IMPACT OF FORMULATION PARAMETERS ON FAST DISSOLVING TABLET OF ONDANSETRON HYDROCHLORIDE PREPARED BY PRESSURIZED HOMOGENIZATION TECHNIQUE

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ABSTRACT
The demand for fast dissolving tablets of OndansetronHCl has been growing during the last decade especially for the geriatric and pediatric patients. OndansetronHCl is a recognized as antiemetic drug, so development of an FDT OndansetronHCl and to evaluate the effect of various concentrations of superdisintegrant and binder on its disintegration time and release profile was the prime objective of this research work. Methods: Tablets were prepared by high pressure homogenization followed by direct compression.22 factorial design was applied in which concentration of superdisintegrant and binder were taken as independent variables and disintegration time and percentage release were taken as dependent variables. The prepared tablets were evaluated for weight variation, hardness, friability, disintegration time, content uniformity, and % drug release. Direct compression process was selected for this formulation of ODT tablets, because porous nature is more in direct compression blend than wet granulation blend, so tablet will facilitates for faster disintegration and dissolution. Results: The optimised batch of fast dissolving tablet of Ondansetron hydrochloride prepared by pressurized homogenization

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using taste masking polymer Eudragit E-100 complies for all evaluation tests as per Indian Pharmacopoeia and applied statistical design was found to be significant.

**Conclusions:** It was concluded that pressurized homogenization technique is a useful method for preparing fast dissolving tablets of ondansetron followed by direct compression.

**Keywords:** Fast dissolving tablets; superdisintegrants; ondansetron; direct compression; factorial design.

**INTRODUCTION**
Tablet is the most popular among all dosage forms existing today because of its convenience of self administration, compactness and easy manufacturing; however hand tremors, dysphasia in case of geriatric patients, the underdeveloped muscular and nervous systems in young individuals and in case of uncooperative patients, the problem of swallowing is common phenomenon which leads to poor patient compliance. To overcome these drawbacks, fast dissolving tablets (FDTs) has emerged as alternative oral dosage forms. Fast dissolving tablets quickly disintegrate and dissolve and provide immediate action, convenient dosing and improves patient compliance [1-3].

Pressurized homogenization followed by direct compression is one of the quickest and quality effective tablet manufacturing technique. Use of conventional equipments, commonly available excipients and limited number of processing steps are the advantages of this technique. Tablets prepared by such method mainly affect the dissolution and disintegration properties of the tablet [4].

OndansetronHCl is a highly selective and potent antagonist of 5-hydroxytryptamine at 5HT3 receptors in the gastrointestinal tract where it blocks both sites of serotonin induced nausea and vomiting (emesis). It is used in the treatment of nausea or vomiting induced treatment and prophylaxis of postoperative or chemotherapy- or radiotherapy-induced emesis and is also used in the early onset of alcoholism [5]. OndansetronHCl is well absorbed from the gastrointestinal tract and undergoes some first-pass metabolism. Taste masked granules was prepared by using Eudragit E100 (cationic copolymer based on dimethyl amino ethyl methacrylate) and ethanol by using pressurized homogenization method with solvent evaporation [6].

The present study was done with the aim of developing fast dissolving tablets of OndansetronHCl by simple and cost effective direct compression method using Eudragit E-
100 as a taste masking agent with the help of pressurized homogenization method.

Materials and Methods

Materials

Ondansetron HCl was obtained as a gift sample from Sun Pharmaceuticals Ltd., Vadodara. Eudragit E-100 (Evonik Degussa India Pvt. Ltd., Mumbai), Lactose, Sodium starch glycolate (IndChem International, Mumbai) and PVP K-30 (Research Lab Fine Chem, Mumbai), Magnesium stearate.

