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RESEARCH ARTICLE

Formulation and Evaluation of Orally Disintegrating Tablets of Aripiprazole Using 3^2 Full Factorial Design

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ABSTRACT

Orally Disintegrating Tablets (ODTs) have the unique property of disintegrating in the mouth in seconds without chewing and the need of water which is advantageous mainly for paediatric, geriatrics, mentally challenged, bed ridden, uncooperative patients and patients having difficulty in swallowing tablets. The current study was aimed to formulate and evaluate orally disintegrating tablets of Aripiprazole commonly used as an atypical antipsychotic. Drug excipients compatibility study checked by DSC showed no interaction between drug and excipients. The tablets were prepared by sublimation technique. The experimental trials were taken using menthol as a sublimating agent and kyron T-314 as a superdisintegrant in different concentrations. A 3^2 full factorial design was applied to investigate the combined effect of two formulation independent variables: amount of Menthol (X_1) and Kyron T-314 (X_2). The disintegration time (Y_1) and wetting time (Y_2) were selected as dependent variables. The prepared tablets were evaluated for post compression parameters like diameter, thickness, weight variation, hardness, friability, hygroscopicity, disintegration time, wetting time, drug content and *in-vitro* drug release. The results indicated that concentration of Menthol (X_1) and Kyron T-314 (X_2) significantly affected the disintegration time (Y_1) and wetting time (Y_2). Batch F9 containing Menthol (14 mg) and Kyron T-314 (8.25 mg) shows less disintegration time (10 Sec.), less wetting time (22 Sec.) and good drug release (99.66%) compared to other batches. Hence it was selected as optimized batch. Stability study conducted as per ICH guidelines and the optimized batch F9 was found to be stable.

KEYWORDS

Orally disintegrating tablets, Aripiprazole, Sublimation, Menthol, Kyron T-314, 3^2 Full Factorial Design

INTRODUCTION

Despite of tremendous innovations in drug delivery, the oral route remains the preferred route for administration of therapeutic agents because of accurate dosage, low cost therapy, self-medication, non-invasive method and ease of administration leading to high level of patient compliance. However, traditional tablets and capsules administered with a glass of water may be inconvenient or impractical for some geriatric patients because of changes in various physiological and neurological conditions associated with aging including difficulty in swallowing/dysphagia, hand tremors, deterioration in their eyesight, hearing, memory, risk of choking in addition to change in taste and smell.[1]

Solid dosage forms also present significant administration challenges in other patient groups, such as children, mentally challenged, bed ridden and uncooperative patients. Pediatric patients may suffer from ingestion problems as a result of underdeveloped muscular and nervous control.

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Moreover, patients travelling with little or no access to water, limit utility of orally administered conventional tablets. Therefore, to cater the needs of such patients, recent advancements in technology have resulted in development of viable dosage alternatives popularly known as Orally Disintegrating Tablets (ODTs). These dosage forms are preferable alternative for oral medication in improving the quality of life and patient acceptability.[2]

ODTs are also known as orodispersible tablets, mouth dissolving tablets, rapimelts, melt-in-mouth tablets, fast disintegrating tablets and rapid dissolving tablets. ODTs are the solid unit dosage forms/entities containing medicinal substances which disintegrate or dissolve rapidly in oral cavity usually within a few seconds even without the need of water or chewing.[3]

Aripiprazole is an atypical antipsychotic that has serotonin 5-HT_{1A} receptor partial agonist and and 5-HT_{2A} receptor antagonist properties as well as being a parial agonist at dopamine D_2 receptors. The molecular weight of Aripiprazole is 448.39 gm/mol. Aripiprazole is white to off-white, crystalline powder. It is freely soluble in dichloromethane; sparingly soluble in toluene; insoluble in methanol and in water. It is mainly used in the management of schizophrenia, Acute treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy and as an adjunct to lithium or valproate, Maintenance treatment of bipolar I disorder, both as monotherapy and as an adjunct to lithium or valproate, Adjunctive treatment of major depressive disorder (MDD) and Treatment of irritability associated with autistic disorder (in Pediatric patients).[4,5]

The fundamental principle used in the development of the Orally Disintegrating Tablets is to maximize its pore structure. A Sublimation Technique is adopted in the present investigation after addition of a sublimating agent to increase porosity of the tablets. It is likely that a porous hydrophilic will easily pick up the disintegrating medium and break quickly. The effect of concentration of different superdisintegrants such as Crospovidone XL 10, Kyron T-314 and different sublimating agents such as Menthol, Camphor and Ammonium Bicarbonate on the tablet properties, disintegration time, wetting time and in vitro drug release also considered.

