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# Formulation and evaluation of clozapine orally disintegrating tablets prepared by direct compression

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In this study, clozapine orally disintegrating tablets (ODTs) were prepared by direct compression method. Disintegration time, resistance to crushing of tablets, porosity, friability, dissolution tests were performed and dissolution profiles of ODTs were investigated. Morphological and interaction studies were also performed. Friability values were found to be less than 1%. All tablet formulations disintegrated within 1 min and fulfilled the 3 min disintegration time required for ODTs given in the European Pharmacopoeia. More than 85 % of the labeled amount of clozapine was dissolved in 15 min from the ODTs. No interaction or changes were found between active substance and excipients. As a result of the studies, ODT formulations developed in this study can be suggested as promising formulations, which assist development and manufacturing a generic product of clozapine.

## 1. Introduction

Orally disintegrating tablets (ODTs) are gaining considerable importance, over the last 30 years. In the European Pharmacopoeia, orally disintegrating tablets are specified as "orodispersible tablets" and defined as "uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed" (European Pharmacopoeia 2008) while in the United States Food and Drug Administration (FDA) Regulation (U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research), they are classified as "orally disintegrating tablets" and defined as "a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue" (Guidance for Industry 2008 December). Orally disintegrating tablet (ODT) formulations, in addition to possessing the advantages of conventional tablet dosage forms, are easy to swallow similar to liquid dosage forms, and are superior to them as their dosing can be adjusted more accurately, they have a better stability, small packaging size and a simpler manufacturing process (Seager 1998; Habib et al. 2000; Brown 2003). Orally disintegrating tablets can be developed by various scientific techniques such as freeze drying (Sznitowska et al. 2005), moulding (Van-Scoik 1992; Mizumoto 1996), spray drying (Mishra et al. 2006), sublimation (Koizumi et al. 1997; Singh 2008; Narmada et al. 2009), direct compression (Bi et al. 1999; Schiermeier and Schmidt 2002; Battu et al. 2007; Swamy et al. 2008), cotton candy process (Cherukuri et al. 1995; Myers et al. 1995; Gupta et al. 2010), mass extrusion (Bhowmik et al. 2009; Zade et al. 2009), melt granulation (Abdelbary et al. 2004), phase transition (Sugimoto et al. 2006; Kuno et al. 2008) and three-dimensional printing (Lee et al. 2003; Yu et al. 2009). Since direct compression method requires less equipment and less manufacturing process, it is commonly used to produce ODTs. In this technique well known excipients with proven safety are used.

ODTs are designed to disperse or dissolve at once when they contact saliva, therefore it is not necessary to chew the tablet or drink water to swallow the entire tablet. Advantages like comfort and increase in patient compliance can be gained with application of orally disintegrating tablets to patients such as the aged, paralyzed and bedridden ones who are not able to swallow as well as to the pediatric, geriatric and psychiatric patients who refuse to swallow (Sastry et al. 2000; Bandari et al. 2008). Patient noncompliance to therapy and especially the schizophrenic patients' refraining from swallowing their medicine by hiding conventional tablets under their tongues is a frequently experienced situation in psychiatry. It is evident that the patients' comfort and quality of life will be increased by means of the rapid ODT technology used in psychiatry (Frijlink 2003). Estimates have been reported that 50% of the population has been affected by this problem which results in ineffective therapy and patient noncompliance to therapy (Seager 1998; Dobetti 2001).

Clozapine is an atypical antipsychotic agent with a dibenzodiazepine structure and indicated for the management of severely ill schizophrenic patients who are refractory or intolerant to standard treatments (Naheed and Green 2001). Although it is the gold standard in treatment of schizophrenia, noncompliance with treatment is even a more important issue during clozapine administration, considering that it is mostly preferred for treatment refractory patients who have severe symptoms and possibly poor insight. In addition, it is reported that the abrupt discontinuation of clozapine may cause a rapid exacerbation of psychosis (Shiovitz et al. 1996). Therefore, development of orally disintegrating tablets of clozapine will surely make the management of such patients easier for the clinicians and the families, and help the patients receive proper treatment.