Methods

Taste masking of drug by forming drug polymer complex

Complex of Ondansetron HCl and Eudragit E-100 was done by pressurized homogenization method. Saturated solutions of both drug and polymer (1:1 w/w) were prepared in isopropyl alcohol and injected with the help of a needle into 20 ml of distilled water with constant stirring at 500 rpm for about 45 mins with the help of IKA homogenizer. Volatile solvent was evaporated by solvent evaporation method and mixture was dried at 65°C in a hot air oven for 24 hrs under vacuum. The dried mixture was used for further studies [7].

Evaluation of tablet blend and fast dissolving tablet

The tablet blend and fast dissolving tablet was prepared (Table 1) and evaluated for following pre-compression parameters and tests [8-12].

Angle of repose

Angle of repose is determined by using funnel method. The accurately weighed blend is taken in a funnel. The height of the funnel is adjusted in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug (as solid dispersion) excipient blend is allowed to flow through the funnel freely on to the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation.

\[ \tan \theta = \frac{h}{r} \]  (1)

Where, h and r are the height of cone and radius cone base respectively. Angle of Repose less than 30° shows the free flowing of the material.

Bulk density

Apparent bulk density is determined by pouring a weighed quantity of blend into a graduated cylinder and measuring the volume and weight. Bulk density can be calculated by using
following formula:

**Bulk density** = Weight of the powder / Volume of the packing (2)

**Tapped density**

It is determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder is allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 second intervals. The tapping is continued until no further change in volume is noted. Tapped density can be calculated by using following formula:

Tapped Density = (Weight of the powder / volume of the tapped packing) (3)

**Compressibility index**

The Compressibility Index of the blends is determined by compressibility index. Compressibility Index can be calculated by using following formula:

Compressibility Index (%) = [(TD-BD) x 100] / TD (4)

**Hausner’s ratio**

A similar index to indicate the flow properties can be defined by Hausner’s ratio. Hausner’s ratio can be calculated by using following formula:

Hausner’s ratio = (Tapped density) / (Poured density) (5)

**Weight variation**

Weight variation was calculated as per method described in Indian Pharmacopoeia (I.P. 2007). 20 tablets were weighed individually and the average weight is calculated.

**Hardness**

Five tablets from each batch were selected and hardness was measured using Monsanto hardness tester to find the average tablet hardness.

**Thickness**

Ten Tablets were selected at random from individual formulations and thickness was measured by using Vernier calliper scale, which permits accurate measurement.

**Friability (%F)**

Twenty tablets from each batch were selected randomly and weighed. These tablets were subjected to friability testing using Roche friabilator for 100 revolutions. Tablets were removed, de-dusted and weighed again.
Following formula was used to calculate the friability:

\[
%F = 1 - \frac{\text{loss in weight}}{\text{initial weight}} \times 100
\] (6)

**Disintegration time**

In a simplest method, 6 ml of phosphate buffer of pH 6.8 was taken in a 25 ml measuring cylinder. Temperature was maintained at 37 ± 2 °C. ODT was put into it and time required for complete disintegration of the tablet was noted.

**In vitro drug release studies:**

The in vitro dissolution study was carried out in the USP dissolution test apparatus type 2 (paddle). 900 ml of the dissolution medium (0.1 N HCl solution) was taken in and the temperature was maintained at 37 ± 0.5 °C. The speed of the paddle was maintained at 100 rpm. Sampling was done for every five min interval. For each sample 5 ml of the dissolution medium was withdrawn and the same amount of dissolution medium was replenished to maintain sink condition. The samples withdrawn were analyzed in the UV spectrophotometer at 249 nm.

