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FORMULATION AND EVALUATION OF DOMPERIDONE ORODISPERSIBLE TABLET

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ABSTRACT: Emesis is a clinical condition which requires immediate treatment. The present work is aimed to formulate Orodispersible Tablet (ODT) of BCS class II drug Domperidone using Kyron T-314 as superdisintegrant and Avicel 102 as disintegrant by direct compression method. The drug-excipients compatibility study was carried out by Fourier Transform Infrared (FTIR) and Differential Scanning Calorimetry (DSC) which reveals no interaction between drug and excipients. A 3^2 factorial design was used to investigate effect of independent variables viz. superdisintegrant (Kyron T-314) and disintegrant (Avicel 102) on dependent responses like friability, disintegration time and percent drug release. Sodium lauryl sulphate (SLS) was used in the formulation to aid the dissolution of drug. All the formulations were evaluated for hardness, friability, disintegration time and dissolution rate. The factorial batch F4 containing 1.5 mg Kyron T-314 and 5 mg Avicel 102 has shown better results for all evaluation parameters with drug release of 99.22% and disintegration time of 29 sec. Therefore, factorial batch F4 was selected as the optimized batch.

INTRODUCTION: Tablet is the most widely used dosage form due to convenience in terms of self-administration, compactness and ease in manufacturing but having the problem of dysphasia (difficulty in swallowing). Hence, demand of more patient-friendly and compliant dosage forms resulted in orodispersible tablets (ODTs) or mouth dissolving tablets more popular. ODTs were rapidly dispersed in mouth hence can be administered anytime and anywhere and also suitable for geriatric, pediatric and travelling patients.

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The aim of present research work is to formulate ODTs of domperidone with sufficient mechanical integrity and to achieve faster disintegration in the oral cavity.

Domperidone is a widely used BCS class II antiemetic drug which acts by an inhibition of the dopaminergic receptors and peripheral gastro-kinetic action. It has low oral bioavailability because of its extensive first pass metabolism. So by formulating ODTs of domperidone, it has been tried to enhance the bioavailability of the drug by avoiding first pass metabolism and improving the dissolution of domperidone by adding SLS in the formulation.

Pearlitol added in the formulation as diluent also works as a sweetener which helps to mask the bitter taste of domperidone. The domperidone ODT formulation was optimised by 3^2 factorial designs

by using Kyron T-314 and Avicel 102 as variables. Formulated tablets were tested for hardness, friability, disintegration, wetting time and *in vitro* dissolution.

MATERIALS AND METHODS:

Materials: Domperidone was a gift sample from Wockhardt Pharmaceutical Industries (Aurangabad, M. S. India) and Avicel 102 was gifted from Colorcon Asia Pvt. Ltd. (Goa). All other reagents and chemicals used were of analytical grade.

Methods:

Preformulation study[8-11]:

1) **Drug- excipient compatibility study:** Drug-excipient compatibility study carried out by using FTIR and DSC analysis. FTIR spectra of all formulations were obtained on IR-Spectrophotometer (Prestige-21-shimadzu). DSC thermogram was obtained by using DSC-60 (Shimadzu) instrument with temperature ranging from 100 to 300ºC.

2) **Preliminary study:** Preliminary study was carried out by using two superdisintegrants namely Kyron T-314, Crosspovidone and Avicel 102 as disintgrant.

3) **Preparation of blend for preliminary batches:** The drug, diluents, superdisintegrants, disintegrant and sweetener were passed through sieve # 40 and properly mixed together by tumbling mechanism. Talc and magnesium stearate were passed through sieve # 80 and mixed with previous blend. All the materials were directly compressible therefore prepared blend was compressed into tablets using 8mm round concave face punch on a Rimek- Rotary Tablet machine by direct compression method. The composition of the batches is shown in **Table 1**.

From preliminary study Kyron T-314 was selected for factorial batches.