The aim of this study is to develop clozapine containing orally disintegrating tablets by means of the convenient and low cost direct compression technology to obtain a cost effective formulation and to evaluate these formulations *in vitro* with regard to uniformity of mass, friability, *in vitro* disintegration time, *in vitro* dissolution test, porosity, scanning electron microscopy, Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), and X-ray diffractometry (XRD). The orally disintegrating tablet formulations developed in this study were prepared with a different technology and known excipients compared to the previous ones produced in other markets (Golden 2008). Aminoalkyl methacrylate copolymer E, mannitol, microcrystalline cellulose, aspartame, crospovidone, sodium bicarbonate, citric acid and magnesium stearate are the some of the inactive ingredients which were used in the other marketed ODT formulations (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021590s024lbl.pdf accessed 15 June 2012). The technology, which used the above mentioned substances, utilises an effervescent disintegration pair that releases gas upon contact with saliva. DuraSolv technology (http://www.cimalabs.com/technology/durasolv/technicalnotes accessed 15 June 2012) which is used for manufacturing of the ODTs is good for tablets containing low amount of active ingredients. However, larger doses of active ingredients may not be used because of the high pressures on compaction. Also, patient can get the bitter taste of the drug due to the fracturing of drug powder coating during compaction (Panigrahi and Behera 2010). In our study, three different superdisintegrants croscarmellose sodium, crospovidone and sodium starch glycolate sodium and two different superdisintegrant ratios (5% and 10%) were used.

## 2. Investigations, results and discussion

### *2.1. Selection of excipients*

Excipient selection is a critical point for designing a dosage form and plays an important role in its quality and performance. Pearlitol® SD 200 which is a direct compressible mannitol and leaves a good feeling in the mouth was selected as a filler (Rowe et al. 2004; Battu et al. 2007). Orally disintegrating tablets prepared by means of direct compression method contain diluents-fillers which dissolve in water at a high rate and disintegrate at a higher rate than conventional tablets in general (Hahm and Augsburger 2008). The diluents-fillers such as micro-crystalline cellulose which do not dissolve in water can cause a gritty feeling and leave an unpleasant taste in the mouth when used in the formulation at a high ratio (Hahm and Augsburger 2008). Therefore, water-dissoluble mannitol was preferred as filler in this study. However, when mannitol was used alone it tends to dissolve rather than disintegrate, and the tablet disintegration time can be delayed. Therefore, mannitol was used with micro-crystalline cellulose (Avicel PH 102) in the formulations. Avicel PH 102 was added to our ODT formulations by 10% of tablet weight. This type of the micro-crystalline cellulose has a granular structure, it has good flowability and is suitable for direct compression. It also has a disintegrant property. One of the most notable properties of orally disintegrating tablets is the short disintegration time in the mouth. To this end, superdisintegrants are used in direct compression. Croscarmellose sodium (Ac-Di-Sol®), crospovidone (Kollidon® CL) or sodium starch glycolate (Vivastar® P) which are widely used and highly effective were used as superdisintegrants in this study. Aspartam was added at a ratio of 1% as the flavoring agent for a pleasant taste in the mouth and relief from the feeling left by the tablet. Patients are more inclined to accept medicines if orally disintegrating tablets leave a nice taste in the mouth (Bandari et al. 2008). It is reported that various flavoring and aromatic agents can be used to achieve this. Sugar-based excipients are usually used as they are highly soluble in water and will dissolve with saliva and leave a nice taste in the mouth. While mannitol is the most widely used excipient in the ODT preparations, aspartam is used extensively as well. In this study, aspartam and Sugartab® as well as mannitol were chosen for giving a nice taste in the mouth. Sugartab® is a directly compressible sucrose while aspartam, which is a flavoring agent 180 to 200 times stronger than sucrose, does not leave a bitter taste in the mouth. Sodium stearyl fumarate (Pruv®) was selected as lubricant in the formulations at a ratio of 1% in ODTs (Battu et al. 2007; Narmada et al. 2009). Magnesium stearate leaves a metallic taste in the mouth therefore, sodium stearyl fumarate was preferred to magnesium stearate. Sodium stearyl fumarate was also preferred based on its direct compressibility and dissolubility in the water.

### *2.2. Evaluation of tablet characteristics*

Diameter depends on the die and punches selected for the compression of tablets. Therefore, no variation is expected between the formulations. The percentage-weight variation of the ODTs is within the EP limits (less than $\pm 5$). Mean thickness of the formulations is almost the same, varying between $2.84 \pm 0.030$ and $2.94 \pm 0.032$ mm. Friability was between 0.68 and 0.88% being below 1% indicating the sufficient mechanical integrity and strength of the prepared tablets. No significant difference was observed between the prepared ODTs' hardness (N) ($p > 0.05$). Based on hardness and friability results, it can be concluded that the prepared ODTs have acceptable mechanical strength. The tablet characteristics of clozapine ODT formulations were given in Table 1.

