Effect of Different Meltable Binders on the Disintegration and Dissolution Behavior of Zolmitriptan Oromucosal Fast Melt Tablets

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Abstract: Objective: Fast melt tablets and sublingual route have been widely used for providing quick onset of action with the avoidance of first pass metabolism. The objective of this work was to compare the effect of different meltable binders namely; polyethylene glycol (PEG) 4000, pluronic F127 and pluronic F68 on the performance of fast release tablets of the model drug zolmitriptan prepared using the melt granulation technique regarding disintegration time (DT) and dissolution rate (DR) as criteria for rapid absorption and hence quick onset of action. Zolmitriptan is a potent antimigraine drug. Current oral zolmitriptan tablets suffer from slow onset of action, poor bioavailability and large inter-subject variability.

Methods: 3³ factorial design was adopted. The effect of binder type, binder concentration and croscarmellose sodium (disintegrant) concentration were studied on DT and DR.

Results: The three factors were found to significantly affect the DR and the inverse square root of DT and significant interactions were elucidated.

Conclusion: Although satisfactory results were obtained regarding DR, modifications using different excipients and or preparation methods should be considered to comply with pharmacopoeia requirement for DT.

Keywords: Melt granulation technique, fast release sublingual tablets, meltable binders, intragranular desintegrant, PEG4000, F68, F127.

1. INTRODUCTION

The interest in fast melt tablets had been increased to augment compliance and hence effectiveness of therapy for elderly patients and children who have swallowing difficulties, to enhance bioavailability of some poorly available drugs and to provide rapid onset of action. In addition, fast melt tablets need no water for administration and thus satisfy patient needs who find no access to water [1].

Different techniques were reported to prepare fast release tablets, such as lyophilization [2, 3], molding [4] and compressing wet powders to obtain highly porous structure [5,6]. The main disadvantages of these methods are, being time and energy consuming and the limited physical resistance especially associated with lyophilization and molding techniques [7].

Using hydrophilic meltable binders, melt granulation has showed success in preparing rapidly disintegrating tablets, immediate release dosage forms and also in enhancing dissolution and bioavailability of some drugs [8-10]. Melt granulation does not require the use of aqueous or organic solvents thus eliminates the risk originating from residual solvents; moreover, the post granulation drying step is eliminated making the entire process less time and energy consuming [11]. The melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by the use of a low melting point binder which is added to the other components of the powder. Once in a molten state, the binder acts as a granulating liquid. The temperature of the mixture is raised to above the melting point of the binder, either by a heating jacket, or by the heat of friction generated by the impeller blades if the impeller speed is high enough [12]. A fast melt tablet has been prepared by combining a low melting point compound, with a water soluble excipient. The heat generated by mixing in a high shear mixer can result in melting the compound, and hence binding of the components together. This combination makes up a fast dissolving granulation. Also, preparation can take place by melting the low melting point compound, then, the water soluble excipient is added. The combination is mixed until congealing takes place to make granules [13]. Many drugs were formulated as fast-melt tablets using the melt granulation technique as ketotifin fumerate [14], carbamazepine and metoclopramide hydrochloride [15]. Polyethylene glycol (PEG) 4000 was employed as a melting binder, in consideration of its favorable solution properties, low
melting point, rapid solidification rate, low toxicity and low cost [16]. PEG 4000 has been widely used as hydrophilic binder in melt granulation technique [17, 18]. Pluronics are a group of non-ionic triblock copolymers of polyoxyethylene–polyoxypropylene–polyoxyethylene (PEO–PPO–PEO) [20]. In this study, two different pluronics were used, F127 and F68 that differ in the length of hydrophobic and hydrophilic chains and their average molecular weight. Pluronic 127 has a molecular weight of 12500 Da and its chemical structure is (PEO100–PPO69–PEO100) [19, 20] whereas the molecular weight of pluronic 68 is 8400 Da and its chemical structure is (PEO80–PPO27–PEO80) [20, 21]. Recently our group succeeded to formulate bioenhanced sublingual tablets of zolmitriptan prepared using novel surfactant binder (Pluronic_F127/Syloid_mixture) [22], in this research a simple method of preparation with different excipients was used. The objective of this work was to prepare zolmitriptan fast melt sublingual tablets using the melt granulation technique and to compare the effect of different meltable binders, namely polyethylene glycol 4000 and two polyoxyethylene-polyoxypropylene-polyoxyethy-lene block copolymers (pluronic F127 and F68) on the performance of fast melt tablets regarding disintegration time and dissolution rate (minimize the disintegration time and maximize dissolution rate) and also, the potential effect of inclusion of intragranular disintegrant (croscarmellose sodium) was investigated.

