ZITA MEDICAL MANAGEMENT

www.hsmc.gr/en/pharmakeftiki-journal/

ΕΡΕΥΝΗΤΙΚΗ ΕΡΓΑΣΙΑ
RESEARCH ARTICLE

ΦΑΡΜΑΚΕΥΤΙΚΗ, 36, I, 2024 | 64-79
PHARMAKEFTIKI, 36, I, 2024 | 64-79

Formulation and Evaluation of Olanzapine Oral Lyophilisates

Rasha Khalid Dhahir[1], Fadia yassir Al-bazzaz[1], * Myasar Al-kotaji[2], Mutasem Rawas-Qalaji[3]
[1]Department of Pharmaceutics, College of Pharmacy, University of Mosul, Mosul, Iraq,
[2]Department of Pharmaceutics, College of Pharmacy, Ninevah University, Mosul, Iraq,
[3]College of Pharmacy, University of Sharjah, Sharjah, United Arab Emirates.

KEYWORDS:
Olanzapine, oral lyophilisates, rapidly disintegrating tablet, freeze drying

ARTICLE INFO:
Received: September 27, 2023
Revised: November 13, 2023
Accepted: January 11, 2024
Available on line: April 4, 2024

*** CORRESPONDING AUTHOR:**
myasar.alkotaji@uoninevah.edu.iq

ABSTRACT

One of the main obstacles to the development and delivery of drugs is poor drug solubility. Lyophilization is one of the common techniques that has been utilized to formulate alternative solid dosage forms that has the potential to improve drug delivery. In the present work, Olanzapine was manufactured using this technique to develop convenient and easy-to-administer rapidly disintegrating tablets as oral lyophilisates for the treatment of psychotic disorders.

By dispersing the medication in an aqueous solution of mannitol, MCC, various binders, and glycine, various formulations of Olanzapine oral lyophilisates were prepared. By assessing the hardness, disintegration time, wetting time, and dissolution time, the effect of mannitol, MCC, and various binders on the oral lyophilisates' properties was investigated. Furthermore, FTIR, DSC, and SEM were used to further characterize the produced oral lyophilisates.

The formed Olanzapine oral lyophilisates resulted in rapid tablet disintegration (11.6 to 23.5 sec) and a drug dissolution of 48.7% to 77.7% within two minutes. The FTIR spectra showed no drug-excipient interactions, while the DSC and SEM results show the crystalline state of Olanzapine in the pure drug and the physical mixture and there is clear evidence of transformation to the amorphous state during the formation of the oral lyophlisates. To conclude, this work succeeded in production of Olanzapine oral lyophilisates (Formula 7) with rapid disintegration, rapid dissolution and with no evidence for drug-excipient interactions.

Introduction

Mental illnesses are quite prevalent. In the US, about 20% of individuals have mental illness in 2019[1]. Although there are several types of drugs (typical and atypical antipsychotic medicines) available for the treatment of mental illnesses, the situation is significantly worse, especially in the case of old individuals for whom simple dose modification and maintenance is crucial[2]. The Food and Drug Administration has authorized the second-generation atypical neuroleptic medication, Olanzapine, (Figure 1) for use as a first-line therapy for the treatment of bipolar disorder-related mania and schizophrenia.

Nevertheless, olanzapine has inconsistent bioavailability due to its poor water solubility (12–44 μg mL-1) and slow dissolving rate. Moreover, the drug undergoes substantial first-pass metabolism[3]. Several formulation strategies, such as intranasal microemulsion, solid dispersion, self-nanoemulsifying drug delivery systems, nanosuspensions, and many more, have been reported to improve Olanzapine's solubility and bioavailability. In addition, orally disintegrating tablets (ODTs) represented a feasible approach that entered the market as a possible treatment for low compliance of patients on antipsychotic drugs[2].

Oral fast dissolving dosage forms, sometimes referred to as fast-dissolving, fast-melting, or orodispersible, are innovative dosage forms that include quick disintegration or dissolution of the system that enters into a solution or suspension in the mouth without the need for water[4]. The dosage form immediately starts to breakdown as it comes into contact with saliva, and it is finished within a few seconds after intake[5].

One advantage of manufacturing the medication in an oral dispersible form is the reduced risk of Olanzapine's metabolic side effects, such as weight gain[6]. This tendency of avoiding peripheral side effects was discovered in 2004 by De Haan et al. They demonstrated that individuals with schizophrenia who converted from regular Olanzapine tablets to the ODTs form had lost weight[6], Olanzapine-related weight gain appears to be correlated with higher food intake because of a post-meal satiety that is delayed. At 5-HT-type receptors both within and outside the brain, olanzapine displays strong binding affinities for serotonin. In contrast to conventional oral tablets, Olanzapine ODTs produce a more rapid onset of absorption. It is hypothesized that this shortens the interaction of olanzapine with the 5-HT2-type receptors in the pylorus as well as the 5-HT3 receptors, which comparatively preserves saturation feedback mechanisms and controls or reduce food intake[6]. An additional supporting rat study showed that central Olanzapine administration does not have the same effects as acute intra-gastric Olanzapine treatment in terms of hyperglycemia and insulin resistance. This suggested that peripheral mechanisms rather than a central role in Olanzapine's metabolic side effects might be involved[7].

