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 D2 and 5-HT2A 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 3² factorial design. The concentration of Crospovidone and Croscarmellose sodium was selected as independent variables, X₁ and X₂ respectively whereas, wetting time, Disintegration time, Results and Discussion: Totally nine formulations were designed, prepared 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, t₅₀%, t₉₀%. Validity of developed polynomial equations were verified by designing 2 check point formulations (C₁, C₂). According to SUPAC guidelines the formulation (F₄) containing combination of 10% Crospovidone and 10% Croscarmellose, is the most similar formulation (similarity factor f₂ = 93.556, dissimilarity factor f₁ = 0.976≤ & No significant difference, t = 0.022) to marketed product (RISPERDAL-4). Conclusion: The selected formulation (F₃) follows First order, Higuchi’s kinetics, mechanism of drug release was found to be Fickian Diffusion (n=0.383).

KEYWORDS: Risperidone, 3²Factorial 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
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 is usually 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 sublingual mucosa, or it can be swallowed as a solution to be absorbed from the gastrointestinal tract.

The sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes. 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 dissolution rate is the limit factor for its absorption1. Hence the drug is selected for formulating Fast Dissolving Tablets by Direct compression method.

It is an important issue 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 of manufacturing2-5.

Hence an attempt is made in this research work to formulate Fast Dissolving Tablets of Risperidone using Crospovidone and Croscarmellose sodium. 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 3² full factorial design was employed to systematically study the drug release profile. A 3² 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. Risperidone was a gift sample from RPG Life Sciences Limited, Mumbai, India. Crospovidone, Croscarmellose, Di Calcium Phosphate, were procured from LobaChemie Pvt 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.

A selected three level, two factor experimental design (3² factorial design) 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 X₁ (Crospovidone) at a concentration of 5%, 10%, 15%. Three levels of factor X₂ (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 Risperidone Fast Dissolving tablet formulation. Totally nine Risperidone Fast Dissolving tablet formulations were prepared employing selected combinations of the two factors i.e. $X_1$, $X_2$ 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 (in a 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.

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>$X_1$</th>
<th>$X_2$</th>
</tr>
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<tbody>
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<td>$F_1$</td>
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<td>$F_2$</td>
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<td>0</td>
</tr>
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<td>$F_3$</td>
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<td>-1</td>
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<tr>
<td>$F_4$</td>
<td>0</td>
<td>1</td>
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<td>0</td>
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<tr>
<td>$F_9$</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>$C_1$</td>
<td>-0.5</td>
<td>-0.5</td>
</tr>
<tr>
<td>$C_2$</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

2.4. Evaluation of Risperidone fast dissolving tablets:

2.4.1. Hardness

The hardness of the tablets was tested by diometric compression using a Monsanto Hardness Tester. A tablet hardness of about 2-4 Kg/cm² is considered adequate for mechanical stability.

2.4.2. Friability

The friability of the tablets was measured in a Roche Friabilator. 20 Tablets were taken, Weighed and Initial weight was noted ($W_o$) 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

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

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 6.8 and 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

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

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

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

Disintegration of fast disintegrating tablets is achieved in the mouth owing to the action of saliv, 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.