MATERIAL AND METHODS

Materials

Aripiprazole, Cherry Flavour and Ferric Oxide Red were obtained as a gift sample from Torrent Research Centre. Menthol and Povidone K-30 were procured from Seva Fine Chemicals. Camphor was procured from SD Fine Chemicals. Ammonium bicarbonate and Isopropyl alcohol were procured from Suvinath Laboratories. Mannitol was procured from Fine Star Industries. Crospovidone XL 10 and Talc were procured from ACS Chemicals. Kyron T-314 was procured from Corel Pharm Chem. Sucralose was procured from Nutrasweet Company. Magnesium Stearate and Sodium Lauryl Sulfate were gifted from Chemdyes Corporation.

Drug - Excipients Compatibility Study by DSC[6]

Differential Scanning Calorimetry study was carried out using Shimadzu DSC-60 instrument to check drug-excipients compatibility. The thermogram of moisture free powdered sample of pure Aripiprazole and drug with excipients in 1:1 ratio was employed for the determination of glass transition temperature.

3^2 Full Factorial Design[7,8]

A 3^2 randomized full factorial design was employed in the present study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed for all 9 possible combinations.

The factors were selected based on preliminary study. The concentration of Menthol (X_1) and concentration of Kyron T- 314 (X_2) were chosen as independent variables in 3^2 full factorial design, while disintegration time (Y_1) and wetting time (Y_2) were taken as dependent variables. (Table 1). Polynomial equation generated by this design is as follow:

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

Where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_1 to b_2 are the regression coefficients. The main effects (X_1 and X_2) represent the average result of changing 1 factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The response values are subjected to multi linear regression analysis to find out relationship between the factors used and response values obtained. After application of 3^2 full factorial design and with the help of produced polynomial terms, amount of formulation variable was optimized.

Table 1: Selection of Levels for Independent Variables and Coding of Variable

Levels	Coded value	Independent Variables	
		Menthol (X_1)	Kyron T-314 (X_2)
Low	-1	10 mg	5.25 mg
Intermediate	0	12 mg	6.75 mg
High	1	14 mg	8.25 mg

Preparation of Aripiprazole Orally Disintegrating Tablets[9,10]

Aripiprazole orally disintegrating tablets were prepared by sublimation technique according to formula given in Table 2. The detailed manufacturing process is as below;

Step 1: Sifting

Active and inactive ingredients were dispensed as per manufacturing formula. All the raw materials were passed through a 100 # screen prior to mixing.

Step 2: Dry Mixing

Required quantity of Aripiprazole, sublimating agent, Mannitol, superdisintegrant were mixed together for 10 minutes in poly bag.

Step 3: Granulation

Binder solution preparation

Required quantity of Povidone K-30 was added to the isopropyl alcohol with continuous stirring until clear solution was obtained.

Binder solution addition and granulation

The binder solution of step 3.1 was added to the mixture of step 2 in a quantity just enough to bind the mass.

Step 4: Sizing

The wet mass was passed through 30 # sieve.

Step 5: Drying

The granules were air dried.

Step 6: Blending

The dried granules were mixed with Sucralose, Talc, Sodium Lauryl Sulfate, Cherry Flavour and Ferric Oxide Red for 10 minutes. The blend was evaluated for different pre-compression parameters.

Step 7: Lubrication

Magnesium stearate were added in above step and mixed for 5 minutes.

Step 8: Compression

The uniformly mixed blend was compressed in to round shaped tablets by using 6 mm punch on tablet compression machine to get a tablet of 150 mg.

Step 9: Sublimation

Then these tablets were subjected to sublimation, by placing in a hot air oven at 60°C for 2 hours to generate a porous matrix, due to removal of volatilizable component. The tablets were weighed at regular intervals until constant weight was achieved ensuring complete removal of the sublimable component. The prepared tablets were evaluated for different post compression parameters.

