breaks. Tensile strength, was computed with help of load require to break the film and cross sectional area to evaluate tensile properties of the films. Tensile strength (TS) Tensile strength is the maximum stress applied to a point at which the film specimen breaks and can be calculated by dividing the maximum load by the original cross-sectional area of the specimen and it was expressed in force per unit area.

Tensile Strength = Force at break (N)/ Cross sectional area (mm^2)

Scanning Electron Microscopy (SEM) of Optimized Film[34]

Films of optimized batch were subjected to Scanning Electron Microscopy (SEM) study and evaluated for the appearance, surface morphology and checked for crystallization of drug as well as other excipients.

Comparison with Marketed Product

Comparison study of Optimized batch F8(Tablet), Optimized formulation of film were carried out with marketed Capsules of Palonosetron Hydrochloride " Palozac".

Stability Study[35]

The stability study was carried out on the optimized formulation F_4 over the period of one month. The F_4 formulation was sealed in aluminum foil and kept in humidity chamber maintained at 40 ± 2°C / 75 ± 5% RH for one month. At the end of studies, a sample was analyzed for the drug content, in vitro drug release, disintegration time.

RESULT AND DISCUSSION

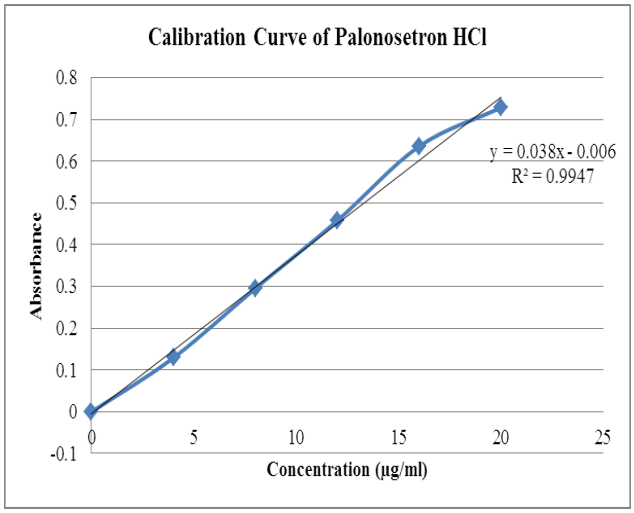

Figure 1: Calibration curve of Palonosetron HCL in 0.1 N HCL

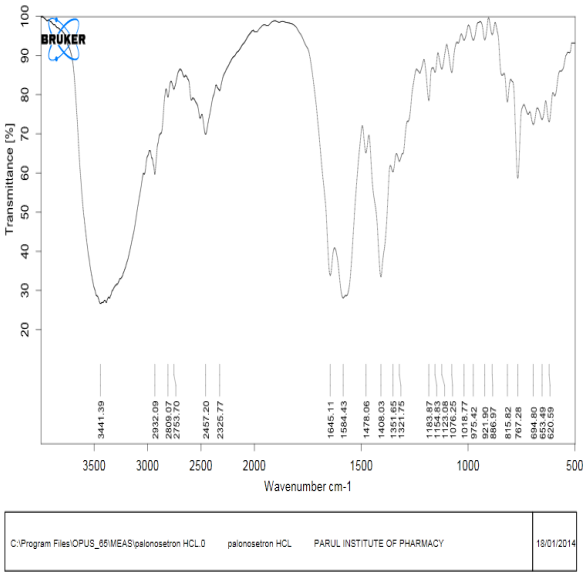

Figure 2: FT-IR spectrum of pure drug

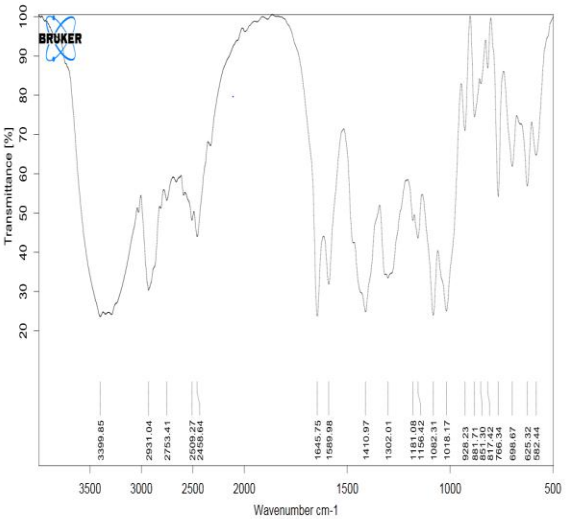

Figure 3: FT-IR spectrum of Physical Mixture

Table 2: Film Evaluation of Mouth dissolving film (Optimization)

Batch	Thickness (mm)	Weight (mg)	Tensile strength (N/mm^2)	Folding endurance	Surface pH	Disintegration time (Sec)	Drug content (%)