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

<table>
<thead>
<tr>
<th>S.No</th>
<th>Formulation Code</th>
<th>Hardness (kg/cm²)</th>
<th>Thickness (mm)</th>
<th>Friability (%)</th>
<th>%Weight Variation</th>
<th>Drug Content(%)</th>
<th>Wetting Time (sec)</th>
<th>Disintegration Time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F₁</td>
<td>2.7±0.15</td>
<td>3.75±0.15</td>
<td>0.165±0.2</td>
<td>Pass</td>
<td>99.715±0.25</td>
<td>29.76±1.3</td>
<td>14.66±1.5</td>
</tr>
<tr>
<td>2</td>
<td>F₂</td>
<td>2.75±0.14</td>
<td>3.65±0.14</td>
<td>0.215±0.3</td>
<td>Pass</td>
<td>99.625±0.70</td>
<td>29.86±1.4</td>
<td>16.23±1.6</td>
</tr>
<tr>
<td>3</td>
<td>F₃</td>
<td>2.7±0.15</td>
<td>3.70±0.16</td>
<td>0.17±0.1</td>
<td>Pass</td>
<td>99.935±0.50</td>
<td>32.94±1.6</td>
<td>17.40±1.8</td>
</tr>
<tr>
<td>4</td>
<td>F₄</td>
<td>2.8±0.13</td>
<td>3.55±0.10</td>
<td>0.225±0.2</td>
<td>Pass</td>
<td>99.485±0.40</td>
<td>32.86±1.4</td>
<td>16.01±1.4</td>
</tr>
<tr>
<td>5</td>
<td>F₅</td>
<td>2.85±0.14</td>
<td>3.45±0.11</td>
<td>0.275±0.3</td>
<td>Pass</td>
<td>99.39±0.90</td>
<td>33.05±1.5</td>
<td>16.31±1.5</td>
</tr>
<tr>
<td>6</td>
<td>F₆</td>
<td>2.8±0.15</td>
<td>3.50±0.12</td>
<td>0.230±0.05</td>
<td>Pass</td>
<td>99.71±0.70</td>
<td>33.75±1.7</td>
<td>17.60±1.7</td>
</tr>
<tr>
<td>7</td>
<td>F₇</td>
<td>2.5±0.16</td>
<td>3.50±0.10</td>
<td>0.255±0.3</td>
<td>Pass</td>
<td>99.927±0.25</td>
<td>33.75±1.3</td>
<td>17.33±1.4</td>
</tr>
<tr>
<td>8</td>
<td>F₈</td>
<td>2.55±0.14</td>
<td>3.40±0.12</td>
<td>0.305±0.32</td>
<td>Pass</td>
<td>99.84±0.30</td>
<td>36.34±1.5</td>
<td>17.90±1.5</td>
</tr>
<tr>
<td>9</td>
<td>F₉</td>
<td>2.5±0.16</td>
<td>3.45±0.11</td>
<td>0.26±0.40</td>
<td>Pass</td>
<td>100.15±0.50</td>
<td>36.67±1.6</td>
<td>19.50±1.7</td>
</tr>
</tbody>
</table>

3. RESULTS AND DISCUSSION:

Fast Dissolving tablets of Risperidone were prepared and optimized by 2² 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 (X₁, X₂), and In vitro dissolution parameters such as t₅₀%, t₉₀%, and Wetting 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 as 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.
Cumulative % Drug release of Factorial Design Formulations F₁₋F₉ 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. Much variation was observed in the Wetting time, Disintegrating time, t₅₀% and t₉₀% due to formulation variables. Formulation F₉ 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, t₅₀% = 8.370 min, t₉₀% = 27.83 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 (R²) 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, t₅₀% and t₉₀% values by backward stepwise linear regression analysising PCP Disso software and Response surface plots were constructed.