Table 2: Composition of 3^2 Full Factorial Design Batches F1 to F9

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Aripiprazole	10	10	10	10	10	10	10	10	10
Menthol	10	12	14	10	12	14	10	12	14
Mannitol	102.78	100.78	98.78	101.28	99.28	97.28	99.78	97.78	95.78
Kyron T-314	5.25	5.25	5.25	6.75	6.75	6.75	8.25	8.25	8.25
Povidone (K-30)	15	15	15	15	15	15	15	15	15
Isopropyl Alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Sucralose	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Talc	2	2	2	2	2	2	2	2	2
Sodium Lauryl Sulfate	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Cherry Flavour	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Ferric Oxide Red	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Total Weight (in mg)	150	150	150	150	150	150	150	150	150

Evaluation Parameters of Aripiprazole Orally Disintegrating Tablets

Diameter[11]

Tablets of each batch were selected and measured for diameter using vernier caliper.

Thickness[11]

Thickness of the tablet was determined for 20 pre weighed tablets of each batch using a digital vernier scale and the average thickness was determined in mm.

Weight Variation[11]

20 tablets selected randomly were weighed collectively and individually. Average weight was determined and standard deviation was calculated.

Hardness[11]

The hardness of the tablets was measured using the monsanto hardness tester. Six tablets from each formulation were randomly selected and used. The average hardness and the standard

deviation were calculated. It is expressed in Kg/cm^2.

Friability[11]

Friability of the tablets was determined using roche friabilator. 6 tablets from each batch were weighed and made to rotate 100 revolutions (25 rpm for 4 min). Tablets were dedusted, reweighed and percentage of weight loss was calculated. Friability below 1% is considered acceptable.

Percent friability = [(initial wt - final wt) / initial wt] x 100

Measurement of Liquid Uptake (Wetting time)[11]

Wetting time of dosage form is related to the contact angle. This gives an insight into the disintegration of the tablets. A lower wetting time indicates a quicker disintegration of the tablet. A piece of tissue paper folded twice was placed in small petridish (internal diameter 6.5cm) containing 6 ml water. A tablet was placed on the tissue paper and the time for complete wetting was measured.

In-vitro Disintegration Time[11]

The disintegration time of prepared formulations was determined according to the procedure stated in USP which involves the use of same apparatus used to evaluate conventional tablets. The European Pharmacopoeia specified limit for ODT within 3 min. The disintegration test was performed using disintegration apparatus USP with distilled water at 37±0.5°C.

In-Vitro Dissolution Studies[12]

In-vitro release rate of Aripiprazole from the formulated orally disintegrating tablets were determined using USP Type II (Paddle) apparatus. Dissolution studies were carried out according to USFDA guidelines.

The dissolution medium was selected 1000 ml acetate buffer pH 4.0 with paddle speed of 75 rpm and medium temperature of 37±0.5°C. Samples (5 ml) were withdrawn at suitable intervals, filtered and absorbance measured at 216.9 nm using UV-Visible Spectrophotometer.

Drug Content[12,13]

20 tablets were accurately weighed and grounded to fine powder. Aripiprazole orally disintegrating tablet powder equivalent to the label claim was accurately weighed and transferred into a 100 ml volumetric flask, few ml of media (0.05 M Phosphoric Acid in water and Acetonitrile 40:60 v/v) was added and sonicated to dissolve and made up the volume with media. The above solution was filtered and diluted to get a final concentration of 10µg/ml. The absorbance was determined at 217.7 nm using UV-Visible Spectrophotometer.

Hygroscopicity (Moisture Uptake Studies)[14]

Ten tablets from each formulation were kept in a desiccator over calcium chloride at 37°C for 24h. The tablets were weighed and exposed to 75% relative humidity, at room temperature for 2 weeks. Required humidity was achieved by keeping saturated sodium chloride solution at the bottom of the desiccator for 3 days. Tablets were weighed and the percentage increase in the weight was recorded.