The effective anti-migraine zolmitriptan was selected as a model drug. It is a white powder that is partially soluble in water (1.3 mg/ml at 25°C) and suffers from low bioavailability. Fast pharmacological response with migraine therapy is expected through oromucosal route because of the abundance of blood supply in the sublingual region that allows excellent drug absorption bypassing the first hepatic metabolism.

2. MATERIALS AND METHODS

2.1. Materials

Zolmitriptan, kindly supplied by Amoun Company for pharmaceuticals. Polyethylene glycol 4000 (melting point 54-58 ºC) (PEG 4000) (Morgan Co., Egypt), Pluronic F127 (Av.MW:12500 Da, melting point: 56°C) and pluronic F68 (Av.MW:8400 Da, melting point:52°C) (F127 and F68, Sigma-Aldrich, Chemie GmbH, Germany) used as binders. Croscarmellose sodium (Ac-di- sol, FMC BioPolymers, USA) used as intragranular disintegrant. Crospovidone (ISP, Switzerland) used as extragranular disintegrant. Granular mannitol (Pearlitol 200, a gift from Roquette Co., France) used as diluent. Mangnesium stearate (El-Nasr Co for Pharmaceutical Industries, Cairo, Egypt) used as lubricant. All other reagents were of analytical grade.

2.2. Experiment Design

To study the effect of independent variables, batches were prepared by using 3^3 factorial design. Three independent variables namely, binder type (PEG, Pluronic F127, Pluronic F68), binder concentration (%), (15, 20, 25) and croscarmellose sodium concentration (%) as intra-granular disintegrant (0, 5, 10) were investigated. Each factor was studied at three levels; hence a 3^3 full factorial was applied. The concentration of extra-granular disintegrant namely crospovidone was kept constant in a concentration of 5%. Each combination was performed twice in two separate replicates. Real and coded values of the evaluated factors are given in Table 1.

2.3. Fast Melt Granulation Technique

Zolmitriptan, intra-granular disintegrant (croscarmellose sodium) and the diluent (granular mannitol) were geometrically mixed using mortar and pestle and the mixing continued for 10 min. PEG 4000 or pluronic (F127 or F68) were heated separately to 65 °C in a water bath. The drug-excipients mixture was added to the melted mass and stirred at 100 rpm for 5 min using a mixer (Mechanika high speed mixer, Poland). The mixture was removed from the water bath and continued to be stirred until complete cooling to room temperature and granules were obtained.

The granules were evaluated for bulk density (d10), tapped density (d100, where a consistent volume was reached). Carr’s index (CI) derived from the following

Table 1: Factors and Respective Levels Investigated in the 3^3 Design

<table>
<thead>
<tr>
<th>Factors</th>
<th>Symbols</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low(-1)</td>
</tr>
<tr>
<td>Binder Type</td>
<td>X1</td>
<td>PEG 4000</td>
</tr>
<tr>
<td>Binder Concentration</td>
<td>X2</td>
<td>15%</td>
</tr>
<tr>
<td>Croscarmellose sodium Concentration</td>
<td>X3</td>
<td>0%</td>
</tr>
</tbody>
</table>
equation: CI = \( \frac{d_{100} - d_{10}}{d_{100}} \) X 100 [12] and Hausner’s ratio given by the relation \( \frac{d_{10}}{d_{100}} \) were calculated.

2.4. Preparation of Fast Melt Tablets

The prepared granules were geometrically mixed with other tablet additives (crospovidone & magnesium stearate) in a plastic bag. All formulations contain 2.5 mg zolmitriptan/tablet, 5% w/w crospovidone as extragranular disintegrant. Finally, magnesium stearate (0.5% w/w) was added as a lubricant to the previous blend just before tabletting. The blend was then compressed into tablets using a single punch tabletting machine (Veego/MaticMD, India) equipped with 7 mm flat punch to prepare tablets with an average weight of 100 mg. The hardness of the tablets was kept constant at approximately 3 kg (HDT-300, Logan Instruments Corp., NJ, USA). The prepared tablets were coded as Tn where n is the number corresponding to granule formula upon which tablet is based as shown in Table 2.