**RESULTS**

**Physical properties of the tablet blend**

The tablet blend of all the batches was evaluated for different derived properties viz., angle of repose (between 23 to 28), bulk density (between 0.4801 to 0.5303 gm/ml), compressibility index (between 13 to 16). The results angle of repose and compressibility indicated that the flowability of blend is significantly good. All the tablets passed weight variation test as the percent weight variation was within the pharmacopoeial limits. Hardness was shown in the range of 3.7±0.38 to 4.1±0.63 kg/cm² all the formulations. The hardness of all tablets was kept within the abovementioned range to compare the disintegration time between the formulations prepared using different disintegrants and their varying concentrations. The friability of all formulations was determined. The friability values of none of the formulations exceeded 1%. The results of friability indicate that the tablets were mechanically stable and can withstand rigors of transportation and handling. Thickness of all tablets was 4.35 ± 0.017 to 4.38 ± 0.018 mm showing fairly uniform tabletting. The results of disintegration values were found to be in the range of 24 to 28 sec.
Physical properties of tablet blend
The tablet blend was evaluated for various physical properties and was found to be satisfactory as shown in Table 2.

Physical properties of tablet
The tablet was evaluated and was found to be satisfactory as shown in Table 3.

Drug release from fast dissolving tablet
All the tablets prepared were subjected for release profile. All the tablets of F1 to F4 batch showed a drug release between 50 to 99 % within 30minutes. Among four batches, batch F2 which contain sodium starch glycolate along with 8 mg of ondansetron was selected as optimized batch because of its lowest disintegration time and highest drug release.

In-vitro dissolution studies
The result of in-vitro dissolution studies of ondansetron hydrochloride tablets was as shown in Table 4 (Figure 1 and Figure 2).

Full factorial design
A $2^2$ Factorial design was chosen for the current formulation optimization study. In this design two factors were evaluated, each at 2 levels, and experimental trials were performed at all 4 possible combination. In the preliminary trial runs, Concentration of sodium starch glycolate and concentration of PVP K-30 showed good results. So these were selected and subjected to further optimization. Concentration of sodium starch glycolate and concentration of PVP K-30 were selected as independent variables whereas disintegration time (DT) and percentage release were measured as responses or dependent variables. Values of full $2^2$ factorial design were used (Table 5), for generation of surface response plots and polynomial equations. The polynomial equation can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign. The responses were analyzed for ANOVA using Design Expert version 8.0.7.1. A mathematical equation was generated for each response parameter. The mathematical models were tested for significance. Response surface plots were generated for each response to study the behaviour of the system[13].

Factorial equation for dependent variables
Factorial equation for disintegration time

$$R_1= 26.25 - 1.25 X_1 +0.75 X_2 +0.25 X_1X_2$$  (7)
Factorial equation indicates proportionality of independent variables with respect to dependent variables. So, sodium starch glycolate have negative correlation whereas PVP-K 30 have positive correlation with disintegration time. Interaction effect of both the factors showed positive impact over disintegration time. Hence when concentration of sodium starch glycolate increases, the formulation shows less disintegration time and as concentration of PVP K-30 was increased, there was positive proportional effect on disintegration time.

**Factorial equation for percentage release**

\[ R^2 = 96.52 + 0.90 X_1 - 0.49 X_2 - 0.72 X_1X_2 \] (8)

Factorial equation in case of percentage drug release from fast dissolving tablet shows sodium starch glycolate have positive correlation and PVP K 30 have negative correlation with respect to drug release. Whereas interaction effect have shown negative impact over response of drug release.

**ANOVA of quadratic model for disintegration time and percent drug release**

ANOVA table used to generate mathematical models as shown in Table 6 and Table 7. The high values of correlation coefficient for disintegration time and percent drug release indicate a good fit i.e. good agreement between the dependent and independent variables. The mathematical model was evolved by applying ANOVA, So the main effect X_1 & X_2 were found significant as p value was < 0.05.

**Response surface plots**

The counter plot & response surface plot shows the effect of concentration of sodium starch glycolate and concentration of PVP K-30 on disintegration time and percentage release. It was observed from the response surface and contour plots that both the factors had influence on disintegration time (Figure 3 and Figure 4) and percentage release (Figure 5 and Figure 6) of the tablets.