### *2.3. In vitro disintegration time and porosity*

Prepared tablets disintegrated in $21.8 \pm 2.7$ and $58.4 \pm 0.89$ s and have fulfilled the disintegration time requirement of 3 min for orodispersible tablets given in EP. Orodispersion of tablets depends on the water absorption and swelling capacities of the disintegrant used (Yunxia et al. 1996; Schiermeier and Schmidt

**Table 1: Tablet characteristics of the clozapine ODT formulations**

| Formulation | Hardness* (N) (n = 10) | Friability (%) | *In vitro* disintegration time* (s) | Dissolved % after 45 min* | Mean mass* (g) (n = 20) | Diameter*(mm) (n = 10) | Thickness* (mm) (n = 10) | Porosity (%) |
|---|---|---|---|---|---|---|---|---|
| 5SgCZ | $82.64 \pm 11.44$ | 0.71 | $31.5 \pm 3.27$ | $90.1 \pm 1.41$ | $0.4010 \pm 0.0033$ | $12.20 \pm 0$ | $2.84 \pm 0.030$ | 10.94 |
| 10SgCZ | $77.45 \pm 14.80$ | 0.76 | $36 \pm 2.68$ | $95.5 \pm 2.51$ | $0.4017 \pm 0.0022$ | $12.20 \pm 0$ | $2.86 \pm 0.05$ | 2.39 |
| 5KrCZ | $76.30 \pm 5.39$ | 0.71 | $21.8 \pm 2.71$ | $95.2 \pm 2.59$ | $0.4006 \pm 0.0037$ | $12.20 \pm 0$ | $2.94 \pm 0.03$ | 4.64 |
| 10KrCZ | $83.80 \pm 9.28$ | 0.88 | $23.4 \pm 9.22$ | $90.4 \pm 1.71$ | $0.4007 \pm 0.0023$ | $12.20 \pm 0$ | $2.93 \pm 0.12$ | 2.57 |
| 5AcCZ | $85.97 \pm 8.32$ | 0.68 | $44 \pm 5.26$ | $88.1 \pm 2.06$ | $0.4023 \pm 0.0037$ | $12.20 \pm 0$ | $2.87 \pm 0.04$ | 3.73 |
| 10AcCZ | $83.62 \pm 3.23$ | 0.71 | $58.4 \pm 0.89$ | $86.8 \pm 4.61$ | $0.4009 \pm 0.0034$ | $12.20 \pm 0$ | $2.86 \pm 0.05$ | 20.91 |

*Mean ± SD

2002; Kuno et al. 2005; Fukami et al. 2006). It also reflects the degree of water penetration to the formulation relatively, and tablet porosity is associated with disintegration time. The porosity of the prepared tablets was between 2.39% and 20.91% (Table 1). It is reported that disintegration time is reduced as the porosity increases (Schiermeier and Schmidt 2002; Fukami et al. 2006). In addition, porosity is more significant for tablets containing disintegrants which make effect with capillary movement (wicking). It is reported that sodium starch glycolate makes effect through swelling, crospovidone through capillary movement and croscarmelose sodium both by swelling and capillary movement (Fukami et al. 2006). The difference between porosities of the ODTs prepared using crospovidone (4.64% for 5KrCZ and 2.57% for 10KrCZ) was not statistically significant ($p > 0.05$). Porosities of the ODTs containing 5% and 10% sodium starch glycolate was 10.94 and 2.39% respectively. However, this difference in porosity was not reflected in the disintegration time of these ODT formulations ($p > 0.05$).

The disintegration times for the ODTs were $21.8 \pm 2.71$ s for 5% crospovidone (5KrCZ), $31.5 \pm 3.27$ s for 5% sodium starch glycolate (5SgCZ) and $44 \pm 5.26$ s for 5% croscarmelose sodium (5AcCZ) containing formulations, with a significant difference among them ($p < 0.05$). The corresponding disintegration times for the ODT containing the same superdisintegrant at a ratio of 10% were $23.4 \pm 9.22$ s, $36 \pm 2.68$ s and $58.4 \pm 0.89$ s, respectively ($p < 0.05$). The disintegration time was not influenced ($p > 0.05$) when the disintegrant concentration increased from 5 to 10% in the ODTs containing sodium starch glycolate or crospovidone. On the other hand, the disintegration time was decreased with a decrease of croscarmelose sodium from 10 (10AcCZ) to 5% (5AcCZ) in the ODTS ($p < 0.05$).