F1	0.064±0.006	28.66±1.69	13.67±0.57	101±2.86	7.20±0.01	13.67±0.57	93.82±0.14
F2	0.075±0.004	34±0.81	25±1.00	108±1.63	7.23±0.02	25±1.00	91.28±0.47
F3	0.078±0.004	40.33±1.24	35.33±1.15	116±0.81	7.28±0.02	35.33±1.15	92.81±0.56
F4	0.068±0.005	29.66±0.81	17.66±1.15	120±1.52	7.32±0.01	17.66±1.15	96.82±1.04
F5	0.079±0.004	34.33±1.24	30±1.00	122±1.63	7.22±0.02	30±1.00	95.1±0.56
F6	0.091±0.004	41.66±1.69	40.67±1.15	127±1.69	7.16±0.01	40.67±1.15	95.8±0.65
F7	0.071±0.006	30±0.81	19.33±0.57	132±2.04	7.34±0.01	19.33±0.57	93.4±0.84
F8	0.084±0.005	34.66±1.24	34.33±0.57	136±1.41	7.31±0.02	34.33±0.57	94.2±0.74
F9	0.098±0.004	42.33±1.69	46.65±1.15	137±1.75	7.28±0.01	46.67±1.15	94.79±0.59

***Mean (±SD), n=3.**

Table 3: % *In vitro* drug release study of Mouth dissolving film (Optimization)

Time	Batch								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
3	64.14%	62.87%	61.47%	63.18%	61.81%	60.84%	59.18%	57.18%	55.26%
6	80.14%	78.17%	74.14%	78.47%	76.87%	72.58%	77.47%	74.14%	72.48%
9	85.14%	84.58%	82.57%	83.14%	82.89%	79.65%	83.08%	81.26%	83.82%
12	89.87%	89.57%	86.14%	88.47%	86.45%	87.34%	87.89%	87.24%	86.41%
15	99.18%	98.57%	97.55%	99.06%	97.45%	96.14%	98.60%	95.84%	94.80%

***Mean (± SD), n=3.**

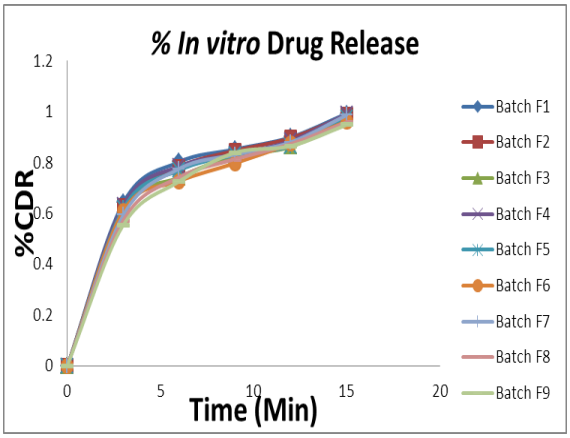

Figure 4 *In-vitro* drug release study of batch no. F1 to F9

Statistical Analysis

On the basis of the preliminary trials a 3^2 full factorial design was employed to study the effect of independent variables i.e. concentration of HPMC (X1) and concentration PEG 400 (X2) on dependent variables Vitro Drug Release % (Y1), Disintegration Time (Y2), Tensile strength (Y3). Analysis and optimization were done by design expert® 7.0 and DOE++® software. The results of factorial design are shown in table below.