**Table 1 Formulation composition of FDT of Ondansetron hydrochloride**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Component</th>
<th>F-1</th>
<th>F-2</th>
<th>F-3</th>
<th>F- 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ondansetron</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>Eudragit E-100</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>Lactose (Anhydrous)</td>
<td>112</td>
<td>112</td>
<td>112</td>
<td>112</td>
</tr>
<tr>
<td>4</td>
<td>Sodium starch glycolate</td>
<td>14</td>
<td>18</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>PVP K-30</td>
<td>8</td>
<td>8</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>Magnesium stearate</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>
Table 2 Physical properties of tablet blend of OndasetronHCl\(^{\circ}\) (Mean ± SD, n = 3)

<table>
<thead>
<tr>
<th>Batch</th>
<th>Bulk Density</th>
<th>Tapped Density</th>
<th>Hausners ratio</th>
<th>Carr’s Index</th>
<th>Angle of repose</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-1</td>
<td>0.4801 ± 0.0010</td>
<td>0.5232 ± 0.0082</td>
<td>1.089 ± 0.0193</td>
<td>8.18 ± 2.34</td>
<td>23.78 ± 0.08</td>
</tr>
<tr>
<td>F-2</td>
<td>0.5205 ± 0.0128</td>
<td>0.5408 ± 0.0126</td>
<td>1.039 ± 0.0128</td>
<td>3.73 ± 1.17</td>
<td>24.39 ± 0.56</td>
</tr>
<tr>
<td>F-3</td>
<td>0.5303 ± 0.0126</td>
<td>0.5830 ± 0.0086</td>
<td>1.099 ± 0.0102</td>
<td>9.067 ± 0.84</td>
<td>26.46 ± 0.34</td>
</tr>
<tr>
<td>F-4</td>
<td>0.5009 ± 0.0080</td>
<td>0.560 ± 0.0094</td>
<td>1.119 ± 0.0344</td>
<td>10.45 ± 2.67</td>
<td>26.84 ± 0.81</td>
</tr>
</tbody>
</table>

Table 3 Evaluation of factorial F1 - F4 batches

<table>
<thead>
<tr>
<th>Batch</th>
<th>Hardness</th>
<th>Thickness</th>
<th>Friability</th>
<th>Weight variation</th>
<th>Disintegration time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-1</td>
<td>4.06 ± 0.10</td>
<td>4.37 ± 0.012</td>
<td>0.18 ± 0.01</td>
<td>154.19 ± 0.2451</td>
<td>27</td>
</tr>
<tr>
<td>F-2</td>
<td>4.06 ± 0.07</td>
<td>4.38 ± 0.018</td>
<td>0.16 ± 0.02</td>
<td>158.08 ± 0.1989</td>
<td>24</td>
</tr>
<tr>
<td>F-3</td>
<td>4.13 ± 0.07</td>
<td>4.35 ± 0.017</td>
<td>0.22 ± 0.01</td>
<td>158.05 ± 0.2012</td>
<td>28</td>
</tr>
<tr>
<td>F-4</td>
<td>3.96 ± 0.125</td>
<td>4.37 ± 0.012</td>
<td>0.19 ± 0.01</td>
<td>162.06 ± 0.1602</td>
<td>26</td>
</tr>
</tbody>
</table>

Table 4 Percentage release of ODT of Ondansetron hydrochloride

<table>
<thead>
<tr>
<th>Time</th>
<th>F-1</th>
<th>F - 2</th>
<th>F - 3</th>
<th>F - 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 min</td>
<td>53.84</td>
<td>52.38</td>
<td>51.70</td>
<td>50.92</td>
</tr>
<tr>
<td>10 min</td>
<td>89.30</td>
<td>91.33</td>
<td>90.57</td>
<td>90.68</td>
</tr>
<tr>
<td>15 min</td>
<td>92.52</td>
<td>94.89</td>
<td>92.74</td>
<td>93.46</td>
</tr>
<tr>
<td>30 min</td>
<td>94.26</td>
<td>97.64</td>
<td>94.67</td>
<td>95.15</td>
</tr>
<tr>
<td>45 min</td>
<td>95.03</td>
<td>98.30</td>
<td>95.34</td>
<td>95.78</td>
</tr>
<tr>
<td>60 min</td>
<td>95.39</td>
<td>98.64</td>
<td>95.84</td>
<td>96.21</td>
</tr>
</tbody>
</table>