The effect of different concentrations (4%, 6% and 8%) of crospovidone, sodium starch glycolate and croscarmelose sodium as superdisintegrants was examined on the fenoverine ODT direct compressed formulations by Battu et al. (2007) It was reported that, as the superdisintegrant concentration was increased, water absorption capacity was also increased while disintegration time decreased. Whereas, the increase of superdisintegrant concentration from 6% to 8% in formulations containing crospovidone and sodium starch glycolate did not affect the disintegration time (Battu et al. 2007). In the study carried out by Martino et al. (2005) effect of disintegrant (L-HPC LH-11, LH-31, Lycatab PGS, Vivasol®, Kollidon® CL or Explotab®) concentration and compression force were investigated on disintegration of tablets in the ODTs prepared by using Zeparox or Pearlitol® 200 as diluent-filler dissoluble in water. It was found that the longest disintegration time was achieved with use of Vivasol®, whereas the shortest disintegration time was achieved with use of Kollidon® CL. It was also observed in our study that the ODTs which contained Ac-Di-Sol® have the longest disintegration time while the ODTs containing Kollidon® CL have the shortest disintegration time. Martino et al. (2005) reported that compression force was more effective on the disintegration time than the crospovidone concentration in the ODTs prepared with Kollidon® CL. It was also observed in our study that the disintegration time was not affected by the Kollidon® CL concentration ($p > 0.05$). It was reported that when Pearlitol® 200 was used as diluent-filler and Vivasol® as disintegrant, disintegration time was more affected from the disintegrant concentration than from the compression force, and that as the concentration increases disintegration time increases distinctly too (Martino et al. 2005). It was seen in this study that the disintegration time of the ODTs containing Ac-Di-Sol® by 10% is more than that of the ODTs containing the Ac-Di-Sol® by 5% ($p < 0.05$). Ac-Di-Sol® swells extensively when it is in touch with water and its fibrous structure enables water wicking in both intraparticular and extraparticular ways at low concentrations (Sunada and Bi 2002). It was reported that 5% is the optimum concentration for Ac-Di-Sol® in the rapidly disintegrating tablet formulations (Sunada and Bi 2002). It was reported that although the hardness of tablets containing 10% Ac-Di-Sol® is less than that of those containing 5% Ac-Di-Sol®, porosity, wetting time and disintegration are improved (Bi et al. 1999). This observation was explained with the structure of Ac-Di-Sol® which is obtained from sodium carboxymethyl cellulose by means of cross-binding reaction (esterification). This cross-binding reduces dissolution of sodium carboxymethyl cellulose in water to a high extent, and without loss of each fiber's integrity, it allows the material to absorb water and swells up to many times of its weight in the water. Nevertheless, approximately 6% of the structure remains soluble in water and when it becomes wet, this part is be predisposed to be viscous and adhesive. It was reported that when Ac-Di-Sol® is added to tablet formulations at a high ratio, water absorption can cause an increase in viscosity of the liquid in the tablet and will delay penetration of more water (Bi et al. 1999).

Fernandes et al. (2009) examined the effect of superdisintegrants (such as sodium starch glycolate, crospovidone, croscarmellose sodium, methacrylic copolymer with divinyl benzene, i.e., Polyflash® P-544D) on the disintegration time of tablets containing tramadol HCl (BCS class 1), diclofenac free acid (BCS class 2) and famotidine (BCS class 4). They reported that the effect of the disintegrant was lower in soluble matrices than in insoluble matrices. Tablets containing high amounts of active substance soluble in water are predisposed to dissolve rather than disintegrate, and this gives rise to slow disintegration. It was determined that in comparison to the other model compounds used in the study, the class 2 diclophenac free acid is predisposed to disintegrate within the shortest period of time possible and is disintegrated within the shortest time.