In-Vitro Evaluation of Bitter Taste of Drug[15]

An accurately weighed 10 mg drug equivalent tablet powder and 10 ml of 0.05 M Phosphoric Acid in water and Acetonitrile was taken in volumetric flask and stirred at 50 rpm. The stirring was stopped at different time intervals, dispersion was filtered and the concentration of Aripiprazole in filtrate was determined. Time to achieve drug concentration corresponding to threshold bitterness in 10 ml 0.05 M Phosphoric Acid in water and Acetonitrile was recorded.

Statistical Analysis[7,8]

Statistical Analysis of the 3^2 Full Factorial Design batches was performed by multiple regression analysis using Microsoft excel. To evaluate the contribution of each factor with different levels to the response, the two- way analysis of variance (ANOVA) was performed using the design expert 8.0.5.2 (STAT – EASE) demo version software.

To graphically demonstrate the influence of each factor on the response, the response surface plots,

Normal plot of residual, Two- Dimensional counter plot, 3-D graph, and overlay plot, were generated using the design expert 8.0.5.2 (STAT – EASE) demo version software.

Checkpoint Analysis[7,8]

A check point analysis was performed to conform the role of the derived polynomial equation and counter plots in predicting the responses. Values of independent variables were taken at 3 points, 1 from each counter plot, and the theoretical values disintegration time and wetting time were calculated by substituting the values in the polynomial equation. The tablets were formulated using the chosen optimal composition and evaluated for disintegration time and wetting time. The observed and predicted responses were critically compared.

Optimization of Formulation[7,8]

The optimization formulation was obtained by applying goals on dependent and independent variables. The models were evaluated in terms of statistically significant coefficients and R^2 values. Various feasibility and grid searches were conducted to find out the optimum parameters. Various 3D responses surface graphs were provided by the design expert 8.0.5.2 (STAT – EASE). The optimized checkpoint formulation factors were evaluated for various parameters.

Stability Studies[16]

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 an environmental factors such as temperature, humidity and enables recommended storage condition, re-test periods and shelf life to be established. Stability studies were carried out on optimized tablet formulation.

A formulation was stored at accelerated stability condition 40°C ± 2°C / 75 ± 5 % RH for 30 days. After 30 days samples was withdrawn and tested with regards to the parameters i.e. Appearance, disintegration time, wetting time, drug content and *in-vitro* drug release pattern and compared with initial results.

RESULTS AND DISCUSSION

Drug – Excipients Compatibility Study by DSC

The DSC thermograms of Aripiprazole and with other excipients are depicted in Figure 1. Here, pure drug has the melting point at 141.65ºC and mixture has the melting point at 142.55ºC. No change in the endotherm peak of the drug was observed in the mixture of drug with other excipients. From this, it was inferred that there was no interaction between the drug and excipients.

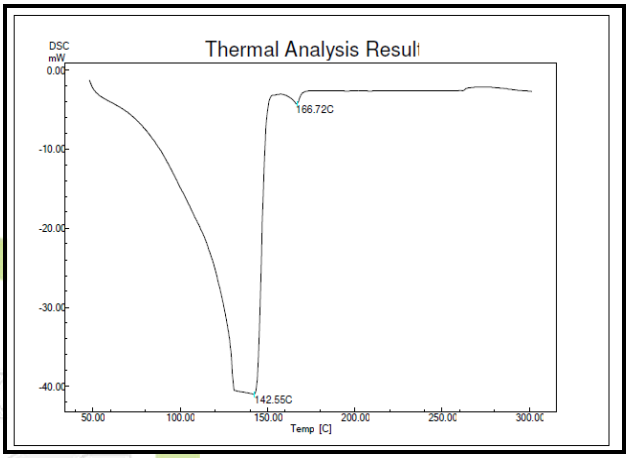

Figure 1: Drug – Excipients Compatibility Study by DSC

Characterization of Orally Disintegrating Tablets

Diameter

Diameter of all the tablets was found in the range of 5.99±0.03 to 6.02±0.02 mm.

Thickness

Thickness of all the tablets was found in the range of 2.85±0.02 to 2.89±0.03 mm.

Weight variation

Weight variation data of the prepared tablets indicated no significant difference in the weight of individual tablet from the average value.

