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Formulation Development and Evaluation of Risperidone Fast Dissolving Tablets

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ABSTRACT

Background: The main aim of present research investigation is to formulate the Risperidone Fast Dissolving tablets. Risperidone, an atypical antipsychotic, belongs to BCS Class-II and used for treating schizophrenia, bipolar mania and autism by blocking D_2 and 5-HT_{2A} receptors. **Methods:** The Fast Dissolving tablets of Risperidone were prepared employing different concentrations of Crospovidone and Croscarmellose sodium in different combinations as a Superdisintegrants by Direct Compression technique using 3^2 factorial design. The concentration of Crospovidone and Croscarmellose sodium was selected as independent variables, X_1 and X_2 respectively whereas, wetting time, Disintegration time, $t_{50\%}$,$t_{90\%}$were selected as dependent variables. **Results and Discussion:** Totally nine formulations were designed, preapred and are evaluated for hardness, friability, thickness, Assay, Wetting time, Disintegration time, *In-vitro* drug release. From the Results concluded that all the formulation were found to be with in the Pharmacopoeial limits and the *In-vitro* dissolution profiles of all formulations were fitted in to different Kinetic models, the statistical parameters like intercept (a), slope (b) & regression coefficient (r) were calculated. Polynomial equations were developed for Wetting time, Disintegration time, $\mathbf{t_{50\%}}$, $\mathbf{t_{90\%}}$. Validity of developed polynomial equations were verified by designing 2 check point formulations (C_1, C_2). According to SUPAC guidelines the formulation (F_5) containing combination of 10% Crospovidone and 10% Croscarmellose, is the most similar formulation (similarity factor f_2= 93.556, dissimilarity factor f_1= 0.976& No significant difference, t= 0.022) to marketed product (**RISPERDAL-4**). **Conclusion:** The selected formulation (F_5) follows First order, Higuchi's kinetics, mechanism of drug release was found to be Fickian Diffusion (n= 0.383).

KEYWORDS: Risperidone, $\mathbf{3^2}$Factorial Design, Crospovidone , Croscarmellose Sodium, Wetting Time, Disintegration Time.

1. INTRODUCTION:

Tablets are the most popular oral solid formulations available in the market and are preferred by patients and physicians alike. Recently fast dissolving formulation is popular as Novel Drug Delivery Systems because they are easy to administer and lead to Patient Compliance.

Difficulty in swallowing (Dysphasia) is a common problem of all age groups, especially elderly and pediatrics, because of physiological changes associated with these groups of patients. Researchers throughout the World are focusing intensively on the methods for the development of new drug delivery systems to enhance patient's compliance.

Fast dissolving tablets become an emerging trend in the pharmaceutical industry. Fast dissolving tablets are ideal for all types of people, including for people who have swallowing difficulties, pediatric, geriatric, and bedridden patients. It is also for active patients who are busy, travelling and may not have access to water. Fast dissolving tablets are also known as orodispersible tablets, mouth-dissolving tablets, orally disintegrating tablets, melt-in mouth tablets, rapimelts, porous tablets, quick dissolving etc. Many drugs have the potentials to be made into orodispersible tablets. They vary from analgesics to neuroleptics and anti-psychotic drugs. However

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only a small percentage of them are researched on and some have been manufactured and marketed.

The speed of solubility of drug affects the rate of absorption of the drug. The faster the drug dissolve into solution, quicker the absorption and onset of clinical effect. They should readily dissolve or disintegrate in the saliva generally within <60 seconds. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach.

The small volume of saliva isusually sufficient to result in tablet disintegration in the oral cavity. The medication can then be absorbed partially or entirely into the systemic circulation from blood vessels in the sublingualmucosa, or it can be swallowed as a solution to be absorbed from the gastrointestinal tract.

Thesublingual route usually produces a faster onset of action than orally ingested tablets and theportion absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolicprocesses.The performance of ODT depends on the technology used in their manufacture.

1.1. Drug Profile and Rationality For Experimental Design:

Risperidone is an antipsychotic with extremely potent serotonin-5HT2 and potent dopamine-D2 antagonistic properties Risperidone is rapidly and very well absorbed after administration orally. It is extensively converted in the liver. Its absorption does not appear to be affected by food. It is belongs to class II of the Biopharmaceutical Classification System (BCS) where dissolutionrate is the limit factor for its absorption[1]. Hence the drug is selected for formulating Fast Dissolving Tablets by Direct compression method.

It is an important issue is to design an optimized formulation with an appropriate dissolution rate in a short time period and minimum trials. Many statistical experimental designs have been recognized as useful techniques to optimize the process variables. For this purpose, response surface methodology (RSM) utilizing a polynomial equation has been widely used. Different types of RSM designs include 3-level factorial design, central composite design (CCD), Box-Behnken design and D-optimal design. Response surface methodology (RSM) is used when only a few significant factors are involved in experimental optimization. The technique requires less experimentation and time, thus proving to be far more effective and cost-effective than the conventional methods ofManufacturing[2-5].

Hence an attempt is made in this research work to formulate Fast Dissolving Tablets of Risperidoneusing Crospovidoneand Croscarmellosesodium. Instead of normal and trial method, a standard statistical tool design of experiments is employed to study the effect of formulation variables on the release properties.

Large scale production needs more simplicity in the formulation with economic and cheapest dosage form. The Fast Dissolving tablets formulation by direct compression method is most acceptable in large scale production.

A **3^2** full factorial design was employed to systematically study the drug release profile. A 3^2 full factorial design was employed to investigate the effect of two independent variables (factors), i.e the amounts of Crospovidone and Croscarmellose on the dependent variables, i.e. Wetting Time, Disintegration time, $t_{50\%}$, $t_{90\%}$,(Time taken to release 50%, 90% respectively).

2. MATERIALS AND METHODS

Materials used in this study were obtained from the different sources. Risperidonewas a gift sample from RPG Life Sciences Limited, Mumbai, India. Crospovidone, Croscarmellose, Di Calcium Phosphate, were procured from LobaChemiePvt.Ltd, Mumbai. Other excipients such as Magnesium Stearate and talc were procured from S.D. Fine Chem. Ltd, Mumbai.

2.1. Formulation Development of Risperidone Fast Dissolving Tablets:

The factorial design is a technique that allows identification of factors involved in a process and assesses their relative importance. In addition, any interaction between factors chosen can be identified. Construction of a factorial design involves the selection of parameters and the choice of responses[6].