### *2.4. Morphological characteristics*

Scanning electron microscopy was used to examine the morphological characteristics of the prepared orally disintegrating tablet formulations. The images of the ODTs (Fig. 1) show that the entire tablets are of a porous structure. It was seen that while the 5AcCZ (croscarmelose sodium 5%) formulation had smaller and many pores, there were greater pores in the 10AcCZ (croscarmelose sodium 10%) formulation. The 5KrCZ (crospovidone 5%) and 10KrCZ (crospovidone 10%) formulations had a similar appearance whereas the 10SgCZ (sodium starch glycolate 10%) formulation had a little firmer structure than the 5SgCZ (sodium starch glycolate 5%) formulation.

### *2.5. Evaluation of drug-excipient interactions*

#### *2.5.1. DSC study*

DSC thermograms were taken for each of the excipients and active substance individually and after pulverization of placebo and clozapine containing tablets. DSC thermograms demonstrated that there was no interaction between excipients and clozapine in the formulations.

#### *2.5.2. X-ray diffractometry*

X-ray diffraction analysis is a functional method for characterization of the changes in the active substance contained in the formulation of a solid dosage form (Palermo 2001). To demonstrate that clozapine was not subjected to a change in the formulation, clozapine, placebo and clozapine containing tablets were pulverized and an X-ray diffraction analysis was

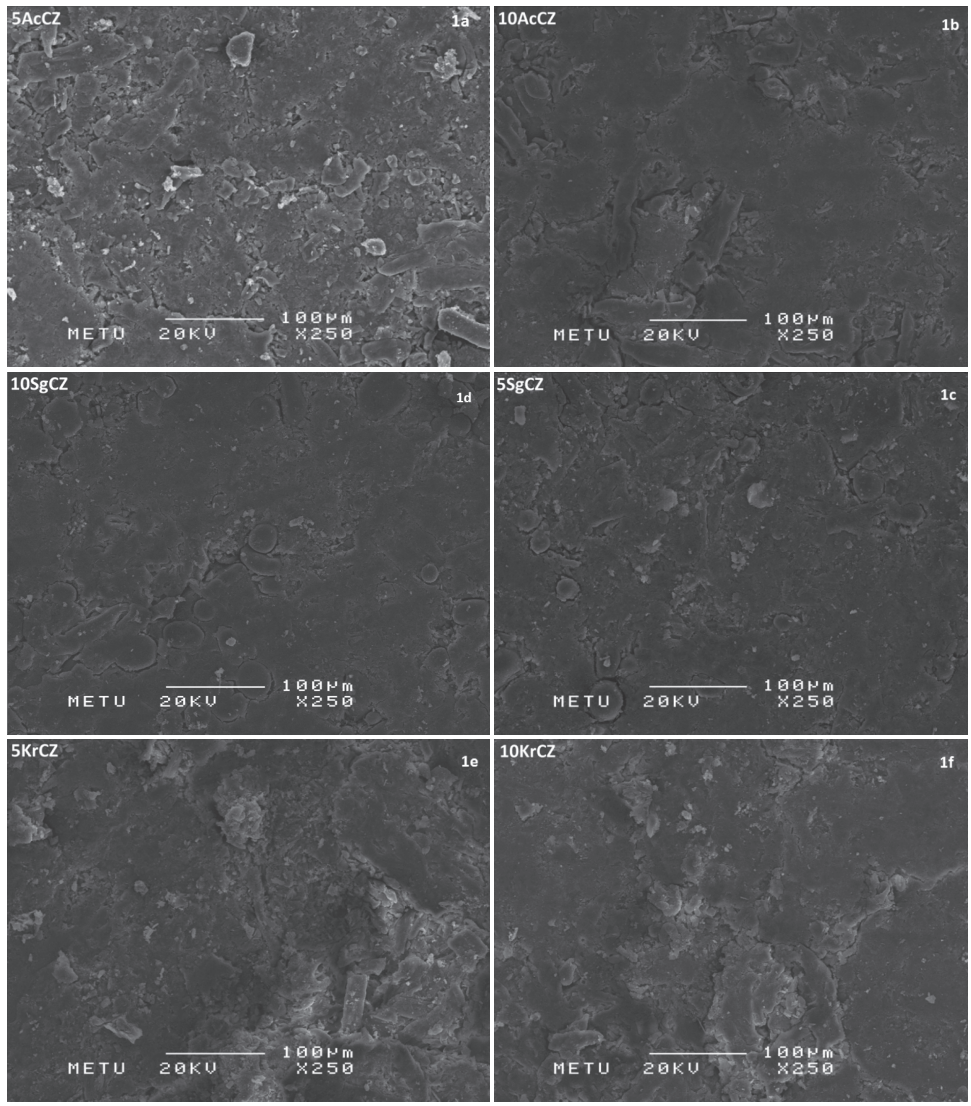


Fig. 1: SEM images of the clozapine ODTs (1a: 5AcCZ Croscarmellose sodium 5%; 1b: 10AcCZ Croscarmellose sodium 10%; 1c: 5SgCZ Sodium starch glycolate 5%; 1d: 10SgCZ Sodium starch glycolate 10%; 1e: 5KrCZ: Crospovidone 5%; 1f: 10KrCZ: Crospovidone 10%)