Hardness

Hardness of the prepared tablets was observed to be within the range of 4.6±0.10 to 5.0±0.10 kg/cm^2.

Table 3: Post Compression Evaluations of Batches F1 to F9

Batch Code	Diameter (mm) ⊙	Thickness (mm) @	Weight Variation (mg) $	Hardness (kg/cm^2) *	Friability (%) ★	Hygroscopicity (% Moisture Uptake)
F1	6.02±0.02	2.86±0.03	149.0±0.67	5.0±0.10	0.11±0.19	0.98%
F2	6.01±0.01	2.88±0.03	149.9±0.85	4.8±0.06	0.09±0.21	0.81%
F3	5.99±0.03	2.86±0.02	150.1±0.57	4.9±0.10	0.09±0.16	0.85%
F4	6.00±0.02	2.85±0.03	150.1±0.69	4.7±0.09	0.09±0.17	0.64%
F5	6.01±0.03	2.87±0.02	150.0±0.72	4.7±0.15	0.08±0.22	0.72%
F6	6.00±0.03	2.89±0.03	150.2±0.37	4.8±0.12	0.09±0.09	0.61%
F7	6.02±0.02	2.85±0.02	149.5±0.47	4.7±0.15	0.08±0.18	0.45%
F8	6.00±0.03	2.86±0.02	149.6±0.75	4.7±0.13	0.06±0.15	0.51%
F9	6.00±0.02	2.87±0.04	148.6±0.51	4.6±0.10	0.06±0.21	0.41%

*All values are expressed as mean ± standard deviation, ⊙=5, @=20, $=20, *=6 and ★=6 tablets*

Batch Code	Disintegration Time (Sec.) ◆	Wetting Time (Sec.) ❖	Drug Content (%) ✦	% Cumulative Drug Release ✡
F1	27±0.25	55±0.30	98.69±0.55	90.32±2.20
F2	25±0.27	51±0.32	98.94±0.71	91.50±2.86
F3	21±0.19	40±0.21	100.10±0.68	93.50±1.94
F4	20±0.31	38±0.31	99.50±0.38	94.00±2.90
F5	18±0.25	33±0.24	99.85±1.14	94.45±1.71
F6	18±0.15	37±0.19	100.50±0.33	95.70±1.96
F7	15±0.22	30±0.20	100.0±0.65	96.50±1.10
F8	11±0.28	25±0.25	102.50±0.75	97.75±1.14
F9	10±0.17	22±0.18	101.30±0.34	99.66±0.45

All values are expressed as mean ± standard deviation, ◆=6, ❖ =6, ✦=5 and ✡=6 tablets

Friability

Friability of all the tablets was found below 1 %.

Measurement of Liquid Uptake (Wetting Time)

The wetting time in all batches was found in the range 22±0.18 to 55±0.30 seconds as shown in Table 3.

In-vitro Disintegration Time

The disintegration time in all batches was found in the range 10±0.17 to 27±0.25 seconds as shown in Table 3.

In-Vitro Dissolution Studies of 3^2 Full Factorial Batches F1 to F9

In-vitro drug release study showed in Fig. 2, it was observed that batches F1 to F3 containing 10, 12, 14 mg of Menthol and 5.25 mg of Kyron T-314 has shown 90.32 % to 93.50 % drug release after 45 min. While batches F4 to F6 containing 10, 12, 14 mg of Menthol and 6.75 mg of Kyron T-314 has shown 94.00 % to 95.70 % drug release after 45 min. Compared to these batches, batches F7 to F9 containing 10, 12, 14 mg of Menthol and 8.25 mg of Kyron T-314 has shown 96.50 % to 99.66 % drug release after 45 min. So, it was concluded that batch F9 containing 14 mg of Menthol as sublimating agent and 8.25 mg of Kyron T-314 as superdisintegrant has shown less disintegration time 10 Sec., less wetting time 22 Sec. and good drug release 99.66 % after 45 min. Hence, this batch was considered as optimized batch from all the batches.