2.5. Evaluation of the Prepared Tablets

The tablets were evaluated for the different physicochemical parameters

2.5.1. Friability and Disintegration Time

The friability of the tablets was determined using a friability tester (FAB-2, Logan Instruments Corp., NJ, USA). The friability is expressed in terms of percentage weight loss of the initial weight [13, 23]. Disintegration time (Logan Instruments Corp.-Disintegration tester, Table 2: Flow Parameters of Granules and Friability of Different Prepared Fast Melt Tablets

<table>
<thead>
<tr>
<th>% Friability</th>
<th>Hausner’s Ratio</th>
<th>Carr’s Index</th>
<th>Formula code</th>
</tr>
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<tr>
<td>0.71</td>
<td>1.04</td>
<td>8.33</td>
<td>T1</td>
</tr>
<tr>
<td>0.83</td>
<td>1.04</td>
<td>11.67</td>
<td>T2</td>
</tr>
<tr>
<td>0.64</td>
<td>1.06</td>
<td>18.46</td>
<td>T3</td>
</tr>
<tr>
<td>1.02</td>
<td>1.02</td>
<td>8.33</td>
<td>T4</td>
</tr>
<tr>
<td>0.88</td>
<td>1.06</td>
<td>13.33</td>
<td>T5</td>
</tr>
<tr>
<td>0.65</td>
<td>1.08</td>
<td>19.69</td>
<td>T6</td>
</tr>
<tr>
<td>0.85</td>
<td>1.06</td>
<td>14.28</td>
<td>T7</td>
</tr>
<tr>
<td>0.72</td>
<td>1.04</td>
<td>16.92</td>
<td>T8</td>
</tr>
<tr>
<td>0.60</td>
<td>1.05</td>
<td>19.12</td>
<td>T9</td>
</tr>
<tr>
<td>2.00</td>
<td>1.04</td>
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<tr>
<td>0.92</td>
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<td>8.58</td>
<td>T14</td>
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<td>16.70</td>
<td>T15</td>
</tr>
<tr>
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<td>1.10</td>
<td>9.07</td>
<td>T16</td>
</tr>
<tr>
<td>0.47</td>
<td>1.07</td>
<td>13.00</td>
<td>T17</td>
</tr>
<tr>
<td>0.91</td>
<td>1.07</td>
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<td>T18</td>
</tr>
<tr>
<td>0.69</td>
<td>1.10</td>
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<tr>
<td>0.61</td>
<td>1.06</td>
<td>9.20</td>
<td>T20</td>
</tr>
<tr>
<td>0.58</td>
<td>1.04</td>
<td>15.48</td>
<td>T21</td>
</tr>
<tr>
<td>1.14</td>
<td>1.04</td>
<td>12.7</td>
<td>T22</td>
</tr>
<tr>
<td>1.01</td>
<td>1.05</td>
<td>9.00</td>
<td>T23</td>
</tr>
<tr>
<td>0.49</td>
<td>1.04</td>
<td>16.47</td>
<td>T24</td>
</tr>
<tr>
<td>0.91</td>
<td>1.10</td>
<td>13.00</td>
<td>T25</td>
</tr>
<tr>
<td>0.23</td>
<td>1.04</td>
<td>15.29</td>
<td>T26</td>
</tr>
<tr>
<td>0.50</td>
<td>1.03</td>
<td>13.79</td>
<td>T27</td>
</tr>
</tbody>
</table>
USA) was determined in distilled water at 37±2°C. The test was conducted in triplicate [14, 24].

2.5.2. Drug Content

The analysis of the zolmitriptan content was carried out in triplicate by dissolving one tablet in suitable quantity of distilled water and the solution was filtered, suitably diluted and the zolmitriptan content was analyzed spectrophotometrically (Shimadzu UV spectrophotometer 2401/PC, Japan) at 282 nm using distilled water as blank [25].

2.5.3. Dissolution

In vitro dissolution test of zolmitriptan tablets (2.5 mg) was performed in the USP paddle dissolution ApparatusII (Pharmatest, Germany). The temperature was maintained at 37 °C and the paddle speed was set at 100 rpm in 250 ml of distilled water as dissolution medium. 5ml sample was collected after 2.5, 10, 15, 20, 25 and 30 min and replaced by distilled water. The amount of drug dissolved was assayed spectrophotometrically at 282 nm. The dissolution tests were performed in triplicate [25].