carried out (Figs. 2 and 3). The X-ray diffractograms revealed that the peaks of clozapine obtained from the raw material and the clozapine containing tablets are consistent with each other indicating that there was no changes in the crystal structure of the clozapine during the preparation of ODTs.

### 2.5.3. *FT-IR spectroscopy*

IR spectrums were taken for clozapine, each of the excipients, placebo tablets and clozapine containing ODTs. Extra peak(s) was/were not viewed. It was observed that the IR bands of the

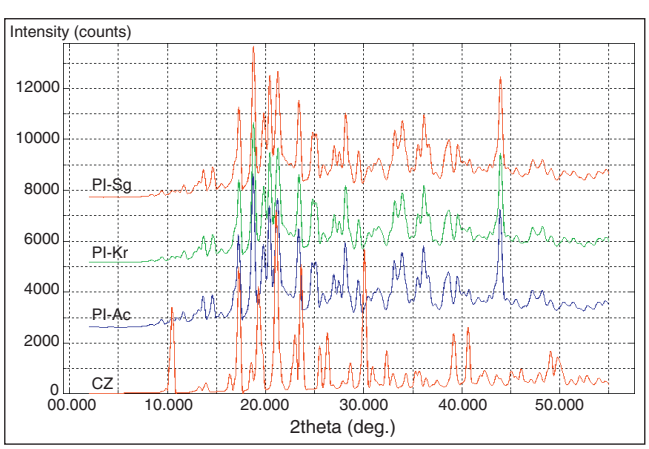


Fig. 2: XRD data for clozapine (CZ) and the placebo (Pl) ODTs (40 kV, 40 mA, 2θ 0.02°/dak) PI-Sg: Sodium starch glycolate 10%; PI-Kr: Crospovidone 10%; PI-Ac: Croscarmellose sodium 10%; CZ: Clozapine

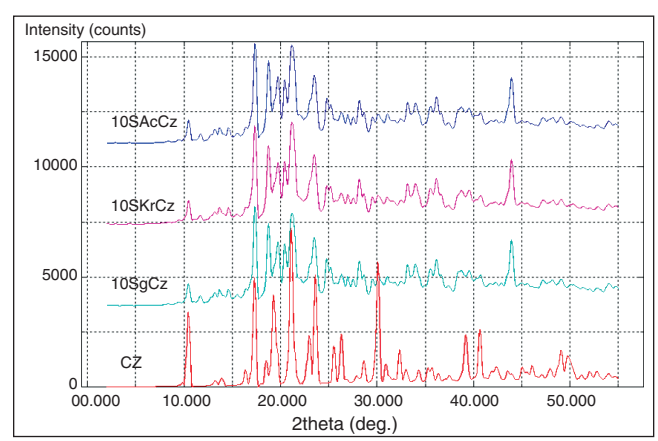


Fig. 3: XRD data for clozapine (CZ) and the clozapine ODTs (40 kV, 40 mA, 2θ 0.02°/dak). 10SgCZ: Sodium starch glycolate 10% and clozapine; 10KrCZ: Crospovidone 10% and clozapine; 10AcCZ: Croscarmellose sodium 10% and clozapine

active substance were similar in the spectrum of the tablets containing active substance as well. FT-IR analysis clearly showed that there was no change in the chemical structure of the active substance after it was combined with other excipients.
The results of the DSC, X-ray diffraction and FT-IR studies indicated that clozapine is compatible with the excipients used in this study.