A selected three level, two factor experimental design (3^2 factorialdesign) describe the proportion in which the independent variables Crospovidone and Croscarmellose were used in formulation of Risperidone Fast Dissolving Tablets. The time required for 50% ($t_{50\%}$), 90% ($t_{90\%}$) drug dissolution, Disintegration Time and Wetting Time were selected as dependent variables. Significance terms were chosen at 95% confidence interval ($p<0.05$) for Final Equations. Polynomial equations were developed for $t_{50\%}$, $t_{90\%}$, Disintegration Time and Wetting Time (step-wise backward Linear Regression Analysis).

The three levels of factor X_1 (Crospovidone) at a concentration of 5%,10%, 15%.three levels of factor X_2 (Croscarmellose) at a concentration of 5%, 10%, 15%. (% with respect to average weight

of Tablet, i.e 100 mg) was taken as the rationale for the design of the RisperidoneFast Dissolving tablet formulation. Totally nine Risperidone Fast Dissolvingtablet formulations were prepared employing selected combinations of the two factors i.eX_1, X_2 as per 3^2 Factorial and evaluated to find out the significance of combined effects of X_1, $X_2$to select the best combination and the concentration required to achieve the desired Fast release/ Dissolution of drug (by means providing large Surface area and Improved Solubility) from the dosage form.

2.2. Preparation of Risperidone Fast Dissolving Tablets:

Risperidone Tablets were prepared by direct compression method. The composition of each tablet is shown in Table No 2 . The drug, diluents, superdisintegrants were passed through sieve #40. All the above ingredients were properly mixed together (ina poly-bag). Talc and Magnesium stearate were passed through mesh #80, mixed and blended with initial mixture in a poly-bag. The powder blend was compressed into tablets on a 8 station rotary punch tableting machine (mini-press) using 8 mm circular punches and same hardness was used for the required number tablets. Compressed tablets were examined as per official standards and unofficial tests. Tablets were packaged in well closed light resistance and moisture proof containers.

2.3. Experimental Design:

Experimental design utilized in present investigation for the optimization of Superdisintegrant concentration such as, concentration of Crospovidone was taken as X_1 and concentration of Croscarmellose sodium was taken as X_2. Experimental design was given in the Table 1. Three levels for the Concentration of Crospovidone were selected and coded as -1= 5%, 0=10%, +1=15%. Three levels for the Concentration of Croscarmellose sodium were selected and coded as -1= 5%, 0=10%, +1=15%. Formulae for all the experimental batches were given in Table 2[7].

Table 1: Experimental Design Layout

Formulation Code	X_1	X_2
F_1	1	1
F_2	1	0
F_3	1	-1
F_4	0	1
F_5	0	0
F_6	0	-1
F_7	-1	1
F_8	-1	0
F_9	-1	-1
C_1	-0.5	-0.5
C_2	0.5	0.5

Table 2: Formulae for the Preparation of Risperidone Fast Dissolving Tablets as Per Experimental Design

Name of Ingredients	Quantity of Ingredients per each Tablet (mg)								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Risperidone	4	4	4	4	4	4	4	4	4
MCC	60	65	70	65	70	75	70	75	80
Crospovidone	15	15	15	10	10	10	5	5	5
Croscarmellose sodium	15	10	5	15	10	5	15	10	5
Peppermint Flavor	2	2	2	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Total Weight	100	100	100	100	100	100	100	100	100

2.4. Evaluation of Risperidone fast dissolving tablets:

2.4.1. Hardness[8]

The hardness of the tablets was tested by diametric compression using a Monsanto Hardness Tester. A tablet hardness of about 2-4 Kg/cm^2 is considered adequate for mechanical stability.

2.4.2. Friability[8]

The friability of the tablets was measured in a Roche Friabilator. 20 Tablets were taken, Weighed and Initial weight was noted (W_0) are dedusted in a drum for a fixed time (100 Freefalls, in a Roche Friabilator) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %

Friability (%) = [(Initial weight- Final weight) / (Initial weight)] x 100

2.4.3. Content Uniformity[8]

In this test, 20 tablets were randomly selected and the percent drug content was determined, the tablets contained not less than 85% or not more than 115% (100±15%)of the labeled drug content can be considered as the test was passed.

2.4.4. Assay[9,10]

Drug content was determined by weighing randomly selected tablets, pulverizing to a fine powder. The powder equivalent to 10 mg Risperidone was weighed and dissolved in 10 ml of methanol in volumetric flask using magnetic stirrer, the volume was adjusted to 100 ml with Phosphate buffer pH 6.8and the solution was filtered. An aliquot of 1.0 ml of solution were diluted to 10 ml Phosphate buffer pH 6.8 in separate volumetric flask. The drug content in was determined spectrophotometrically at 280 nm.

2.4.5. Thickness[8]

Thickness of the all tablet formulations were measured using vernier calipers by placing tablet between two arms of the vernier calipers.

2.4.6. Wetting time[11,12]

To measure Wetting time of the Tablet, a piece of Tissue paper folded twice was placed in a small petri dish (Internal Diameter is= 6.5 cm) containing 5 ml of Distilled water. A Tablet placed on the paper, and the time for complete wetting of the tablet was measured in seconds.

2.4.7. In-vitro Dissolution Study[12]

The *In-vitro* dissolution study for the Risperidone Fast Dissolving tablets were carried out in USP XXIII type-II dissolution test apparatus (Paddle type) using 900 ml of Phosphate buffer pH 6.8 as dissolution medium at 50 rpm and temperature 37±0.5°C. At predetermined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The resultant samples were analyzed for the presence of the drug release by measuring the absorbance at 280 nm using UV Visible spectrophotometer after suitable dilutions. The determinations were performed in triplicate (n=3).

2.4.8. Disintegration test[12]

Disintegration of fast disintegrating tablets is achieved in the mouth owing to the action of saliva, however amount of saliva in the mouth is limited and no tablet disintegration test was found in USP and IP to simulate *in vivo* conditions. A modified method was used to determine disintegration time of the tablets. A cylindrical vessel was used in which 10 mesh screen was placed in such way that only 2 ml of disintegrating or dissolution medium would be placed below the sieve. To determine disintegration time, 6 ml of Sorenson's buffer (pH 6.8), was placed inside the vessel in such way that 4 ml of the media was below the sieve and 2 ml above the sieve. Tablet was placed on the sieve and the whole assembly was then placed on a shaker. The time at which all the particles pass through the sieve was taken as a disintegration time of the tablet. Six tablets were chosen randomly from the composite samples and the average value was determined.