A variety of methods, including tablet molding, spray drying, sublimation, lyophilization, solid dispersion, and the inclusion of disintegrants, might be used to create the ODTs[8]. But due to the straightforward and affordable manufacturing process, lyophilised tablets have been one of the most often used type[1,9,10].

Lyophilized formulations have the benefit of being very soluble, light, and porous products. The freeze-dried dosage forms have great stability, quick reconstitution, and good preservation. For the production of freeze-drying tablets, a porous matrix must be created by water sublimation from the previously frozen preparations[11]. In addition to the quick disintegration time brought on by water seeping through the highly porous matrix in which the active ingredient is trapped or dissolved, the lyophilized ODT will decompose into a liquid with a pleasant mouthfeel. Before lyophilization, the API is normally dissolved in or held in suspension of a liquid bulk formulation. When compared to compressed ODTs, a liquid formulation is simpler to dose volumetrically than a powder combination, which typically results in improved dosage accuracy. Also, the prepossessing procedures are significantly safer since all of the components are moist and contained within the bulk formulation[12].

The matrix of the lyophilised tablets should have two components that operate in tandem to ensure the formation of a good formulation. The first ele-

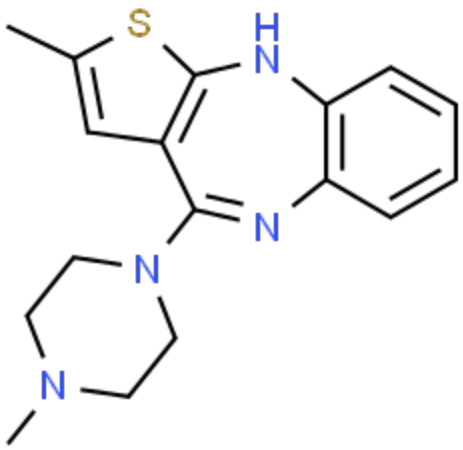


Figure 1: *Chemical structure of olanzapine*

ment that keeps the shape of the tablets and gives them mechanical strength is the matrix former. Alginate, gelatin, dextrin, and maltodextrin are examples of water-soluble polymers that frequently make up the matrix[13]. The second component consists of matrix-supporting and disintegration-enhancing components like sucrose and mannitol that operate by adhering to the porous framework made by the water-soluble polymer and accelerating the breakdown of the fast-dissolving tablets[11].

The purpose of this research is to create an oral disintegrating tablet (lyophilised) Olanzapine. Different additives and matrix formers have been tested. Additionally, the selected formulations and the already marketed product were compared.

Materials and Methods

Materials

Al Kindi pharmaceutical company (Iraq), generously, provided Olanzapine powder, the active medicinal component. Microcrystalline cellulose (MCC) PH-102 was supplied by JRS pharma, US. Mannitol powder was purchased from Scharlau, Spain. Schisolazine® 5mg tablet purchased from Wadi El Neel Benta , Egypt. All other ingredients were of analytical grade.

Methods

Olanzapine oral lyophilisates preparation

Through the lyophilization technique, ten distinct formulations of Olanzapine orally disintegrating tablets (5 mg) were developed. Table 1 demonstrates the different types and concentrations of matrix formers and binders used. The matrix formers were mannitol and microcrystalline cellulose[14], the latter also acts as a disintegrant and binder[15]. According to their concentrations, polyvinylpyrrolidone and poloxamer were used as stabilizers[16] , and hydroxy propyl methyl cellulose was used as viscosity modifier and as binder , glycine was used as disintegration accelerant[15].

For each formula, 15 ml suspension was prepared. The stated amounts of each of the matrix formers, binder polymers, and the bulking agents have been dispersed in distilled water and stirred with a magnetic stirrer (Fisher Scientific, Korea) for about 30 min. Then Olanzapine was dispersed in the former solutions, with stirring, to produce 5mg/ 0.5 ml and yield a total amount of 150 mg for each formulation[17].

The needed quantity of the suspension was placed into blister packs with a cavity depth of 3 mm and a diameter of 13 mm using a syringe. The blister packs were then wrapped in aluminum foil and perforated. The formulations were frozen at about -70 ºC for 2 hr, and lyophilised in a lyophilizer (OLABO, China) for 24 hrs at a temperature of less than -50 and pressure drop of less than 10 Pa,[18]. Finally, the resultant formulations were coded and stored in sealed containers for further different evaluation.