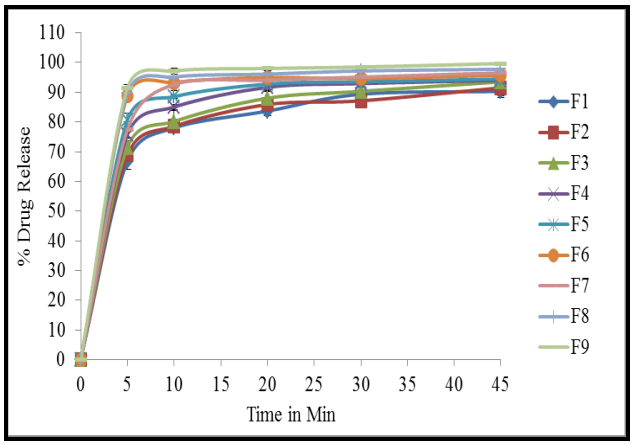

Figure 2: *In-Vitro* Drug Release of 3^2 Full Factorial Design Batches F1 to F9

Drug Content

The drug content was found in the range 98.69±0.55 to 102.50±0.75% as shown in Table 3. This ensured uniformity of drug content in the tablets.

Hygroscopicity (Moisture Uptake Studies)

All batches moisture uptake results were below 2.0 %. Hence it can be concluded that prepared formulations are slightly hygroscopic in nature.

In-Vitro Evaluation of Bitter Taste of Drug

The time for this threshold bitterness concentration to be achieved in buffer of salivary pH showed that the drug is not released in saliva to attain threshold bitterness concentration there by masking the bitter taste satisfactorily.

Statistical Analysis

The experimental runs with independent variables and corresponding responses for the 9 formulations are presented in Table 4. The dependent variables were the disintegration time (Y_1), and wetting time (Y_2). Based on the 3^2 factorial design, the factor combinations resulted in different results. Various models, such as linear, 2FI, quadratic and cubic, were fitted to the data for these responses simultaneously using Design Expert software and adequacy and good fit of the model was tested using analysis of variance (ANOVA). The multiple correlation coefficient (R^2), adjusted multiple correlation coefficient (adjusted R^2) and the predicted residual sum of square (PRESS) provided by Design-Expert software were used as factors for selection of adequate models. Results of ANOVA for response Disintegration Time (Y_1) and Wetting Time (Y_2) are listed in Table 5.

A mathematical relationship in the form of polynomial equation for disintegration time and wetting time are as follows:

$$\mathbf{Y_1 = 18.333 - 2.167X_1 - 6.167X_2 + 0.250\ X_1\ X_2 + 0.500X_1^2 - 0.500\ X_2^2, R^2 = 0.9756}$$

$$\mathbf{Y_2 = 36.780 - 4.000X_1 - 11.500X_2 + 1.75X_1\ X_2 + 0.667X_1^2 + 1.667X_2^2, R^2 = 0.9396}$$

The R^2 was high indicating the adequate fitting of the linear model. The polynomial equations can

also be used to draw conclusions considering the magnitude of co-efficient and the mathematical sign it carries; i.e. positive or negative. The negative coefficient of variable X_1 i.e. concentration of Menthol and X_2 i.e. concentration of Kyron T-314 in case of responses i.e. disintegration time (DT) and wetting time (WT) indicates that, as the Menthol and Kyron T-314 concentration was increased, the DT and WT was decreased. The data clearly indicate that the dependent variables are strongly dependent on the independent variables. The relationship between the variables was further elucidated by using the response surface plot (Figure 3 & 4). A high level of factor X_1 and X_2 gave a least disintegration and wetting time. The "Pred R-Squared" is close to the "Adj R-Squared" as one might normally expect. This may indicate a good fitting of the model. The faster disintegration time and wetting time of Menthol and Kyron T-314 may be attributed to its rapid disintegration property.

Table 4: Result of Effect of Independent Variables on Responses

Batch code	Independent variables		Dependent variables	
	X_1	X_2	Y_1	Y_2
F1	10	5.25	27	55
F2	12	5.25	25	51
F3	14	5.25	21	40
F4	10	6.75	20	38
F5	12	6.75	18	33
F6	14	6.75	18	37
F7	10	8.25	15	30
F8	12	8.25	11	25
F9	14	8.25	10	22
X_1 = Concentration of Menthol (in mg) X_2 = Concentration of Kyron T-314 (in mg)			Y_1 = Disintegration Time (in sec.) Y_2 = Wetting Time (in sec.)	