2.6. Statistical Analysis

All experiments were performed in randomized order. All data were statistically analyzed using Design-Expert® software (version 7; Stat-Ease, Inc., Minneapolis, MN)). Means were compared by ANOVA factorial and suitable regression models were driven to enable navigation of the experimental space. Significance level was set at p<0.05. The response variables were the dissolution rate at 10 minutes and the disintegration time. In order to improve the statistical properties of the analysis the inverse square root transformation of disintegration time response values was applied

3. RESULTS

In this study twenty seven formulae of zolmitriptan fast melt tablets were prepared using melt granulation technique adopting 3^3 factorial design. The effect of binder type, namely, PEG 4000, F68 and F127, binder concentration, namely, 15%, 20% and 25% and croscarmellose sodium concentration, namely, 0%, 5% and 10% were studied on dissolution rate (DR_{10}) and disintegration time DT.

3.1. Evaluation of the Prepared Tablets

3.1.1. Flowability, Drug Content and Friability

It was previously published that powders with compressibility index CI between 5 and 18% and Hausner’s ratio below 1.25 are suitable for producing tablets [26]. All studied formulation adhered to these values except T3, T6 and T9 which showed CI values above 18% (Table 2). However, we could compress them into tablets and they were included in the comparative factorial study. The mean percentage of drug content of the prepared tablets was in the range of 99± 1.52 to 101± 0.98%.

All formulations exhibited friability values below 1% except T10-T13 and T22 so they were excluded. For rapidly disintegrating tablets, European Pharmacopoeia states disintegration time less than 3 min but there are no requisites regarding either hardness or friability [24].

3.2. Statistical Analysis Results of the 3^3 Factorial Design

Dissolution rate (DR_{10}) and disintegration time were in the range of 62.57±6.066 and 250±0.0 µg.min^{-1} and 97.5±26.16 and 487.5±105.5 sec respectively as shown in Table 3.

The dissolution rate and disintegration time were found to be governed by the three variables as well as three-factors interaction between these factors p<0.05.

The data of values obtained for the dissolution rate and the disintegration time were subjected to analysis of variance (ANOVA) using statistical software Design-Expert (version 7; Stat-Ease, Inc., Minneapolis, MN). The equation fitted for dissolution rate and the disintegration time was:

\[ Y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_12X_1X_2 + \beta_13X_1X_3 + \beta_123X_1X_2X_3 \]

Where Y represents the measured response, X1-X3 represent the independent variables \( \beta_0 \) is a constant, and \( \beta_1-\beta_3 \) represent the regression coefficient computed from the responses of the formulations. X1, X2, X1X3, X2X3 and X1X2X3 are the interaction terms showing how response changes when two factors are simultaneously changed [27].

The values of the coefficients X1, X2 and X3 are related to the effect of these variables on the response. The polynomial equations can be used to draw conclusions after considering the magnitude of the coefficient and the mathematical sign it carries (i.e., positive or negative). A positive sign of coefficient indicates that the output increases with an increase in parameter level, and negative coefficients that the output increases with a decrease in parameter level. The larger coefficient means the independent variable
Table 3: The Composition and Observed Responses of the 3 3 Factorial Design with Trials Listed in the Standard Order of this Design (n=2)

<table>
<thead>
<tr>
<th>Batch code</th>
<th>X1. Binder Type</th>
<th>X2 Binder Conc.</th>
<th>X3 Ac-di-sol Conc.</th>
<th>Dissolution rate (µg.min⁻¹) (Mean± SD)</th>
<th>Disintegration time* (sec) (Mean± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>210.95±12.47</td>
<td>226±11.31</td>
</tr>
<tr>
<td>2</td>
<td>-1</td>
<td>-1</td>
<td>0</td>
<td>161.54±39.3</td>
<td>177±9.89</td>
</tr>
<tr>
<td>3</td>
<td>-1</td>
<td>-1</td>
<td>1</td>
<td>183.91±14.11</td>
<td>174.5±6.36</td>
</tr>
<tr>
<td>4</td>
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<td>0</td>
<td>-1</td>
<td>201.87±25.49</td>
<td>182±24.04</td>
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<tr>
<td>5</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>135.84±17.27</td>
<td>194±1.44</td>
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<td>85.3±6.37</td>
<td>224±8.48</td>
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<td>99.36±10.83</td>
<td>194±1.44</td>
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<tr>
<td>9</td>
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<td>57.75±10.59</td>
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<td>223.5±19.019</td>
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<td>133.75±22.98</td>
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<tr>
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<tr>
<td>27</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>62.57±6.066</td>
<td>487.5±105.5</td>
</tr>
</tbody>
</table>

*The inverse square root transformation of response values was applied in order to improve the statistical properties of the analysis.

has more potent influence on the response. The high values of the correlation coefficients for the dependent variables indicate a good fit [28].