2.4.9. Kinetic modeling of drug release[13-16]

The dissolution profile of all the formulations was fitted in to zero-order, first-order, Higuchi and Korsmeyer-peppas models to ascertain the kinetic modeling of drug release.

3. RESULTS AND DISCUSSION:

Fast Dissolving tablets of Risperidone were prepared and optimized by 3^2 factorial design in order to select the best combination of different Superdisintegrants, Crospovidone, Croscarmellose sodium and also to achieve the predicted rapid release of drug from the dosage form(by Disintegrating quickly). The two factorial parameters involved in the development of formulations are, quantity of Crospovidone&Croscarmellose sodium as independent variables (X_1, X_2), and *In vitro* dissolution parameters such as $t_{50\%}$, $t_{90\%}$ andWetting time, Disintegrating Time as dependent variables Totally nine formulations were prepared using 3 levels of 2 factors and all the formulations containing 4 mg of Risperidone were prepared as a Fast Dissolving tablet dosage form by Direct Compression technique as per the formulae given in Table 2.

All the prepared tablets were evaluated for different post compression parameters, drug content, mean hardness, friability, mean thickness, Weight variation as per official methods and results are given in Table 3. The hardness of tablets was in the range of **2.5±0.16-2.85±0.14 Kg/cm².** Weight loss in the friability test was not more than **0.305±0.32%**. Drug content of prepared tablets was within **acceptance range only**. The Wetting Time of tablets was in the range of **29.76±1.30-36.67±1.6 sec.** The Disintegration Time of tablets was in the range of **14.66±1.5-19.50±1.7 sec.**Results for all Post-compression parameters were tabulated or shown in Table 3. *In-vitro* Dissolution studies were performed for prepared tablets using Phosphate buffer pH 6.8 as a dissolution media at 50 rpm and temperature 37±0.5°C. The *In-vitro* dissolution profiles of tablets are shown in Fig.1 and the dissolution parameters are given in Table 4.

Table 3: Post-Compression Parameters for the Formulations (n = 3)

S.No	Formulation Code	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	%Weight Variation	Drug Content(%)	Wetting Time(sec)	Disintegration Time (sec)
1	F_1	2.7±0.15	3.75±015	0.165±0.2	Pass	99.715±0.25	29.76±1.3	14.66±1.5
2	F_2	2.75±0.14	3.65±0.14	0.215±0.3	Pass	99.625±0.70	29.86±1.4	16.23±1.6
3	F_3	2.7±0.15	3.70±0.16	0.17±0.1	Pass	99.935±0.50	32.94±1.6	17.40±1.8
4	F_4	2.8±0.13	3.55±0.10	0.225±0.2	Pass	99.485±.40	32.86±1.4	16.01±1.4
5	F_5	2.85±0.14	3.45±0.11	0.275±0.3	Pass	99.39±0.90	33.05±1.5	16.31±1.5
6	F_6	2.8±0.15	3.50±0.12	0.230±0.05	Pass	99.71±0.70	33.75±1.7	17.60±1.7
7	F_7	2.5±0.16	3.50±0.10	0.255±0.3	Pass	99.927±0.25	33.75±1.3	17.33±1.4
8	F_8	2.55±0.14	3.40±0.12	0.305±0.32	Pass	99.84±0.30	36.34±1.5	17.90±1.5
9	F_9	2.5±0.16	3.45±0.11	0.26±0.40	Pass	100.15±0.50	36.67±1.6	19.50±1.7

Cumulative % Drug release of Factorial Design Formulations F_1-F_9 at 45 min were found to be in the range of **99.94±0.21-100.06±0.15 %**. From the result it reveals that the release rate was higher for formulations containing High level of Crospovidone / Croscarmellose sodium compared with other Formulations containing Lower level, due to High concentration of Superdisintegrant in combination, shows various disintegration mechanism such as wicking and swelling etc more compared with lower concentration and alone, drug may release rapidly and shows improved bioavailability. Therefore, required release of drug can be obtained by manipulating the composition of Crospovidone and Croscarmellose sodium.

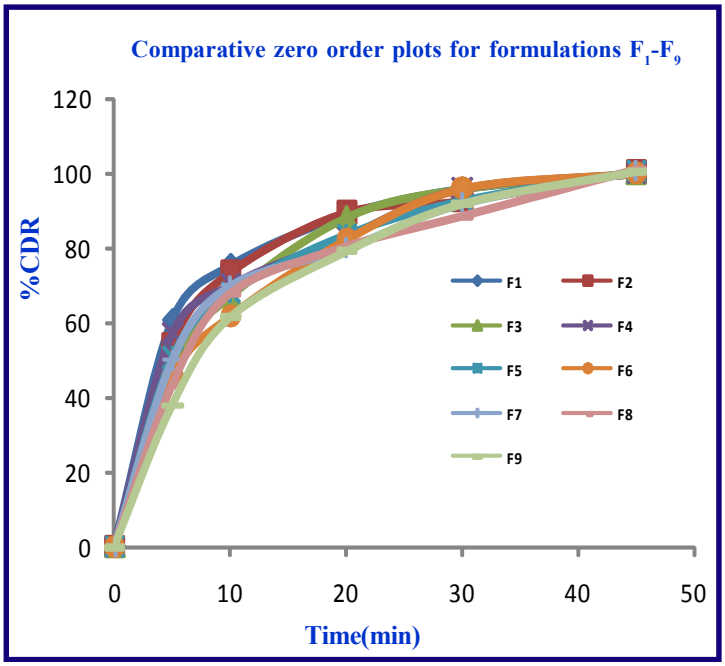

Fig.1 Comparative Zero order plots for Formulation F_1-F_9

Much variation was observed in the Wetting time, Disintegrating time, $t_{50\%}$and $t_{90\%}$ due to formulation variables. Formulation F_5 containing 10 mg of Crospovidone, 10 mg of Croscarmellose sodium showed promising dissolution parameter (**Wetting time**_33.05±1.5sec **, Disintegrating time**_16.31±1.5 sec **,** $\mathbf{t_{50\%}}$_8.370 min **,** $\mathbf{t_{90\%}}$_27.813 min). The difference in burst effect of the initial time is a result of the difference in the Concentration of Superdisintegrants mixtures. This reveals that increased concentration of superdisintegrants resulted in a corresponding decrease in the Wetting Time, which might be due to the result of wicking and other possible disintegrating mechanisms. Disintegration time is directly proportional to wetting time.