TABLE 1: FORMULA FOR FACTORIAL BATCHES

Ingredients	Factorial batches								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Domperidone	10	10	10	10	10	10	10	10	10
Kyron T-314	0.5	0.5	0.5	1.5	1.5	1.5	2.5	2.5	2.5
Avicel 102	5	10	15	5	10	15	5	10	15
Sucralose	2	2	2	2	2	2	2	2	2
Mg. stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1	1	1	1	1	1	1	1	1
SLS	1	1	1	1	1	1	1	1	1
Pearlitol	79	74	69	78	73	68	77	72	67
Total	100	100	100	100	100	100	100	100	100

Determination of powder flow properties of factorial batches [12-14]: The powder flow properties such as angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio were determined. The powder flow character is related with flow properties as follows.

TABLE 2: FLOW PROPERTY RANGES

Flow character	Angle of repose	Carr's index	Hausner's index
Excellent	<25	<10	1.00-1.11
Good	25-30	11-15	1.12-1.18
Fair	_	16-20	1.19-1.25
Passable	30-40	21-25	1.26-1.34
Poor	>40	26-31	1.35-1.45
Very poor	_	32-37	1.46-1.59

Evaluation of Domperidone Orodispersible Tablet [15-21]:

1. **Weight variation:** Indian Pharmacopoeia procedure for uniformity of weight is as follow: Twenty tablets were taken and their weights were determined individually and collectively

on a Shimadzu digital weighing balance (Model AUX 220). The average weight of tablets was calculated. All determinations were made in triplicate.

2. **Tablet hardness:** Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The hardness of the tablets was determined by diametral compression using a Monsanto Hardness Tester.

3. **Tablet friability:** The friability of tablets was determined by using Roche Friabilator. 20 tablets were dedusted, weighed and rotated at 25 rpm. Then tablets were removed, dedusted again and reweighed. Percentage friability was calculated from loss in weight. The weight loss should not be more than 1%.

$$\% \text{ friability} = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \text{x } 100$$

4. **Drug content:** Ten tablets were powdered and equivalent to 10mg of domperidone weighed. Dissolved the weighed powder in 0.1N HCl and solution was filtered through 0.45 µm membrane filter. Drug content was analyzed using UV Spectrophotometer (UV- 1700 Pharmaspec Shimadzu) at λ_{max} 285 nm.

5. **Disintegration test:** The test was carried out by using 6 tablets on Digital Tablet Disintegration Tester ED-20 (Electrolab, Mumbai, India).Water was used as a disintegration media at 37ºC ± 2ºC and the time was measured in seconds for complete disintegration of the tablets with no palpable mass remaining in the disintegration chamber.

6. ***In-vitro* dissolution study:** The release rate of domperidone from ODT was determined using United State Pharmacopoeia (USP) XXIV dissolution test apparatus II (paddle apparatus) on tablet Auto Dissolution Test apparatus-TDT 06P (Electrolab, Mumbai). The dissolution test was performed using 900 ml of 0.1 N HCl dissolution medium at 37 ± 0.5ºC and 50 rpm. 5ml solution was withdrawn from the dissolution media at interval of 2, 5, 10, 15, 20, 25 and 30min and the samples were replaced with same amount of fresh dissolution medium to maintain the sink condition. The samples were filtered through a 0.22µ membrane filter, absorbance of solutions was measured at 284 nm using a Shimadzu UV-1700 PharmaSpec double beam UV spectrophotometer and cumulative percentage of drug release was calculated.

7. **Wetting time:** Five circular tissue papers of 10 cm diameter were placed in a petridish. 10 mL of water-containing Eosin (a water soluble dye) was added to petridish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet was noted as a wetting time.

Factorial design: 3^2 factorial design was implemented for the optimization of ODTs of domperidone (Design Expert 8.0.7.1). The two independent factors concentration namely Kyron T-314 (X_1) and Avicel 102 (X_2) were set to three different levels (Kyron T-314 as 0.5, 1.5, 2.5 and Avicel 102 as 5, 10, 15, respectively) and experimental trials were performed at all nine possible combinations. The dependent responses measured were disintegration time, friability and percent drug release.

Validation of the Factorial Design: In order to validate the experimental design using a polynomial equation, two parameters viz. disintegration time and percent drug release were selected. The following second order polynomial equation was applied as a tool of mathematical modeling

$$Y= b0+b1\ X_1+b2\ X_2+b12\ X_1X_2+b11X_{12}+b22X_{22}$$

Where, Y is the dependent variable, b0 is the arithmetic mean response of the nine runs and bi (b1, b2, b12, b11 and b22) is the estimated coefficient for corresponding factor Xi (X_1, X_2, X_{12}, X_{11} and X_{22}), which represents the average results of changing one factor at a time from its low to high value. The interaction term (X_1X_2) depicts the changes in the response when two factors are simultaneously changed. The polynomial terms (X_{12} and X_{22}) are included to investigate nonlinearity.