3.2.1. Dissolution Rate (DR)

The dissolution rate is one of the most important parameters from pharmaceutical viewpoint in the evaluation of sublingual tablets. One of our important goals was the maximization of zolmitriptan dissolution rate within the first 10 minutes of dissolution (DR₁₀). Figure 1 is a representative dissolution figure showing the effect of polymer concentration, (A) and polymer type, (B) on zolmitriptan dissolution rate. Concerning the response variable; dissolution rate: the binder type, the binder concentration and the disintegrant concentration, as well as three-factors interaction between these factors, were found to be significant factors p<0.05 (data not shown). Equations 1-3 represent the linear regression models for the PEG, F68 and F127, respectively, as obtained from the factorial study.

Effect of PEG

\[
DR=171.9247222+1.682166667X2+4.7855X3-0.90556667X2X3
\]  

Effect of F68

\[
DR=7.316111111+9.761X2+21.532X3-0.90556667X2X3
\]  

Effect of F127

\[
DR=368.2786111-6.07833333X2+6.21383333X3-0.90556667X2X3
\]
In case of the three binders used, both binder concentration ($X_2$) and croscarmellose sodium concentration ($X_3$) showed significant effect on the dissolution rate at 10 min ($P$-value = 0.0102 and <0.01, respectively). However, the croscarmellose sodium content effect was more pronounced as it was proved from higher coefficient value.

3.2.1.1. Binder Type Effect

Regarding the effect of binder type, changing binder type led to a significant change in DR after 10 min, $p<0.0001$. The performance of different binders regarding effect on DR could be descendingly ranked as follows: F68>PEG4000>F127

3.2.1.2. Binder Concentration Effect

Upon increasing the binder concentration, an increase in dissolution rate was observed when using PEG and F68 as binder. This was deduced from the positive coefficients of ($X_2$) in Equations 1 and 2. Conversely, when using F127 as a binder, increasing its concentration had a negative effect on dissolution rate.

3.2.1.3. Intra-Granular Disintegrant Concentration Effect

Increasing the disintegrant concentration from 0% to 10% enhanced the dissolution rate. Such findings are in agreements with earlier reports, [29] where high disintegrant concentrations improved the rate and extent of liquid uptake and penetration into the tablets, exposing the drug particles to the dissolution medium and improving the contact between drug particles and solvent molecules.

3.2.2. Disintegration Time (DT)

The disintegration of a tablet can be regarded as the first step toward the bioavailability and pharmaceutical action of an active ingredient. To achieve sufficient disintegration, a disintegrant must normally be added to the tablet formulation [30].

Concerning the response variable inverse of square root of disintegration time, the binder type, the binder concentration, the disintegrant concentration as well as three-factors interaction between these factors, were found to be significant factors $p<0.05$ (data not shown) Equations 4-6 represent the linear regression models for the PEG, P68 and F127, respectively, as obtained from the factorial study. The polynomial term $X_2^2$ is included to investigate non linearity.

Effect of PEG

\[
\frac{1}{\text{square root disintegration time}} = 0.170069758 - 0.011462039X_2 + 0.004798827X_3 - 0.000263818X_2X_3 + 0.000321001X_2^2
\]

Effect of F68

\[
\frac{1}{\text{square root disintegration time}} = 0.202464423 - 0.013288115X_2 + 0.004798827X_3 - 0.000263818X_2X_3 + 0.000321001X_2^2
\]

Effect of F127

\[
\frac{1}{\text{square root disintegration time}} = 0.176924642 - 0.012271726X_2 + 0.004798827X_3 - 0.000263818X_2X_3 + 0.000321001X_2^2
\]

In case of the three binders used, both binder concentration ($X_2$) and Ac-di-sol concentration ($X_3$) showed significant effect on the inverse of square root of disintegration time ($P$-value= 0.0010 and 0.0451, respectively). However, the binder concentration effect was more pronounced as it was proved from higher coefficient value and lower $p$ value.