The *In -vitro* dissolution data of Risperidone Fast Dissolving formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer-Peppas models to assess the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in Table 4 and plots shown in fig.1-4. It was observed from the above that dissolution of all the tablets followed First order kinetics with co-efficient of determination (R^2) values in the range of **0.936-0.992**. The values of r of factorial formulations for Higuchi's equation was found to be in the range of **0.939-0.987**, which shows that the dissolution data fitted well to Higuchi's square root of time equation confirming the release followed diffusion mechanism. Kinetic data also treated for Peppas equation, the slope (n) values ranges from **0.272-0.464** that shows Fickian diffusion mechanism.Fig.5, 6 shows Wetting Time Chart and Disintegration Time chart respectively. Polynomial equations were derived for Wetting time, Disintegrating time, $t_{50\%}$ and $t_{90\%}$ values by backward stepwise linear regression analysisusing **PCP Disso** software and Response surface plots were constructed

Table 4: Regression Analysis Data of 3^2 Factorial Design Formulations of Risperidone Fast Dissolving Tablets

S.No	Formulation Code	Kinetic Parameters											
		Zero Order			First Order			Higuchi			Korsmeyer-Peppas		
		a	b	r	a	b	r	a	b	r	a	b	r
1	F_1	38.257	1.743	0.791	1.894	0.044	0.99	16.7	14.557	0.939	0.464	1.041	0.831
2	F_2	35.467	1.799	0.815	1.881	0.038	0.973	14.104	14.782	0.951	0.426	1.064	0.834
3	F_3	31.868	1.897	0.848	2.173	0.067	0.966	10.598	15.249	0.968	0.368	1.102	0.85
4	F_4	34.681	1.8	0.828	2.264	0.077	0.936	13.79	14.659	0.958	0.424	1.061	0.847
5	F_5	31.891	1.855	0.851	1.923	0.036	0.992	11.194	14.884	0.97	0.383	1.086	0.849
6	F_6	28.292	1.954	0.879	2.166	0.061	0.972	7.688	15.351	0.981	0.32	1.127	0.866
7	F_7	31.554	1.841	0.853	1.914	0.033	0.983	11.137	14.734	0.969	0.387	1.081	0.845
8	F_8	28.764	1.896	0.872	1.915	0.03	0.98	8.541	14.959	0.977	0.341	1.109	0.847
9	F_9	25.165	1.995	0.899	1.977	0.035	0.997	5.035	15.426	0.987	0.272	1.155	0.864
10	MP	32.72	1.836	0.842	2.34	0.082	0.909	11.894	14.821	0.966	0.394	1.08	0.847

F_1 to F_9 are factorial formulations, r-correlation coefficient, a-Intercept, b-Slope and MP-Marketed Product.