Table 5 2\(^2\) Full factorial design layout for factorial batches

<table>
<thead>
<tr>
<th>Batch</th>
<th>Independent Variable in coded form</th>
<th>Independent Variable in actual form</th>
<th>Dependent variable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Factor 1</td>
<td>Factor 2</td>
<td>Superdisintegrant conc. (mg)</td>
</tr>
<tr>
<td>F 1</td>
<td>-1</td>
<td>-1</td>
<td>14</td>
</tr>
<tr>
<td>F 2</td>
<td>+1</td>
<td>-1</td>
<td>18</td>
</tr>
<tr>
<td>F 3</td>
<td>-1</td>
<td>+1</td>
<td>14</td>
</tr>
<tr>
<td>F 4</td>
<td>+1</td>
<td>+1</td>
<td>18</td>
</tr>
</tbody>
</table>

Table 6 ANOVA Response surface quadratic model for DT

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
<th>Df</th>
<th>MS</th>
<th>R(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>8.75</td>
<td>3</td>
<td>2.92</td>
<td>1</td>
</tr>
<tr>
<td>A Conc. Of Superdisintegrant</td>
<td>6.25</td>
<td>1</td>
<td>6.25</td>
<td></td>
</tr>
<tr>
<td>B Conc. Of binder</td>
<td>2.25</td>
<td>1</td>
<td>2.25</td>
<td></td>
</tr>
<tr>
<td>AB</td>
<td>0.25</td>
<td>1</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Cor Total</td>
<td>8.75</td>
<td>3</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
Table 7 ANOVA Response surface quadratic model for percentage release

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
<th>Df</th>
<th>MS</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>6.33</td>
<td>3</td>
<td>2.11</td>
<td></td>
</tr>
<tr>
<td>A Conc. Of Superdisintegrant</td>
<td>3.28</td>
<td>1</td>
<td>3.28</td>
<td>1</td>
</tr>
<tr>
<td>B Conc. Of binder</td>
<td>0.98</td>
<td>1</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>AB</td>
<td>2.07</td>
<td>1</td>
<td>2.07</td>
<td></td>
</tr>
<tr>
<td>Cor Total</td>
<td>6.33</td>
<td>3</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1 Graph of percentage release v/s Time

Figure 2 Comparative Graph of percentage release v/s Time
Figure 3 Response surface plot for Disintegration Time

Figure 4 Contour plot for disintegration time

Figure 5 Response surface plot for percentage release
CONCLUSIONS

The study conclusively demonstrated complete taste masking of OndansetronHCl and rapid disintegration and dissolution of fast dissolving tablet. Taste masking and rapid disintegration of tablets formulated in this investigation may possibly help in administration of OndansetronHCl in a more palatable form without water during emesis. Thus, the “patient-friendly dosage form” of bitter drugs, especially for pediatric, geriatric, bedridden, and non-co-operative patients, can be successfully formulated using this technology.

List of abbreviations
FDT: Fast dissolving tablet
ODT: Orodispersible tablet
TD: Tapped density
BD: Bulk density
UV: Ultraviolet spectrophotometer
PVP K-30: Polyvinyl pyrrolidone K-30
DT: Disintegration time
ANOVA: Analysis of variance

Competing interests: The authors declare that they have no competing interests.
Authors' contributions
SSS, PAK and AK have made substantial contributions to conception, design, acquisition, analysis and interpretation of data. NMB and SSS have designed manuscript for important intellectual content. MSB have given final approval of the version to be published.

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REFERENCES