RESULT AND DISCUSSION [22-25]:

Preformulation study:

1. **Drug- excipient compatibility study by FTIR and DSC:** The FTIR spectra of pure drug and tablet blend were taken and shown in **figure 1 and 2** respectively

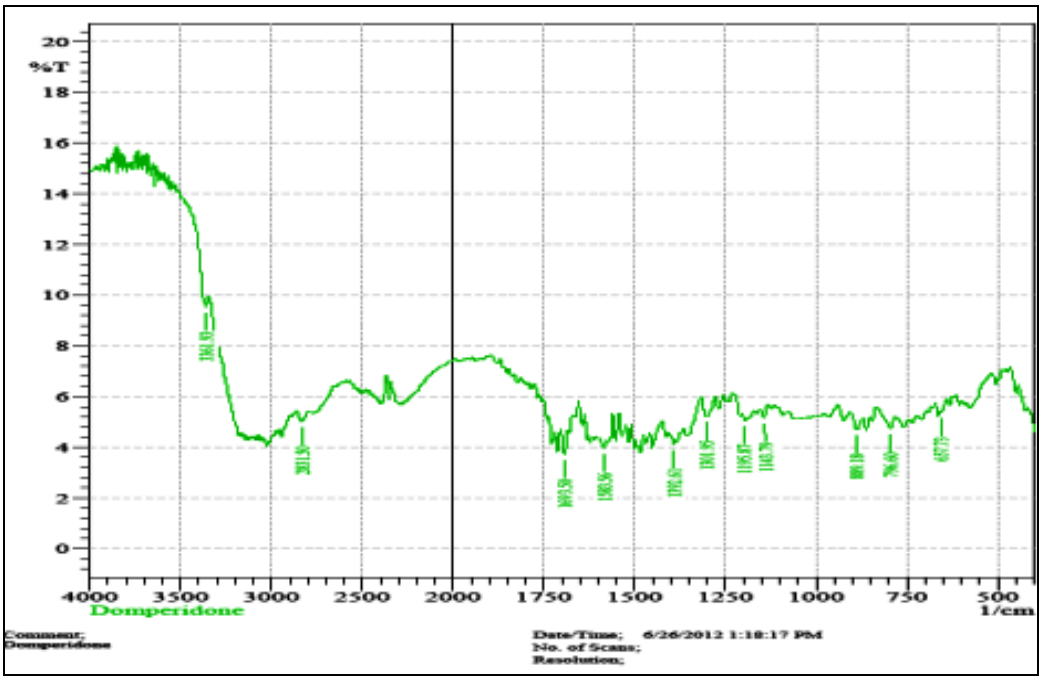

FIGURE 1: FTIR SPECTRA OF DOMPERIDONE

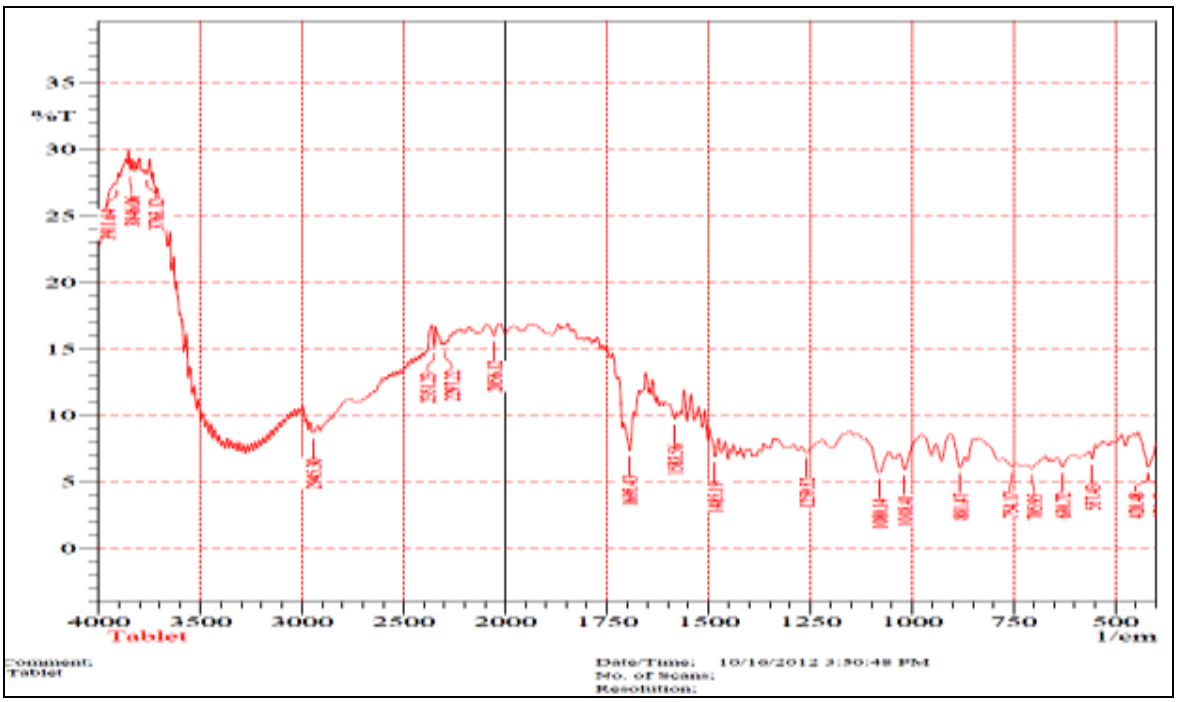

FIGURE: 2 FTIR SPECTRA OF FACTORIAL TABLET

These spectra revealed that there is no significant change or shifting in absorption peaks in tablet blend as compared to pure drug. It proves that there is no significant interaction between drug and excipients.

DSC thermogram of pure drug and drug with polymer were carried out and shown in **figure 3 and 4** respectively.