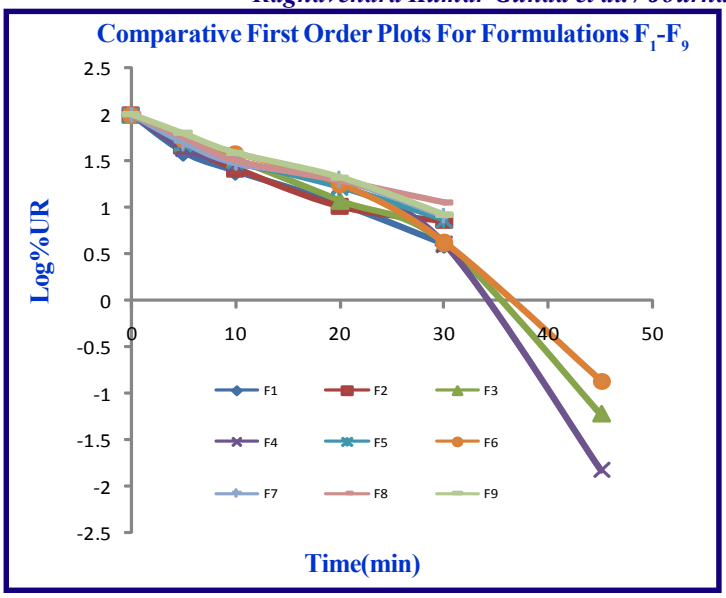

Fig.2 Comparative First order plots for Formulation F_1-F_9

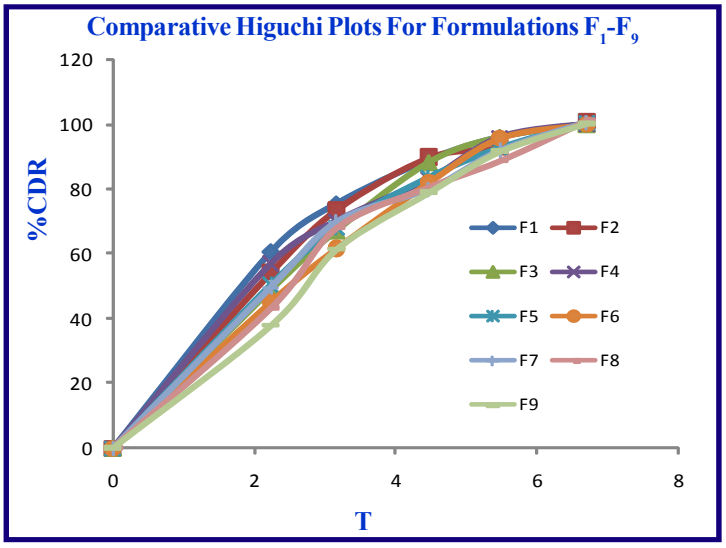

Fig.3 Comparative Higuchi plots for Formulation F_1-F_9

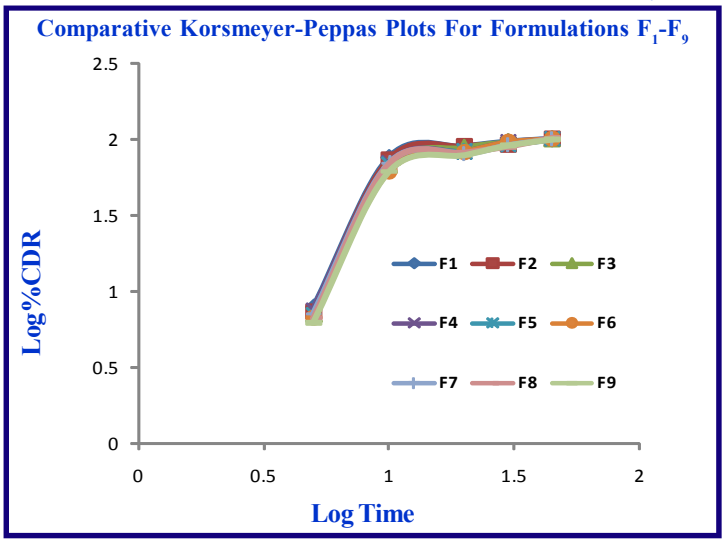

Fig.4 Comparative Korsmeyer-Peppas plots for Formulation F_1-F_9

using **SIGMAPLOT V13**software.The Linear Contour plots, Response surface plotsandColour Contour plots were shown in Fig.7-18 for Wetting time,Disintegrating time, $t_{50\%}$ and $t_{90\%}$ using X_1 and X_2 on both the axes respectively. The dissolution data (Kinetic parameters) of factorial formulations F_1 to F_9 are shown in Table 5.

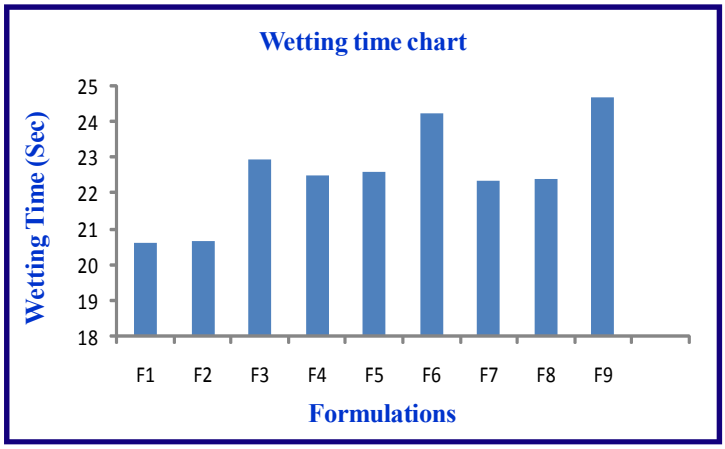

Fig.5 Wetting Time Chart for Formulation F_1-F_9

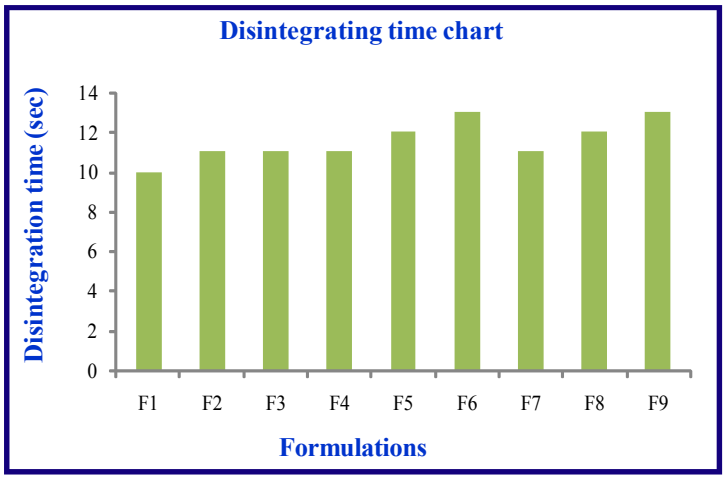

Fig.6 Disintegration Time Chart for Formulation F_1-F_9

Table 5: Dissolution Parameters of Risperidone Fast Dissolving Tablets 3^2 Full Factorial Design Batches (n = 3)

S.No	Formulation Code	Kinetic Parameters			
		$t_{1/2}$(min)	$t_{90\%}$ (min)	WT(Sec)	DT(Sec)
1	F_1	6.874	22.842	29.76±1.3	14.66±1.5
2	F_2	8.013	26.628	29.86±1.4	16.23±1.6
3	F_3	4.507	14.977	32.94±1.6	17.40±1.8
4	F_4	3.913	13.002	32.86±1.4	16.01±1.4
5	F_5	8.37	27.813	33.05±1.5	16.31±1.5
6	F_6	4.963	16.493	33.75±1.7	17.60±1.7
7	F_7	8.991	29.875	33.75±1.3	17.33±1.4
8	F_8	9.963	33.108	36.34±1.5	17.90±1.5
9	F_9	8.63	28.678	36.67±1.6	19.50±1.7