3.2.2.1. Binder Type Effect

The performance of different binders regarding effect on DT could be ascendingly ranked as follows:
F68=PEG4000<F127. Figure 2 shows effect of binder type on the inverse square root of disintegration time. F68 and PEG significantly increased the inverse square root of disintegration time (decreased DT) when compared to F127.

3.2.2.2. Binder Concentration Effect

The negative sign in equation indicated that the increase in concentration of the binder PEG 4000, F68 or F127 led to a decrease in the reverse of disintegration time (increased disintegration time). The increase in binder concentration was also accompanied by an increase in the tablet DT.

3.2.2.3. Intra-Granular Disintegrant Concentration Effect

An inverse relationship between croscarmellose sodium concentration and disintegration time was also observed.

4. DISCUSSION

4.1. Dissolution Rate (DR10)

4.1.1. Binder Type Effect

The reason of the better performance of F68 compared to PEG 4000 could be correlated to its chemical structure. Pluronic F68 being a block copolymer has the properties to self-assemble into micelles in aqueous solution [20]; the hydrophobic core (PO block) can act as reservoir for the drug, while the hydrophilic portion (EO) acts as interface between the aqueous medium and the drug. Thus, the increased DR of F68 granules containing tablets with respect to PEG ones could be explained with its better performance as solubilizing agent, hypothesizing the formation of polymeric micelles able to solubilize the drug [21,31]. On the other hand, the better performance of F68 compared to F127 could be inferred regarding the higher molecular weight and higher proportion of hydrophobic polyoxypropylene part of the latter, i.e. lower HLB value. Higher molecular weight provides better conditions for gel layer formation when in contact with water, which consequently acts as a diffusion barrier and delays drug release [32]. It was previously found that increasing the viscosity of the binder significantly increased the time required to achieve equilibrium and led to a decreased breakage of the granules [33].

4.1.2. Binder Concentration Effect

The increase in dissolution rate associated with PEG and F68 higher concentration could be attributed to the higher hydrophilic character of the system due to the presence of water-soluble carriers and that part of the drug could be dissolved in the binders [34,35].

Another reason could be that, at higher concentration of binder the number of formed micelles also increased. This effect was much more prominent in case of F68 when compared to PEG. The slowing down effect of higher F127 concentration on DR may be due to the fact that Pluronic F127 is widely used as viscosity-increasing agent in conventional dosage forms. Raising the concentration of the polymer caused a gradual increase in the disintegration time and consequently decreased the dissolution rate of the tablets. This could be attributed to the water imbibing and swelling nature of the polymer [36].

4.1.3. Intra-Granular Disintegrant Concentration Effect

A possible explanation for the observed positive effect of croscarmellose sodium concentration on DR is; water uptake has been identified as the necessary first step in any disintegration process necessary for dissolution [37-39] and swelling is main the mechanism of tablet disintegration. Matching our findings it was previously found that when croscarmellose sodium was mixed with ethenzamide granules at different concentrations, faster ETZ dissolution from the tablets was observed in a concentration-dependent manner [30] this could be attributed to that croscarmellose sodium has high water absorption and swelling abilities since it is a well-known swelling-type disintegrant.

4.2. Disintegration Time

4.2.1. Binder Type Effect

The more pronounced negative effect of the binder F127 on disintegration time could be explained on the basis that F127 is a viscosity imparting agent that may
cause an increase in the tablet hardness and consequently its DT [36].

4.2.2. Binder Conc Effect

This could be attributed to melting of polymers during compression followed by solidification of the fused material upon release of the tabletting pressure that would form solid bridges between the particles [9]. Higher binder concentration causes greater consolidation of powder particles into the tablets during compaction and more pronounced interparticle bonding between particles [32].

Ford and Rubinstein [40] previously reported that the break up of the tablets was governed by the rate at which the binder dissolved, since the latter was distributed across the particle surface [41].

4.2.3. Intra-Granular Disintegrant Concentration Effect

The increase in disintegration time with the increase of croscarmellose concentration could be attributed to partial gelling that could form a viscous barrier and delay entry of water into the tablet [42].

4.3. Contour Plots Interpretation

4.3.1. Dissolution Time

Contour plots were obtained by fixing the X1 and varying (X2) and (X3) over the range used in the factorial study.