Table 4: Results of optimization study by Factorial Design

Batch	Factor 1	Factor 2	Response Variables		
	A:Conc of HPMC E-5 Mg	B:Conc of PEG 400 %	in Vitro Drug Release %	Disintegration Time (Sec)	Tensile strength (N/mm^2)
F1	100.00	15.00	99.18 ± 0.62	13.67±0.57	13.67±0.57
F2	150.00	15.00	98.57 ± 0.76	25.00±1.00	25±1.00
F3	200.00	15.00	97.55 ± 0.89	35.33±1.15	35.33±1.15
F4	100.00	20.00	99.06 ± 0.16	17.66±1.15	17.66±1.15
F5	150.00	20.00	97.45 ± 0.85	30.00±1.00	30±1.00
F6	200.00	20.00	96.14 ± 0.68	40.67±1.15	40.67±1.15
F7	100.00	25.00	98.60 ± 0.76	21.33±0.57	19.33±0.57
F8	150.00	25.00	95.84 ± 0.57	34.33±0.57	34.33±0.57
F9	200.00	25.00	94.80 ± 69	46.67±1.15	46.65±1.15

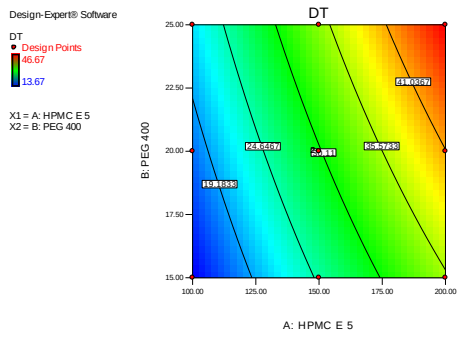

Fig. 5 Contour Plot of Disintegration Time

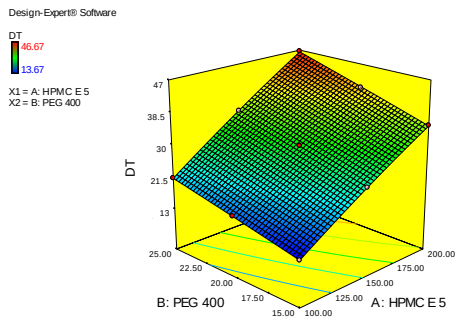

Fig. 6 Response Surface Plot of Disintegration Time

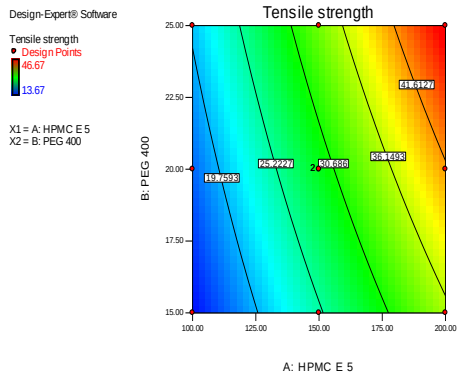

Fig. 7 Contour Plot of Tensile strength

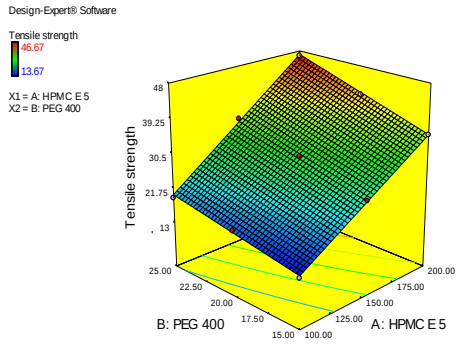

Fig. 8 Response Surface Plot of Tensile strength

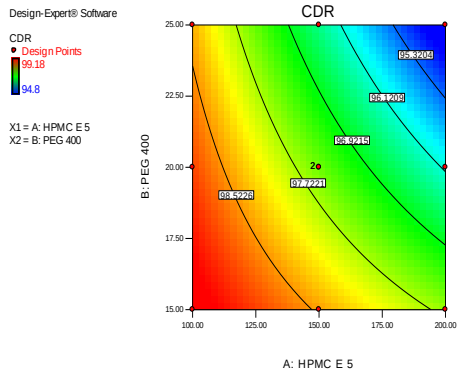

Fig. 9 Contour Plot of %CDR

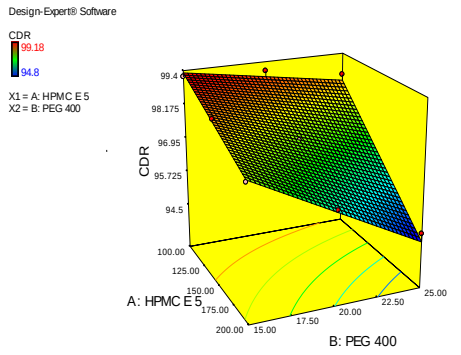