Table 5: Results of ANOVA

ANOVA for Response Y_1					
	df	**SS**	**MS**	**F**	**Significance F**
Regression	5	257.58	51.516	24.08	0.0125
Residual	3	6.4166	2.1388		
Total	8	264			
ANOVA for Response Y_2					
	df	**SS**	**MS**	**F**	**Significance F**
Regression	5	905.36	181.07	9.334	0.0476
Residual	3	58.194	19.398		
Total	8	963.55			

ANOVA indicates analysis of variance; Df, degrees of freedom; SS, sum of squares; MS, mean of squares; F, Fischer's ratio.

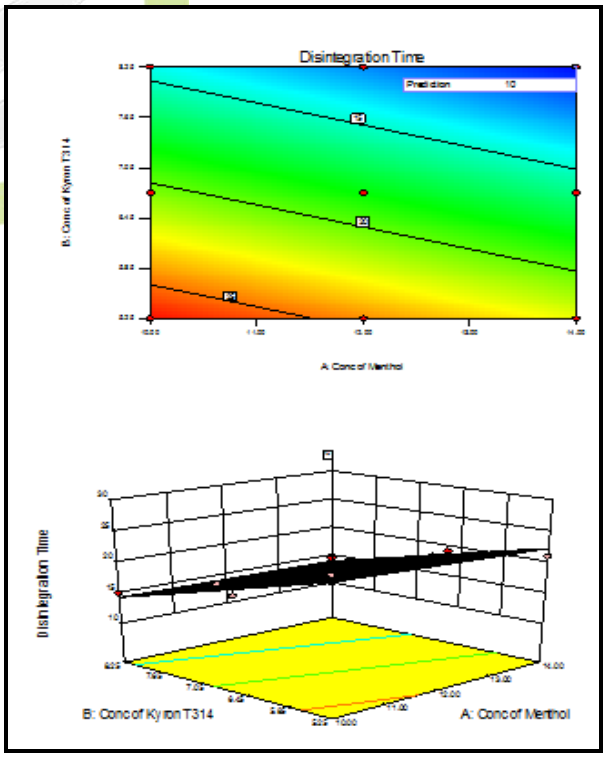

Figure 3(A): Contour Plot and (B) 3D Graph Showing Effect of Menthol (X_1) and Kyron T-314 (X_2) on Disintegration Time (Y_1)

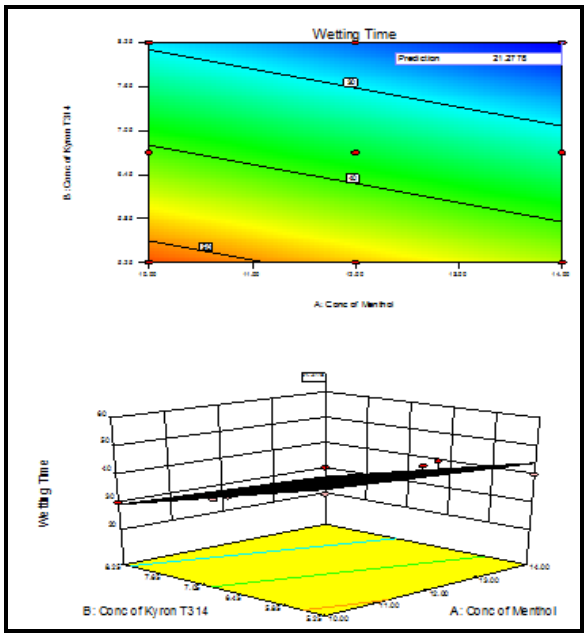

Figure 4(A): Contour Plot and (B) 3D Graph Showing Effect of Menthol (X_1) and Kyron T-314 (X_2) on Wetting Time (Y_2)

Checkpoint Analysis

Three check point batches were prepared and evaluated for disintegration time and wetting time as shown in Table 6. Results indicated that measured values matches well with expected values. When measured disintegration time and wetting time values were compared with predicted disintegration time and wetting time values, the difference were found to be not significant. Thus, it can be concluded that the obtained mathematical equation is valid for predicted values.