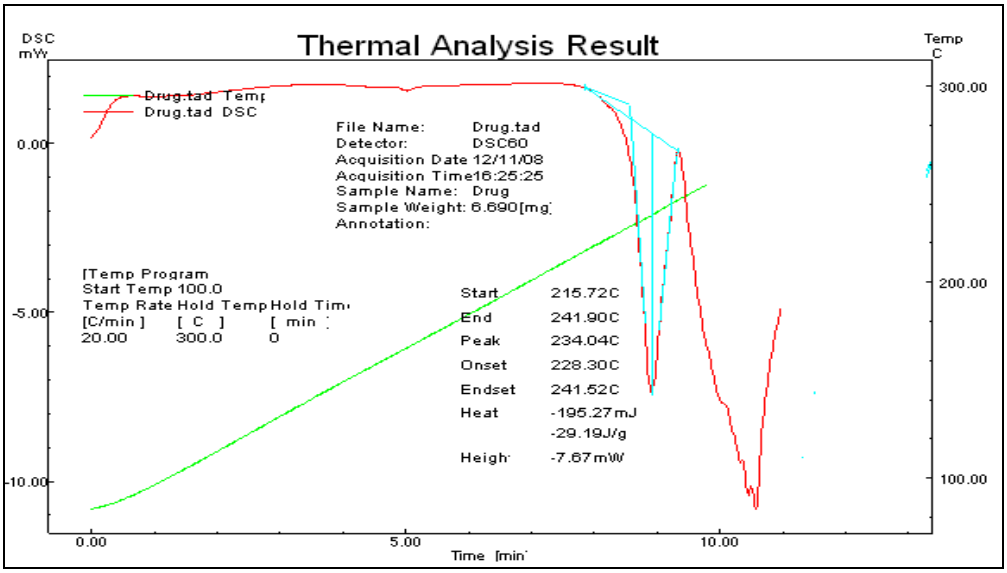

FIGURE 3: DSC THERMOGRAM OF DOMPERIDONE

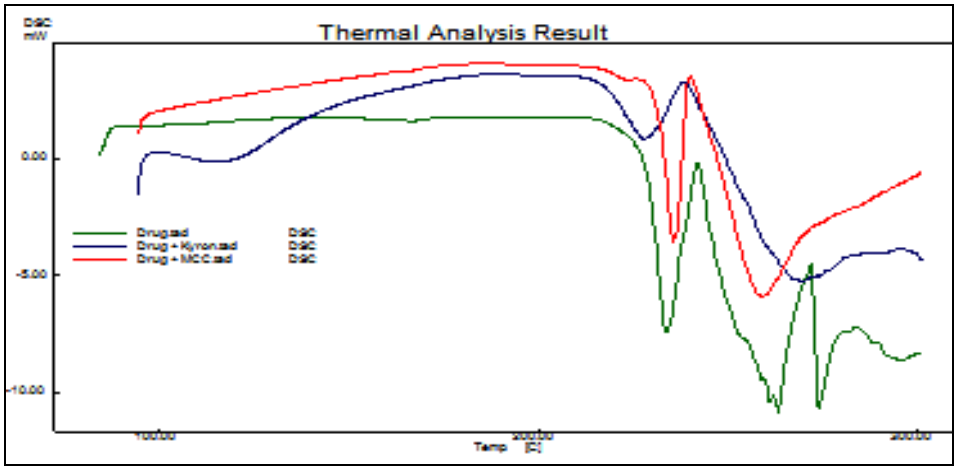

FIGURE 4: DSC THERMOGRAM OF DRUG AND POLYMERS

From the above DSC thermograms it is observed that pure domperidone drug gives melting point peak at 234.04^0 C whereas drug with polymers shows melting point peak near about same to the pure drug. Therefore it is revealed that polymer blend does not show significant shifting in DSC peak due to absence of any interaction with the drug showing good compatibility.

Determination of powder flow properties of factorial batches: From preliminary study, it has been observed that Kyron- T 314 shows better drug release as compared to crosspovidone for which 3^2 factorial design was applied along with Avicel 102 as disintgrant.

TABLE 3: POWDER FLOW PROPERTIES

Formulation batches	Angle of Repose	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Cars index	Hausner's Ratio
Domperidone	**35.11**	**0.55**	**0.41**	**17.1**	**1.07**
F1	16.43	0.7605	0.8303	15.09	1.05
F2	16.13	0.7587	0.8216	15.71	1.06
F3	16.23	0.7522	0.8487	14.83	1.10
F4	14.51	0.7287	0.8162	13.02	1.04
F5	15.18	0.7666	0.8666	12.26	1.05
F6	16.07	0.7302	0.8586	13.09	1.06
F7	17.34	0.7411	0.8287	12.73	1.05
F8	17.13	0.7320	0.8861	13.95	1.07
F9	14.13	0.7511	0.8667	14.25	1.09

Angle of repose: The angle of repose was found to be within the range of 14.13º to 17.34º indicating excellent flowability for factorial blend.

Bulk density: The bulk density was between 0.7287 to 0.7666 gm/cm^3 for factorial batches indicating excellent flowability for factorial batches.