Fig. 10 Response Surface Plot of %CDR

Selection of optimized batch

The overlay plot (figure) reflects that the yellow reason of the area shown is the area of interest (experimental region). From the polynomial equation and the contour plots batch was the optimized. The selected optimized batch was subjected to stability study. Formulation of optimized batch is given in Table 5.

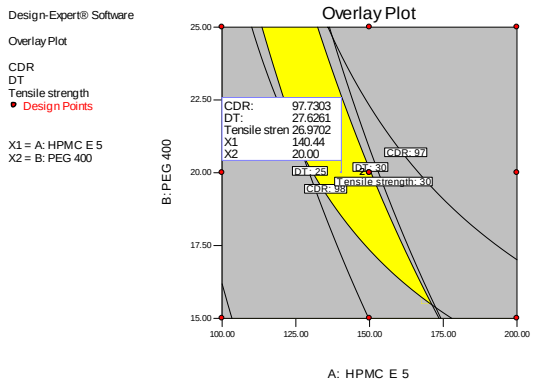

Figure 11: Overlay plot

Table 5: Formulation ingredient of optimized batch

Ingredients	Quantity
Palonosetron HCl	10
HPMC E 5 LV (mg)	140
PEG 400 (% W/W of polymer)	20
Aspartame (mg)	1
Water (ml)	20

Evaluation of optimized batch F5

Table 6: Evaluation of Mouth dissolving film of optimized batch

Batch	F5
Thickness (mm)	0.084±0.011
Weight (mg)	34.33±1.24
Tensile strength	20.18
Folding endurance	124±1.63
Surface pH	7.20±0.14
Disintegration time (Sec)	28±1.00
Drug content (%)	96.1±0.67

***Mean (± SD), n=3.**

Table 7: % *In-vitro* drug release study of optimized Film

Time (min.)	In-vitro drug release (%)
0	0
3	66.19±0.25
6	80.19±1.01
9	89.30±1.12
12	97.10±0.92
15	99.20±0.45