Optimization of Formulation

An Optimization technique using the desirability approach was employed to develop a new formulation with the desired responses. The optimum formulation was selected based on the criteria of attaining minimum disintegration time and wetting time. Upon "trading off" various response variables, constraints like minimizing the disintegration time and wetting time were set at appropriate limits and importance. Upon comprehensive grid searches, the formulation composition with 14 mg of Menthol, and 8.25 mg of Kyron T-314 fulfilled maximum requisites of an optimum formulation because of less disintegration time and wetting time. Optimization of Statistical Model by Overlay Plot showed in Figure 5.

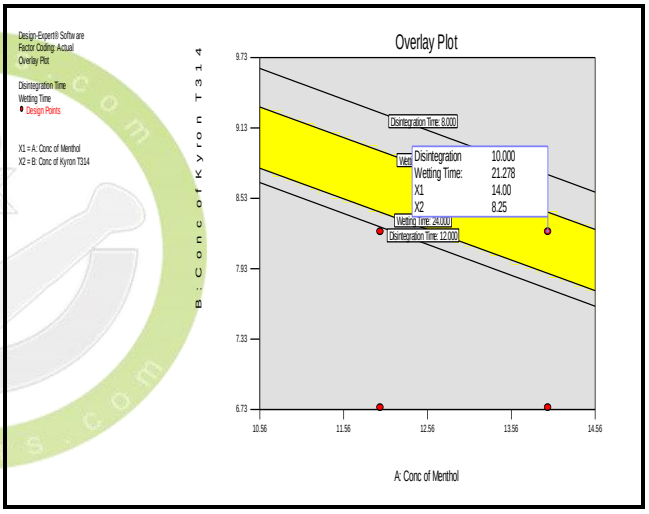

Figure 5: Optimization of Statistical Model by Overlay Plot

Table 6: Checkpoint Batches with Predicted and Measured Disintegration Time and Wetting Time

Batch Code	X_1	X_2	Disintegration Time (Y_1)		Wetting Time (Y_2)	
			Measured	Predicted	Measured	Predicted
F10	0	0.5	15.01	15.12	31.40	31.45
F11	0.5	1	10.79	10.83	25.91	25.99
F12	1	0.5	13.50	13.58	28.87	28.99

Stability Studies

Stability studies were carried out on optimized tablet formulation (Batch F9) as per ICH guidelines Q1C. A formulation were stored at accelerated stability condition 40°C ± 2°C / 75 ± 5 % RH for 30 days. After 30 days samples was withdrawn and tested with regards to the parameters i.e. appearance, disintegration time, wetting time, drug content and *in-vitro* drug release pattern and compared with initial results. After 1 month storage the results showed no significant change in appearance, disintegration time, wetting time, drug content and *in-vitro* drug release pattern. The result of short term stability studies indicates that the formulation was stable on the required storage condition.

CONCLUSION

An attempt was made to formulate and evaluate orally disintegrating tablets of Aripiprazole for the effective treatment of psychosis. The tablets were prepared by Sublimation technique to enhance the dissolution rate. Drug excipients compatibility study showed no interaction between drug and excipients. Experimental trials were taken using Menthol as a sublimating agent and Kyron T-314 as a superdisintegrant in different concentrations. A 3^2 full factorial design was applied to investigate the combined effect of two formulation independent variables: amount of Menthol and Kyron T-314. The disintegration time and wetting time were selected as dependent variables. The result indicated that concentration of Menthol and Kyron T-314 significantly affected the disintegration time and wetting time. Regression analysis and numerical optimization were performed to identify the best batch. Batch F9 containing Menthol (14 mg) and Kyron T-314 (8.25 mg) shows less disintegration time (10 Sec.), less wetting time (22 Sec.) and good drug release (99.66 %) after 45 min. compare to other batches. Hence, it was selected as optimized batch. Stability study conducted as per ICH guidelines and the optimized batch F9 was found to be stable. In conclusion, formulation of orally disintegrating tablets of Aripiprazole using sublimation method is able to enhance the dissolution rate. This approach is effective, economical and industry feasible.

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