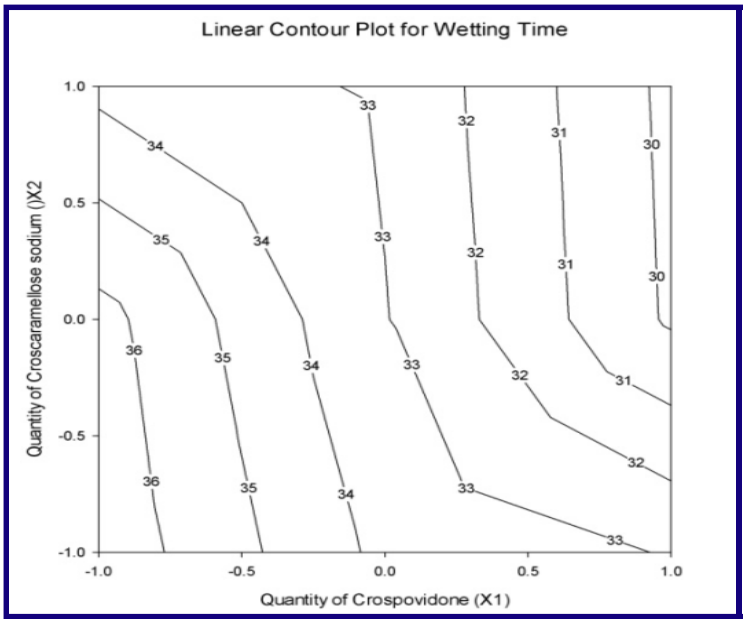

Fig.7 Linear Contour plot for Wetting Time

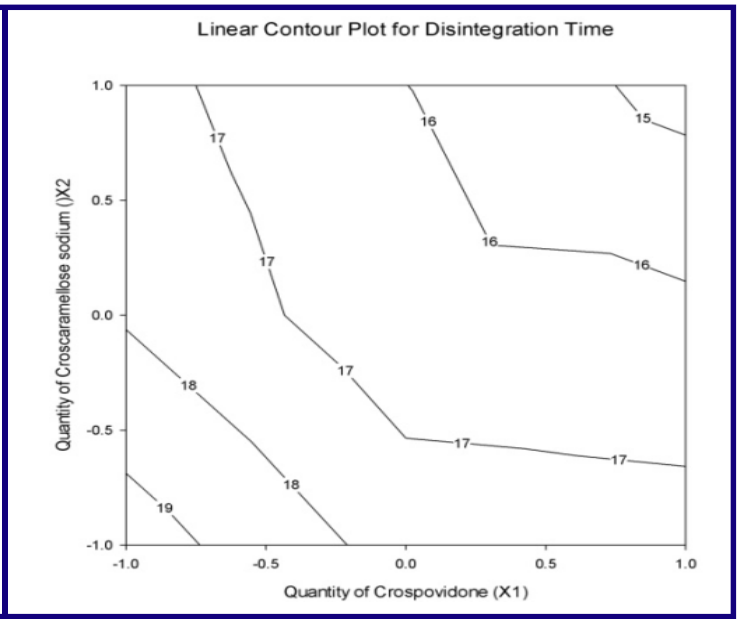

Fig.8 Linear Contour plot for Disintegration Time

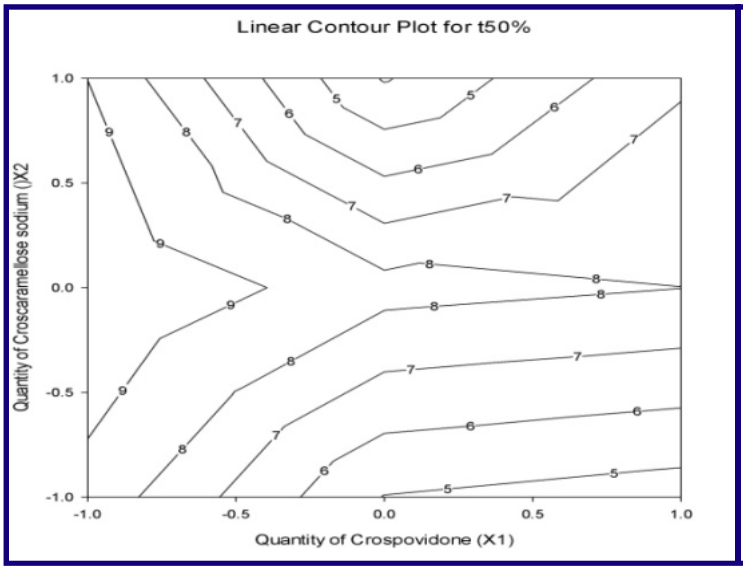

Fig.9 Linear Contour plot for $t_{50\%}$

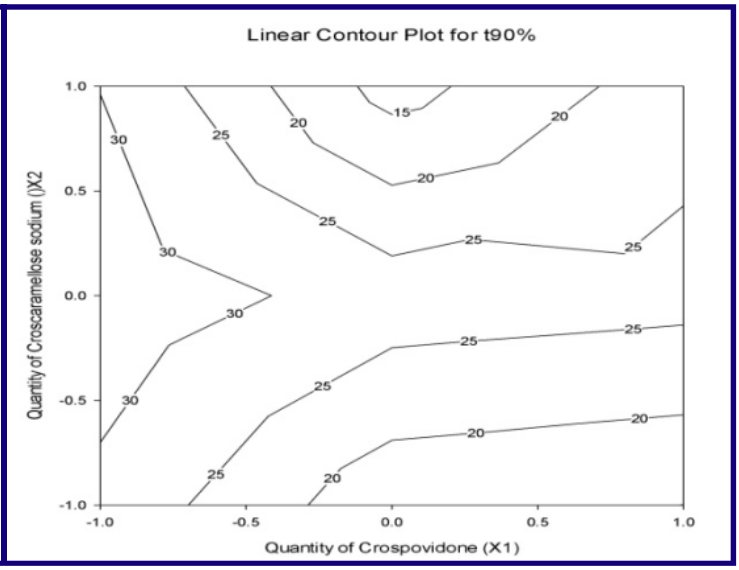

Fig.10 Linear Contour plot for $t_{90\%}$

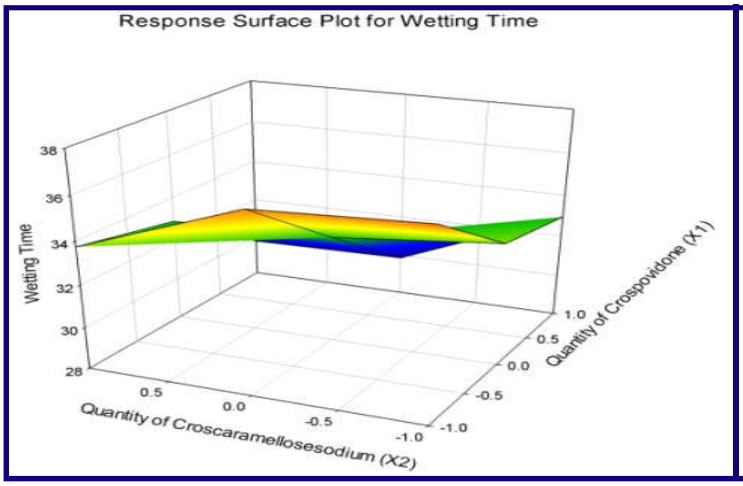

Fig.11 Response Surface plot for Wetting Time

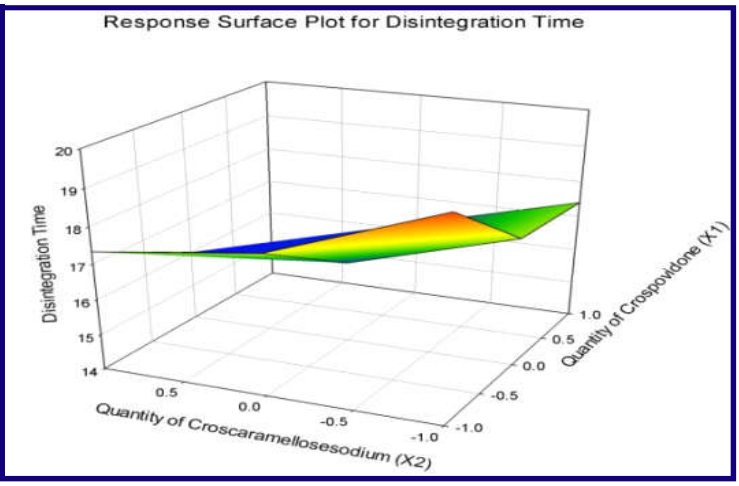

Fig.12 Response Surface plot for Disintegration Time

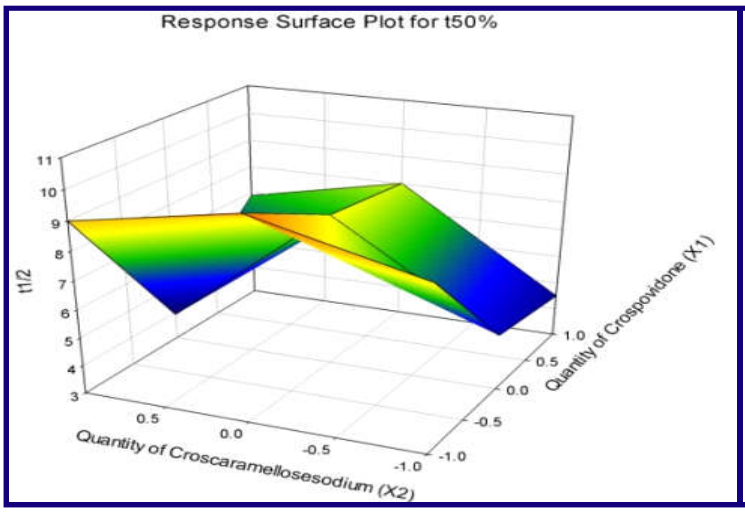

Fig.13. Response Surface plot for $t_{50\%}$

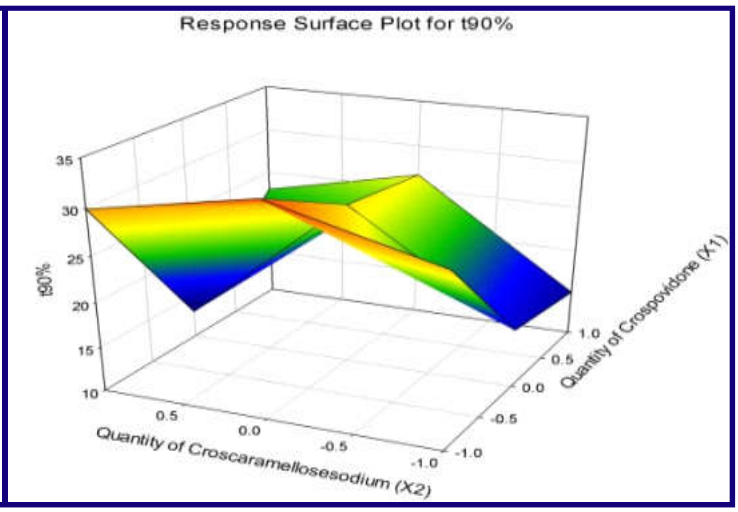

Fig.14. Response Surface plot for $t_{90\%}$

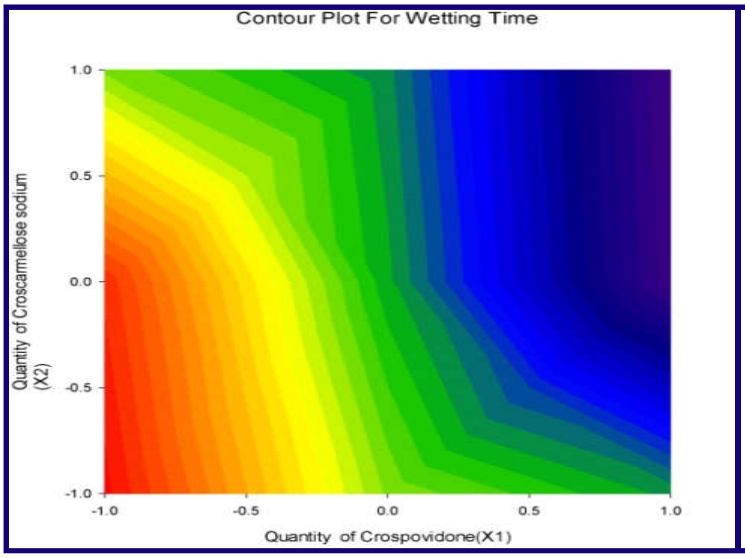

Fig.15. Colour Contour plot for Wetting Time

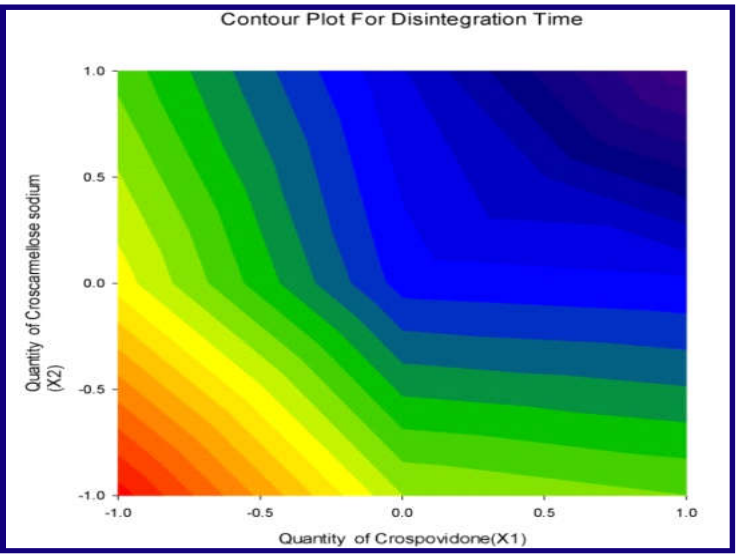

Fig.16. Colour Contour plot for Disintegration Time

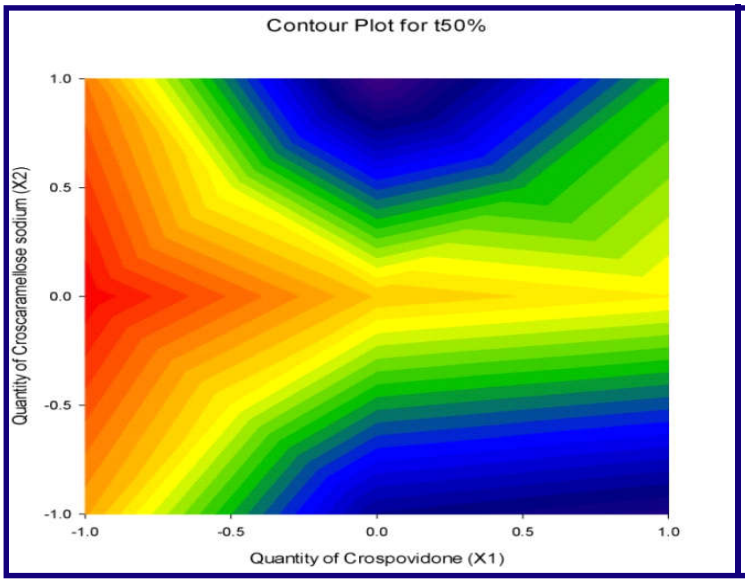

Fig.17.Colour Contour plot for $t_{50\%}$

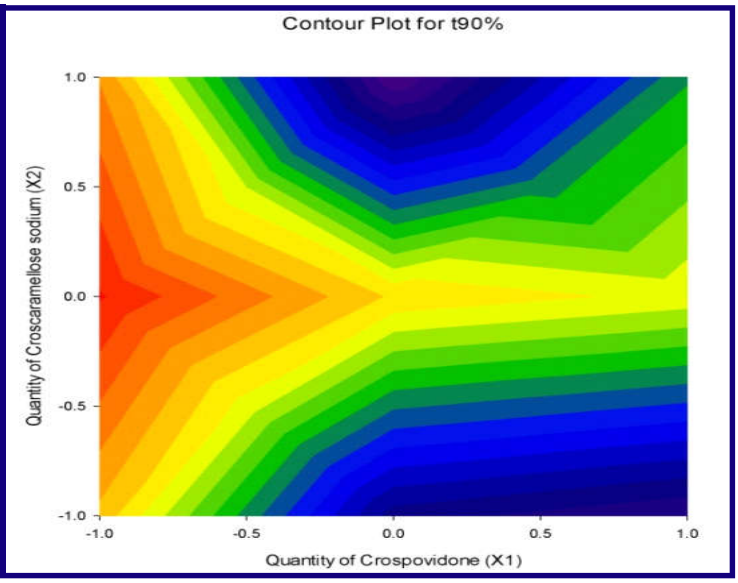

Fig.18.Colour Contour plot for $t_{90\%}$

Table 6: Dissolution Parameters for Predicted and Observed Values for Check Point Formulations

Formulation Code	Predicted Value				Actual Observed Value			
	WT(Sec)	DT(Sec)	$t_{50\%}$ (min)	$t_{90\%}$ (min)	WT(Sec)	DT(Sec)	$t_{50\%}$ (min)	$t_{90\%}$ (min)
C_1	35.121	18.235	7.707	25.61	35.23	18.45	7.79	25.632
C_2	31.59	16.08	6.621	22.003	31.93	16.27	6.652	22.59

Polynomial equation for 3^2 full factorial designs is given in Equation

$$\mathbf{Y=b_0+b_1X_1+b_2X_2+b_{12}X_1X_2+b_{11}X_1^2+b_{22}X_2^2\ldots}$$