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**Table 4: Regression Analysis Data of 3² Factorial Design Formulations of Risperidone Fast Dissolving Tablets**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Formulation Code</th>
<th>Zero Order a</th>
<th>Zero Order b</th>
<th>Zero Order r</th>
<th>First Order a</th>
<th>First Order b</th>
<th>First Order r</th>
<th>Kinetic Parameters Higuchi a</th>
<th>Kinetic Parameters Higuchi b</th>
<th>Kinetic Parameters Higuchi r</th>
<th>Kinetic Parameters Korsmeyer-Peppas a</th>
<th>Kinetic Parameters Korsmeyer-Peppas b</th>
<th>Kinetic Parameters Korsmeyer-Peppas r</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F₁</td>
<td>38.257</td>
<td>1.743</td>
<td>0.791</td>
<td>1.894</td>
<td>0.044</td>
<td>0.99</td>
<td>16.7</td>
<td>14.557</td>
<td>0.939</td>
<td>0.464</td>
<td>1.041</td>
<td>0.831</td>
</tr>
<tr>
<td>2</td>
<td>F₂</td>
<td>35.467</td>
<td>1.799</td>
<td>0.815</td>
<td>1.881</td>
<td>0.038</td>
<td>0.973</td>
<td>14.104</td>
<td>14.782</td>
<td>0.951</td>
<td>0.426</td>
<td>1.064</td>
<td>0.834</td>
</tr>
<tr>
<td>3</td>
<td>F₃</td>
<td>31.868</td>
<td>1.897</td>
<td>0.848</td>
<td>2.173</td>
<td>0.067</td>
<td>0.966</td>
<td>15.598</td>
<td>15.249</td>
<td>0.968</td>
<td>0.368</td>
<td>1.102</td>
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<tr>
<td>4</td>
<td>F₄</td>
<td>34.681</td>
<td>1.8</td>
<td>0.828</td>
<td>2.264</td>
<td>0.077</td>
<td>0.936</td>
<td>13.79</td>
<td>14.659</td>
<td>0.958</td>
<td>0.424</td>
<td>1.061</td>
<td>0.847</td>
</tr>
<tr>
<td>5</td>
<td>F₅</td>
<td>31.891</td>
<td>1.855</td>
<td>0.851</td>
<td>1.923</td>
<td>0.036</td>
<td>0.992</td>
<td>11.194</td>
<td>14.884</td>
<td>0.97</td>
<td>0.383</td>
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<tr>
<td>6</td>
<td>F₆</td>
<td>28.292</td>
<td>1.954</td>
<td>0.879</td>
<td>2.166</td>
<td>0.061</td>
<td>0.972</td>
<td>7.688</td>
<td>15.351</td>
<td>0.981</td>
<td>0.32</td>
<td>1.127</td>
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<tr>
<td>7</td>
<td>F₇</td>
<td>31.554</td>
<td>1.841</td>
<td>0.853</td>
<td>1.914</td>
<td>0.033</td>
<td>0.983</td>
<td>11.137</td>
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<td>0.969</td>
<td>0.387</td>
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<td>F₈</td>
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<td>1.896</td>
<td>0.872</td>
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<td>0.98</td>
<td>8.541</td>
<td>14.959</td>
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<td>0.341</td>
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<td>0.899</td>
<td>1.977</td>
<td>0.035</td>
<td>0.997</td>
<td>5.035</td>
<td>15.426</td>
<td>0.987</td>
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<td>1.836</td>
<td>0.842</td>
<td>2.34</td>
<td>0.082</td>
<td>0.909</td>
<td>11.894</td>
<td>14.821</td>
<td>0.966</td>
<td>0.394</td>
<td>1.08</td>
<td>0.847</td>
</tr>
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</table>

F₁ to F₉ are factorial formulations, r-correlation coefficient, a-Intercept, b-Slope and MP-Marketed Product.
Comparative First Order Plots For Formulations F₁-F₉

![Comparative First Order Plots For Formulations F₁-F₉](image)

Wetting time chart

![Wetting Time Chart for Formulation F₁-F₉](image)

Comparative Higuchi Plots For Formulations F₁-F₉

![Comparative Higuchi plots for Formulation F₁-F₉](image)

Disintegrating time chart

![Disintegration Time Chart for Formulation F₁-F₉](image)

Comparative Korsmeyer-Peppas Plots For Formulations F₁-F₉

![Comparative Korsmeyer-Peppas plots for Formulation F₁-F₉](image)