Tapped density: The tapped density was found to be 0.8162 to 0.8861 gm/cm^{3}for factorial batches indicating excellent flowability for factorial batches.

Carr's index: The Carr's index is indicator of compressibility. The value below 10 % shows excellent compressibility. It was found to be 12.26 to 15.71 % for factorial blend indicating good compressibility.

Hausner's ratio: The Hausner's ratio is another parameter indicating the flow property. The value of ratio below 1.25 indicates good flow while above 1.25 indicates the poor flow. It was found 1.04 to 1.10 for factorial batches indicating good flowability.

Evaluation of the Tablets:

TABLE 4: TABLET EVALUATION PARAMETERS

Factorial Batch	Weight variation (±S.D)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Wetting time (sec)	DT (Sec)	% Drug release
F1	100±2.09	3.6	0.42	98.08	43	41	91.521
F2	100±1.089	3.6	0.40	99.34	40	39	89.784
F3	100±1.073	3.4	0.39	97.09	39	36	84.591
F4	100±0.419	3.4	0.30	101.02	35	29	92.322
F5	100±1.345	3.4	0.33	98.02	33	28	85.581
F6	100±1.037	3.2	0.32	98.54	30	25	79.209
F7	100±2.271	3.6	0.37	99.75	26	22	88.92
F8	100±1.312	3.2	0.27	100.84	24	17	81.684
F9	100±0.251	3.4	0.31	99.56	21	15	80.874

The weight variation was taken in triplicate and found to be within 100 ± 0.251 to 100±2.271. The weight variation was found to be within acceptable limits. The tablet hardness was found to be within 3.2 to 3.6. The friability was found to be within 0.27 to 0.42. The friability is within acceptable limit range. Drug content analysis was found in the range of 97.09-101.02%.