### *2.6. In vitro dissolution test*

USP I (basket) method was specified as 100 rpm for the clozapine conventional tablet in its monograph (The United States Pharmacopeia-USP32 2008). Nevertheless, USP II (paddle) method with 50 rpm of paddle speed is usually recommended for the ODT dissolution test (Klancke 2003; Siewert et al. 2003). A better discrimination between *in vitro* dissolution profiles are observed at low paddle speeds. However, it is expressed that tablet fragments or disintegrated tablet masses may be trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, thus yielding irreproducible dissolution profiles (Klancke 2003). For this reason, paddle method was used for the dissolution tests of the developed ODTs.
It was found that the prepared ODTs complied the USP requirement for clozapine tablets (dissolved more than 85 % of the labeled amount of clozapine in 45 min) (Fig. 4). According to the guidelines, calculation of the similarity factor (f2) is suggested for comparison of the dissolution profiles of the prepared tablets. The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in percentage (%) of dissolution between the two curves (Guidance for Industry 2000 August). When the similarity factor is between 50 and 100, the dissolution profiles are considered similar. On the other hand, if 85% of the labeled amount is dissolved within 15 min, the dissolution profiles are accepted similar without any mathematical calculation. In this study, for all formulations, more than 85% were dissolved within 15 min, thus a f2 value was not calculated and the dissolution profiles of the ODTs were not statistically different ($p > 0.05$). The dissolution data are shown in Fig. 4.

## 3. Experimental

### *3.1. Materials*

Clozapine (CZ) was kindly provided by ADEKA Pharmaceutical Company, İstanbul, Turkey. Sodium stearyl fumarate (Pruv®) and sucrose (Sugartab®) were obtained as gift sample from JRS Pharma, Germany. Croscarmellose sodium (Ac-Di-Sol®) (CP Kelco BV/Holland), sodium starch glycolate (Vivastar® P) (JRS Pharma, Germany), Avicel PH102 (MCC) (JRS Pharma, Germany), crospovidone (Kollidon® CL) (BASF AG/Germany) and aspartame were kindly provided by Abdi İbrahim Pharmaceutical Company, İstanbul, Turkey. Pearlitol® SD200 was obtained as a gift sample from Roquette Freres/France.

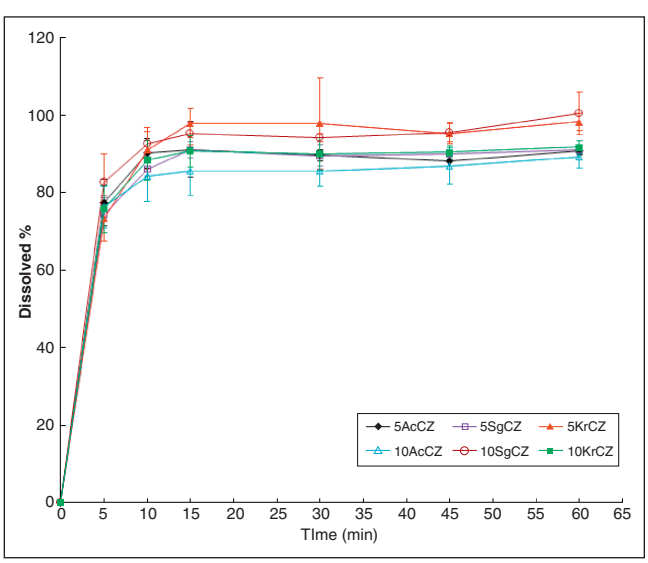


Fig. 4: Dissolution profiles of the clozapine ODTs (mean ± SD, n = 6, pH 4.0 acetate buffer, $\lambda_{max}$ = 292 nm)

**Table 2: Clozapine containing ODT formulations**

| Ingredients | Formulations (mg) | | | | | |
|---|---|---|---|---|---|---|
| | 5SgCZ | 10SgCZ | 5KrCZ | 10KrCZ | 5AcCZ | 10AcCZ |
| Clozapine | 100 | 100 | 100 | 100 | 100 | 100 |
| Pearlitol® SD 200 | 180 | 160 | 180 | 160 | 180 | 160 |
| Avicel PH 102 | 40 | 40 | 40 | 40 | 40 | 40 |
| Sugartab® | 52 | 52 | 52 | 52 | 52 | 52 |
| Aspartame | 4 | 4 | 4 | 4 | 4 | 4 |
| Sodium starch glycolate | 20 | 40 | — | — | — | — |
| Crospovidone | — | — | 20 | 40 | — | — |
| Croscarmellose sodium | — | — | — | — | 20 | 40 |
| Sodium stearyl fumarate | 4 | 4 | 4 | 4 | 4 | 4 |
| Total weight | 400 | 400 | 400 | 400 | 400 | 400 |