Evaluation of Olanzapine oral lyophilisates

Hardness

A tablet's strength is determined by how much power is required to break it, which is how hard it is. The force was expressed in Newtons. Using a tablet hardness tester (YD-1, Lpmie, China), ten of the manufactured Olanzapine oral lyophilisates were evaluated for hardness[19].

Table 1: The composition of different formulae of Olanzapine lyophilisate

Ingredients %(w/v)	***F1***	***F2***	***F3***	***F4***	***F5***	***F6***	***F7***	***F8***	***F9***	***F10***
Olanzapine	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*
Mannitol	*50*	*75*	*75*	*90*	*90*	*90*	*50*	*90*	*90*	*90*
MCC-PH 102	-	-	*25*	-	*10*	*15*	-	*10*	*10*	*10*
PVP-K30	*0.3*	*0.3*	*0.3*	*0.3*	*0.3*	*0.3*	*0.2*	*0.6*	-	-
Poloxamer-188	-	-	-	-	-	-	-	-	*0.3*	*0.6*
HPMC-K4M	-	-	-	-	-	-	*2*	-	-	-
Glycine	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*

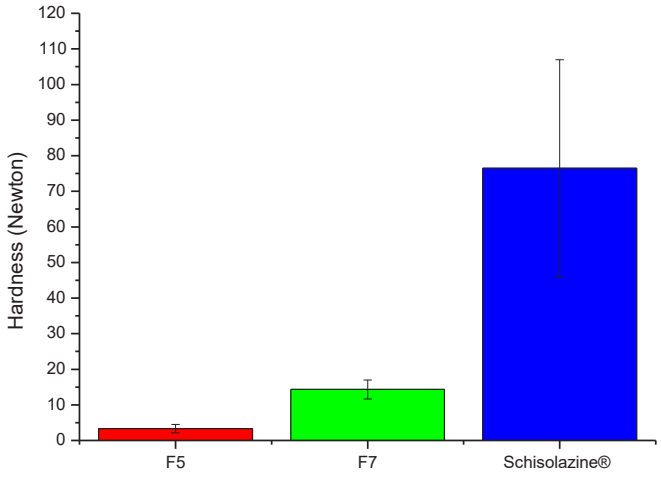


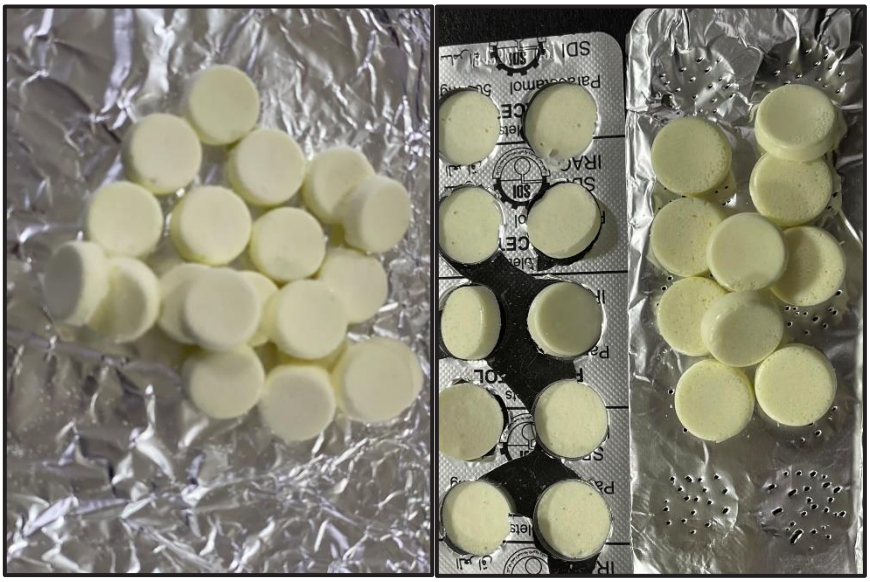
Figure 2: *Comparison of hardness of the tablets from the successful formulations F5, F7, and Schisolazine® 5mg marketed tablets*

Weight variation

Using an electronic balance (Adam Equipment, PW 124, UK), 20 of the prepared Olanzapine oral lyophilisates were weighed. Both the average weight and weight variation were computed[20].

Drug content

From the optimized formulations, ten Olanzapine oral lyophilizate tablets were randomly chosen, crushed, and mixed. An amount equivalent to 5 mg of Olanzapine was weighed, mixed with 50 ml of 0.1N HCl solution[21], and then filtered via a 0.45 micrometer filter. Using a UV-visible spectrophotometer (Labomed UVD-3000, USA) and 0.1N HCl as a blank, 1ml of the solution was obtained, diluted to 10 ml with 0.1N HCl, and then tested for drug concentration at 258 nm. The measurement was carried out three times[22].