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

<table>
<thead>
<tr>
<th>S.No</th>
<th>Formulation Code</th>
<th>t₁₂₅ (min)</th>
<th>t₉₅₅ (min)</th>
<th>WT (Sec)</th>
<th>DT (Sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F₁</td>
<td>6.874</td>
<td>22.842</td>
<td>29.76±1.3</td>
<td>14.66±1.5</td>
</tr>
<tr>
<td>2</td>
<td>F₂</td>
<td>8.013</td>
<td>26.628</td>
<td>29.86±1.4</td>
<td>16.23±1.6</td>
</tr>
<tr>
<td>3</td>
<td>F₃</td>
<td>4.507</td>
<td>14.977</td>
<td>32.94±1.6</td>
<td>17.40±1.8</td>
</tr>
<tr>
<td>4</td>
<td>F₄</td>
<td>3.913</td>
<td>13.002</td>
<td>32.86±1.4</td>
<td>16.01±1.4</td>
</tr>
<tr>
<td>5</td>
<td>F₅</td>
<td>8.37</td>
<td>27.813</td>
<td>33.05±1.5</td>
<td>16.31±1.5</td>
</tr>
<tr>
<td>6</td>
<td>F₆</td>
<td>4.963</td>
<td>16.493</td>
<td>33.75±1.7</td>
<td>17.60±1.7</td>
</tr>
<tr>
<td>7</td>
<td>F₇</td>
<td>8.991</td>
<td>29.875</td>
<td>33.75±1.3</td>
<td>17.33±1.4</td>
</tr>
<tr>
<td>8</td>
<td>F₈</td>
<td>9.963</td>
<td>33.108</td>
<td>36.34±1.5</td>
<td>17.90±1.5</td>
</tr>
<tr>
<td>9</td>
<td>F₉</td>
<td>8.63</td>
<td>28.678</td>
<td>36.67±1.6</td>
<td>19.50±1.7</td>
</tr>
</tbody>
</table>
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 $t_{90\%}$
Polynomial equation for 3² full factorial designs is given in Equation

\[
Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_{11} X_1^2 + b_{22} X_2^2 \ldots
\]

Where, Y is dependent variable, b_i estimated co-efficient for factor X_i. The main effects (X_i and X_j) represent the average result of changing one factor at a time from its low to high value. The interaction term (X_i X_j) shows how the response changes when two factors are simultaneously changed. The polynomial terms (X_i² and X_j²) are included to investigate non-linearity. Validity of derived equations was verified by preparing Two Check point Formulations of Intermediate concentration(C_i, C_j).

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

\[
Y_{1} = 33.220-2.367X_1-1.165X_2+0.065X_1 X_2+0.205X_1^2 \quad \text{(for Wetting time)}
\]

\[
Y_{2} = 16.993-1.073X_1-1.083X_2-0.143 X_1 X_2+0.53 X_1^2+0.27 X_2^2 \quad \text{(for Disintegrating time)}
\]

\[
Y_{3} = 7.136-1.365X_1+0.279X_2-0.502 X_1 X_2+2.08 X_2^2-2.47 X_2^2 \quad \text{(for } t_{50\%} \text{)}
\]

\[
Y_{4} = 23.713-4.536X_1+0.929X_2+1.667 X_1 X_2+6.92 X_1^2-8.21 X_2^2 \quad \text{(for } t_{90\%} \text{)}
\]

The positive sign for co-efficient of X_i in Y_1, Y_2, Y_3 and Y_4 equations indicates that, as the concentration of Crosipvidone 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 Crosipvidone) 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 Disintegrating 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_1) is compared with marketed product (RISPERDAL-4) shows similarity factor (f_1) 93.556, difference factor (f_2) 0.976 (There is no significant difference in drug release because \(t_{cal}\) is<0.05).

4. CONCLUSION

The present research work envisages the applicability of Superdisintegrants such as Crosipvidone and Croscarmellose sodium in the design and development of Fast Dissolving tablet formulations of Risperidone utilizing the 3² 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 be Fickian Diffusion, first order release type. On the basis of evaluation parameters, the optimized formulation F_1 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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REFERENCES


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