Where, Y is dependent variable, b_0 arithmetic mean response of nine batches, and b_1 estimated co-efficient for factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction term (X_1X_2) shows how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity. Validity of derived equations was verified by preparing Two Check point Formulations of Intermediate concentration(C_1, C_2).

The equations for Wetting time, Disintegrating time, $t_{50\%}$ and $t_{90\%}$ developed as follows,

$Y_1= 33.220-2.367X_1-1.165X_2-0.065X_1X_2+0.205X_2^2$ **(for Wetting time)**

$Y_2= 16.993-1.073X_1-1.083X_2-0.143\ X_1X_2+0.53\ X_1^2+0.27\ X_2^2$ **(for Disintegration time)**

$Y_3= 7.136-1.365X_1+0.2797X_20.502\ X_1X_2+2.08\ X_1^2-2.47\ X_2^2$ **(for $t_{50\%}$)**

$Y_4= 23.713-4.536X_1+0.929X_2+1.667\ X_1X_2+6.92\ X_1^2-8.21\ X_2^2$ **(for $t_{90\%}$)**

The positive sign for co-efficient of X_1 in Y_1, Y_2, Y_3 and Y_4 equations indicates that, as the concentration of Crospovidone decreases, Wetting time, Disintegrating time, $t_{50\%}$ and $t_{90\%}$ value increases(inversely proportional relationship). In other words the data demonstrate that both X_1 (amount of Crospovidone) and X_2 (amount of Croscarmellose sodium) affect the time required for drug release (Wetting time, Disintegrating time, $t_{50\%}$ and $t_{90\%}$). From the results it can be concluded that, and increase in the amount of the Superdisintegrant leads to decrease in Disintegration time of the Dosage form and drug release pattern may be changed by appropriate selection of the X_1 and X_2 levels. The Dissolution parameters for predicted from the polynomial equations derived and those actual observed from experimental results are summarized in Table 6. The closeness of Predicted and Observed values for Wetting time, Disintegrating time $t_{50\%}$ and $t_{90\%}$ indicates validity of derived equations for dependent variables. The Response surface Plots were presented to show the effects of X_1 and X_2 on Wetting time, Disintegrating time $t_{50\%}$ and $t_{90\%}$. The final best (Optimized) formulation (F_5) is compared with marketed product (**RISPERDAL-4**) shows similarity factor (f_2) 93.556, difference factor (f_1) 0.976 (There is no significant difference in drug release becauset$_{cal}$is<0.05).

4. CONCLUSION

The present research work envisages the applicability of Superdisintegrants such as Crospovidone and Croscarmellose sodium in the design and development of Fast Dissolving tablet formulations of Risperidone utilizing the 3^2 factorial design. From the results it was clearly understand that as the concentration of Superdisintegrant increases the release rate of drug was RAPID (Improved Solubility) and both of these Superdisintegrants can be used in combination since do not interact with the drug which may be more helpful in achieving the desired fast Dissolving of the dosage form for rapid action and improved Bioavailability. The optimized formulation followed Higuchi's kinetics while the drug release mechanism was found to beFickian Diffusion, first order release type. On the basis of evaluation parameters, the optimized formulation F_5 may be used for the effective management of schizophrenia, bipolar mania, and autism.This may improve the patient compliance by showing rapid action via disintegration without difficult in swallowing and side effects which will ultimately improve the therapeutic outcome.we could be able to minimize the per oral cost of the Formulation.

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