***Mean (± SD), n=3.**

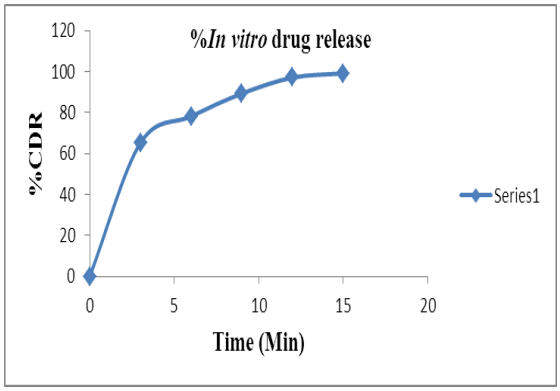

Figure 12: %*In-vitro* drug release of optimized batch F8

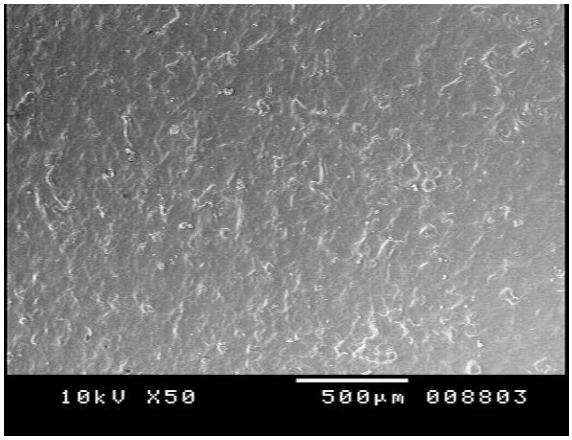

Figure 13: SEM Image of Final Formulation

Table 8: Comparison with marketed product (*In vitro* drug release)

Marketed Product "Palozac"		Optimized batch of film	
Time (min)	***In-vitro* drug release (%) pH 1.2**	**Time (min)**	***In-vitro* drug release (%) pH 6.8**
0	0	**0**	0
5	16.36±1.23	**3**	66.19±0.25
10	30.93±1.12	**6**	80.19±1.01
15	43.83±1.63	**9**	89.30±1.12
20	59.95±1.50	**12**	97.10±0.92
25	71.55±1.77	**15**	99.20±0.45
30	83.10±1.38		
35	89.46±1.74		

***Mean (± SD), n=3.**

DISCUSSION

Calibration curve of Palonosetron HCl was prepared in Phosphate buffer pH 6.8 at λmax 255 nm. Regression value (R^2) was found to be 0.9947, in the range of 2-20 µg/ml. Compatibility of drug with excipients was carried out by taking FTIR spectra of pure drug and Physical mixture spectrum's shown in Figure indicate absence physic chemical interaction in between drug and studied excipients.

On the basis of the preliminary trials a 3^2 full factorial design was employed to study the effect of independent variables i.e. concentration of HPMC (X1) and concentration PEG 400 (X2) on dependent variables Vitro Drug Release % (Y1), Disintegration Time (Y2), Tensile strength (Y3). Analysis and optimization were done by design expert® 7.0 and DOE++® software. All 9 batches were checked for these 3 parameters. Now, optimization was done by considering above 3 parameters and optimized batch was found to be batch F5. All other evaluations like blend and film evaluation

were done for optimized batch F5. Thickness was found to be 0.084 mm, Weight was found to be 34.33 mg, Tensile strength was found to be 20.18, Folding endurance was found to be 124, Surface was found to be pH 7.20, Disintegration time and Drug content were found 28 seconds and 96.1% respectively.

From the graph of response surface methodology it shows that Disintegration time decreases with decrease in concentration of HPMC.

Comparison study of Optimized batch F5 is carried out with marketed Capsules of Palonosetron Hydrochloride "Palozac" and fast dissolving tablet. It was found that the drug release at initial and after 15 min of Optimized batch F8 99.12±0.45%. In comparison with marketed formulation and our dosages form Mouth Dissolving Tablet, our dosages form Mouth Dissolving film is expected to gives fast onset of action as absorption starts through oral cavity and the drug will bypass hepatic first pass metabolism.

Optimized batch was tested for stability study at 40±2℃ / 75% ± 5% RH and at room temperature for 3 month Indicated, no significant changes with respect to Disintegration time, Drug content, Wetting time and % *In vitro* drug release at 15 min initially and after three month.

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