All the results were found within acceptable ranges because of shaking of blend for optimum time and resulting in uniform distribution of drug throughout the blend prepared.

The minimum wetting time was found to be 21sec for F9 and maximum 43 sec for F1 batch which was within accepted limits for ODTs.

Disintegration test: In the present study, all tablets disintegrated in less than 55 seconds fulfilling the official requirement for DT as per IP (< 3min) for ODTs. DT is found to be within 15 sec to 41 sec. As the concentration of superdisintegrant and disintegrant increases the disintegration time decreases.

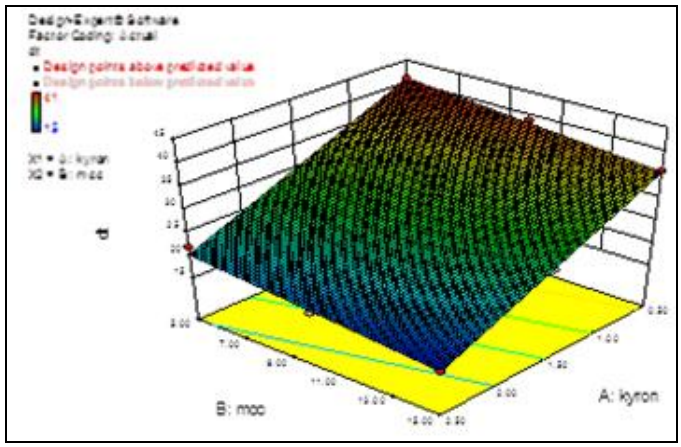

FIGURE: 5 3D RESPONSE GRAPH FOR DISINTEGRATION TIME

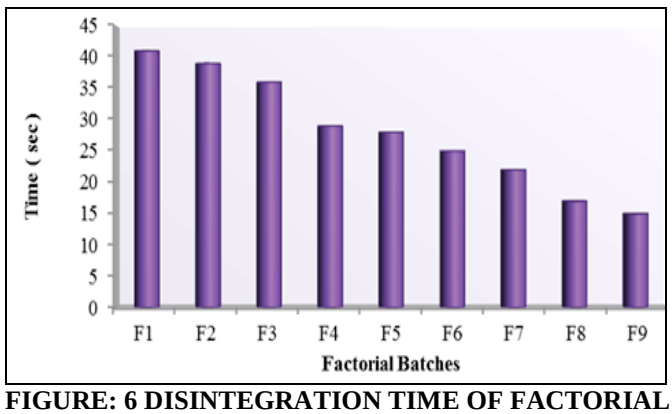

FIGURE: 6 DISINTEGRATION TIME OF FACTORIAL BATCH

***In-vitro* dissolution study:** *In -vitro* dissolution process of tablet depends upon the wetting followed by disintegration of the tablet. Disintegration time of tablet decreases with increase in concentration of Kyron T-314 and Avicel 102. Tablet showing lower disintegration time will show higher drug release. *In –vitro* dissolution profile (**fig. 7**) revealed minimum percent drug release as 79.209 for F6 batch and maximum percent release as 92.322 for F4 batch within 30 min. From above data factorial batch F4 was selected as optimized batch.