Figure 3 depicts contour plots which show the effects of X2 and X3 on DR in case of PEG, F68 and F127 respectively. Analysis of the contour plot in case of PEG (Figure 3A) reveals that increasing binder concentration from 15 to 25% at low croscarmellose sodium level led to an increase in DR. On the other hand, increasing binder concentration at high croscarmellose level led to a decrease in DR.

An increase in DR could be achieved by using high PEG concentration and keep croscarmellose concentration at its lower level, as large concentration of croscarmellose at high PEG concentration could compete with the drug for the solvent so led to a decrease in dissolution rate.

Analysis of contour plots in case of F68 (Figure 3B) reveals that at low croscarmellose sodium concentration, increasing binder concentration led to a decrease in DR. However, at high croscarmellose concentration, increasing binder concentration led to an increase in DR. For F127 (Figure 3C), increasing binder concentration led to an increase in DR regardless of the croscarmellose concentration.

Figure 3: Contour Plot showing effect of binder concentration and Ac-di-sol concentration on the dissolution rate when using (A) PEG (B) F68 and (C) F127 as binders.
concentration (0% w/w) increasing binder concentration from 15 to 25% led to an increase in dissolution rate. On the other hand, increasing binder concentration at high croscarmelose sodium concentration (10% w/w) led to a non significant change in dissolution rate. An increase in binder concentration from low to high level led to an increase in dissolution rate. Generally an increase in DR could be achieved in case of F68 by using high binder concentration and keeping croscarmelose sodium concentration at its lower or higher level.

Figure 3C demonstrates the effects of X2 and X3 when using F127 as binder. Analysis of the contour plot in case of F127 reveals that increasing croscarmellose sodium concentration from 0 to 10 % w/w and binder concentration from 15 to 25% w/w led to a significant decrease in DR. The concentration of F127 and croscarmellose should be kept at minimum to obtain high dissolution rate.

As previously discussed, this could be attributed to the nature of F127 which is widely used as viscosity-increasing agent in conventional dosage forms. Raising the concentration of the polymer caused a gradual increase in the hardness of the tablet, and disintegration time and consequently the dissolution rate [36].

4.3.2. Contour Plots Interprétation (Disintegration Time)

Contour plots were obtained by fixing the X1 and varying (X2) and (X3) over the range used in the factorial study. Figure 4A-C depicts contour plots which show the effects of X2 and X3 on inverse of square root of disintegration time in case of PEG, F68 and F127 respectively.

Analysis of the contour plot in case of PEG and F127 (Figure 4A and 4B) reveals that at low croscarmellose sodium concentration, increasing the binder concentration; either PEG or F127 led to an increase in inverse of square root of disintegration time (decreased the DT). On the other hand, when using high croscarmellose sodium concentration, the increase in both binders concentration led to a decrease in inverse of square root of disintegration time (increased DT). The reduction in disintegration efficacy at high excipients levels (high croscarmellose...
concentration and high binder conc) might be attributed to increased compactness of tablets accompanying increase in binder concentration may retard disintegrant action of croscarmellose sodium which imparts its disintegrating effect by absorbing water and swelling. Generally for a decrease in disintegration time concentration of binder PEG or F127 must be kept at minimum and croscarmellose concentration must be kept high or if high concentration of PEG or F127 was used it must be combined with low croscarmellose sodium level. Both ingredients, binder and disintegrant must not be kept at their high level.

Analysis of the contour plot in case of F68 (Figure 4C) reveals that at both low and high croscarmellose sodium concentration increasing the binder concentration led to a decrease in inverse square root of disintegration time (an increase in DT). To obtain low disintegration time F68 concentration must be kept at its minimum level. It was previously published that F68 must be reduced to a lower concentration in order to achieve good disintegration time (DT) since pluronics appeared to control most of the effects observed on tablet disintegration [43]. It is worthy to mention that nearly most of prepared tablets showed high DT except T10, T11, T12 but unfortunately this decrease in disintegration time was accompanied by high friability.

4. CONCLUSION

F68 was found superior as a melttable binder compared to F127 and PEG regarding enhancement in dissolution rate, however, the effect of polymers concentration and disintegrant concentration cannot be interpreted separately, since it was found that the interaction between polymers concentration and disintegrant concentration (X2X3) significantly influenced the DT and DR of zolmitriptan tablets. Satisfactory results were obtained regarding the DR but concerning DT, modifications using different excipients and or preparation method should be considered to comply with pharmacopoeia requirement to obtain tablets with low disintegration time and better physical properties (low friability).

DECLARATION OF INTEREST

None.

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