### *3.2. Preparation of formulations*

Avicel PH102 (MCC), Sugartab®, pearlitol® SD200 were selected as the basic excipients. Pruv® (1%) was used as lubricant, and aspartame as sweetener. Croscarmellose sodium, sodium starch glycolate or crospovidone were used as superdisintegrants. To prepare 400 mg tablets, all these excipients and 100 mg clozapine were mixed thoroughly for 10 min by a roller mixer and then compressed by Erweka AR 400 Korsch/Germany at around 80 N hardness. The ODT formulations developed for clozapine and their contents are given in Table 2.

### *3.3. Evaluation of tablet characteristics*

All clozapine ODTs developed were evaluated according to the European Pharmacopeia (EP 6.0) (European Pharmacopoeia 2008) and USP XXXII (The United States Pharmacopeia-USP32 2008).

#### *3.3.1. Uniformity of mass*

Twenty tablets were randomly selected from each formulation and weighed using a Shimadzu digital balance. The mean ± standard deviation (SD) were recorded. According to EP, no more than 2 of individual masses should deviate from the average mass by more than 5 % and none deviate by more than twice of that percentage (European Pharmacopoeia 2008).

#### *3.3.2. Thickness and diameter*

Ten tablets from each formulation were taken randomly and their diameter and thickness were measured simultaneously using a tablet hardness tester (Pharma test PTB, Germany).

#### *3.3.3. Resistance to crushing of tablet*

Ten tablets from each formulation were taken randomly and resistance to crushing of tablets, which is defined as the force required to break a tablet by radial compression, was measured using a tablet hardness tester (Pharma test PTB, Germany) (European Pharmacopoeia 2008).

#### *3.3.4. Friability*

Friability of the tablets was determined using a friabilator (Smiths/England). Pre-weighed tablets (n = 20) were placed in a plastic chambered friabilator, rotated at 25 rpm/min for 4 min, and then the tablets were de-dusted, reweighed and percentage weight loss (friability) was calculated (European Pharmacopoeia 2008).

### *3.4. In vitro disintegration time and porosity*

*In vitro* disintegration time of the ODTs was determined using an USP disintegration test apparatus without disk (Pharma test PTB, Germany) for six tablets. The 1000 mL of distilled water at 37 ± 1 °C was used as test fluid at

the rate of 30 ± 2 cycles/min (European Pharmacopoeia 2008). Porosity was determined by a mercury porosimeter up to a pressure of 50 psi (Poremaster 60, Quantachrome Corporation/USA).

### 3.5. Morphological characteristics

The morphological examination of the ODTs was performed using a scanning electron microscope (SEM) (Jeol 6400, Japan). Samples of ODTs were mounted on carbon adhesive stubs and coated with a gold layer of appropriate thickness.

### 3.6. Evaluation of drug-excipient interactions

#### 3.6.1. DSC study

A differential scanning calorimetry (DSC) study was performed using DSC-60, Shimadzu/Japan at 20–300 °C.

#### 3.6.2. X-ray diffractometry

X-ray powder diffraction patterns were recorded using a Rigaku X-ray Diffractometer (D/Max 2200/PC, Japan) powder diffractometer. The samples were scanned at room temperature at 40 kV voltage and the scanning rate employed was 0.02°/min over a diffraction angle of $2\theta$ and range of 2°–55°.

#### 3.6.3. FT-IR spectroscopy

A Fourier Transform Infrared (FTIR) spectroscopy study was performed. The spectra of excipients, placebo and clozapine containing tablets were recorded using Perkin-Elmer Spectrum BX FT-IR at λ=600–4000 $cm^{-1}$.

### 3.7. In vitro dissolution test

The *in vitro* dissolution test was performed according to USP XXXII (The United States Pharmacopeia-USP32 2008) using the paddle method (Apparatus II) at 50 rpm in pH 4.0 acetate buffer utilizing a dissolution system (Sotax CH 4123, Switzerland). Samples (5 mL) were collected at predetermined time intervals (5, 10, 15, 30, 45 and 60 min) and replaced with equal volume of fresh medium and filtered by Whatman filter paper. The detection of clozapine was performed spectrophotometrically at 292 nm.

### 3.8. Statistical analysis

Statistical analysis was performed using SPSS 17.0 for Windows. The significance level was set at 0.05.

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