TABLE 5: DISSOLUTION PROFILE OF FACTORIAL BATCHES IN SIMULATED GASTRIC FLUID

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	33.97	27.54	18.63	34.91	20.98	22.47	22.47	31.19	20.61
5	50.62	56.80	40.07	59.15	29.91	43.50	847.09	52.47	39.97
10	57.11	61.69	54.63	78.03	51.36	55.81	57.60	62.93	55.51
15	80.63	73.26	74.87	84.40	74.81	70.47	79.76	80.01	73.20
20	87.99	83.04	77.96	89.78	82.29	78.09	87.43	81.24	83.47
25	91.45	83.97	83.90	92.38	86.87	77.90	91.33	80.75	83.16
30	91.52	89.78	84.59	92.32	85.58	79.20	88.92	81.68	80.87

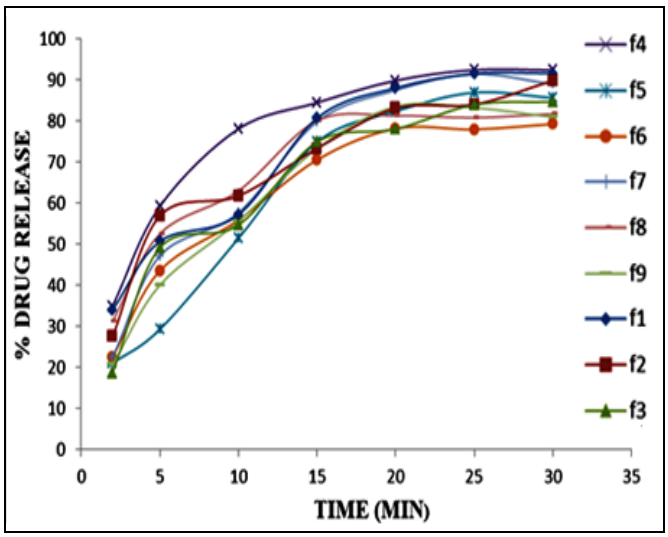

FIGURE 7: PERCENT DRUG RELEASE OF FACTORIAL BATCHES

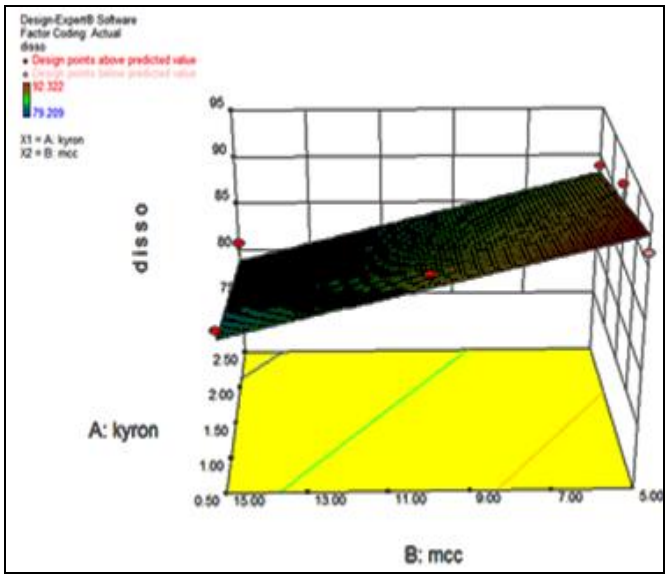

FIGURE 8: 3D RESPONSE GRAPH OF DISSOLUTION

Kyron T-314 and Avicel-102 enhanced the disintegration of the tablets. The combination of superdisintegrant and disintegrant act by absorbing a large amount of saliva when they are placed in mouth which results in breakdown of tablet and showed faster disintegration. Generally Regarded as Safe (GRAS) concentration of SLS is 1%.

Therefore, it has been added in the same concentration to enhance the dissolution of BCS class II domperidone drug. It has been found that batch F4 shows good disintegration and better dissolution as compared to other batches. As the concentration of Kyron T-314 and Avicel 102 increased the disintegration time decreases and % release of the drug increases. Talc is used as glidant to improve the flow properties of the formulation.

CONCLUSION: In the present study, orally dispersible tablets of domperidone were prepared by direct compression technique. The prepared tablets were found to be within the official limits with respect to all the parameters of evaluation. The disintegration time and dissolution studies were performed for the F1-F9 formulations. Among these formulations **F4** and **F7** showed the optimum disintegration time and cumulative percentage drug release after 30 min. But formulation batch **F4** was found to be less friable and also requires less amount of Kyron T-314 as compared to batch **F7**. Therefore batch **F4** was most robust formulation and considered to be optimized batch.

As a result, orally fast disintegrating tablet administration of domperidone may appear to be a promising alternative drug delivery to conventional drug delivery.

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