(A) ***(B)***

Figure 3: *The successful formulations of Olanzapine oral lyophilizates; (A) F5, and (B) F7*

In vitro disintegration test

The in vitro disintegration test for uncoated tablets was carried out in accordance with USP 33-NF 28[21]. The disintegration time was evaluated using the disintegration instrument (BJ-2 Huanyu, China) with distilled water 900 ml as a medium [20] held at 37± 0.5°C using six randomly selected Olanzapine oral lyophilisates. The findings were calculated as average values (n = 6)[23].

Wetting time and water absorption ratio

The commercially available tablets (Schisolazine®) and those from the best formulations were carefully placed on a circular piece of tissue paper with a diameter of 10 cm, which was immersed in a petri dish with a 5 ml aqueous solution of orange dye (1% w/v). The amount of time it takes water to reach the surface of the tablet is known as the wetting time. To calculate the water absorption ratio, R, the pill's weight before and after soaking was measured in the same way as previously.

R= 100 (Wa - Wb/Wb) …. (1)

Wb = Weight of tablet before absorption of water
Wa = Weight of tablet after water absorption[19].

Dissolution test

The USP dissolution apparatus type II (Copely, UK) was used to determine the dissolution profile of Olanzapine oral lyophilisates, with a paddle rotation speed of 50 rpm. At 37.5°C, the test was conducted using 900 ml of 0.1N HCl. After 1, 2, 4, 6, 8, 10, 15, 20, 25, and 30 min, 5 ml sample of the best formulations and that of the commercial Olanzapine oral lyophilisates were withdrawn and filtered. Fresh medium was added to compensate the amount for each sample that was removed. Utilizing a UV-visible spectrophotometer (Labomed UVD-3000, USA), the concentration of the medication that had been released was determined at 258 nm. The measurement was carried out three times[24].

Differential scanning calorimetry

Thermal properties of olanzapine, physical mixture,

Table 2: Evaluation parameters for lyophilized orally disintegrating tablets

Formulas	***Friability***	***Hardness (N)[a]***	***weight variation (%)[b]***	***Drug content (%)***	***Disintegration time (sec)[c]***	***Wetting time(sec)[d]***	***Water absorption ratio (%) after 10 sec[d]***	***2 min drug release (%) [c]***
F1	*No tablets*	-	-	-	-	-	-	-
F2	*No tablets*	-	-	-	-	-	-	-
F3	*Fragile tablet*	*3.33±1.15*	*1.07±0.008*	-	*10±0.00*	-	-	-
F4	*Fragile tablets*	-	*4.92±0.031*	-	*60.26±0.09*	-	-	-
F5	*Good tablets*	*5.8±1.05*	*1.79±0.020*	*103.72%±2.20*	*11.6±2.08*	*14.5±0.707*	*46.5%±2*	*48.65±1.35*
F6	*Fragile tablets*		*1.30±0.001*		*7±1*	-	-	-
F7	*Good tablets*	*14.33±2.68*	*2±0.017*	*101.27%±1.91*	*23.5±1.5*	*39±8.485*	*5.3%±0.54*	*77.67±0.37*
F8	*Fragile tablets*	-	*6.43±0.025*		*22±8.18*	-	-	-
F9	*No tablets*	-	-	-	-	-	-	-
F10	*No tablets*	-	-	-	-	-	-	-
Schisolazine® 5mg tablet	-	*76.43±30.5*	*1.443±0.75*	*97.12%±1.54*	*23.43±2.9*	*52.4±4.4*	*82.1%±4.5*	*96.55±1.3*

[a] Data are expressed as mean±S.D, n =10, [b] Data are expressed as mean±S.D, n =20, [c] Data are expressed as mean ±S.D, n =6, [d] Data are expressed as mean ±S.D, n =3

and the lyophilized tablet formulations were investigated using differential scanning calorimetry (DSC) (Q2000 TA Instruments, New Castle, DE, USA). Samples weighing 5-20 mg were sealed in aluminum pans and heated at a rate of 10 °C/min under nitrogen purging throughout a temperature ranging from 20 to 200 °C for DSC analysis[25].

Scanning electron microscopy

Samples of the pure drug (olanzapine), physical mixture, and the lyophilized tablet formulations were investigated for their crystals' shape, morphology, and topography using a scanning electron microscope (SEM) (Thermo Scientific Apreo, FEI Company, Hillsboro, Oregon, USA). Samples were gold-coated using a sputter coater (Quorum Technology Q150TS, Ashford, Kent, UK) before scanning. The sputtering gas used was argon, the chamber was under a pressure of 10-2 mbar, and the applied voltage was 1 kV with a plasma current of 18 mA for a total of 120 sec. The scanning by SEM was performed and photomicrographs were

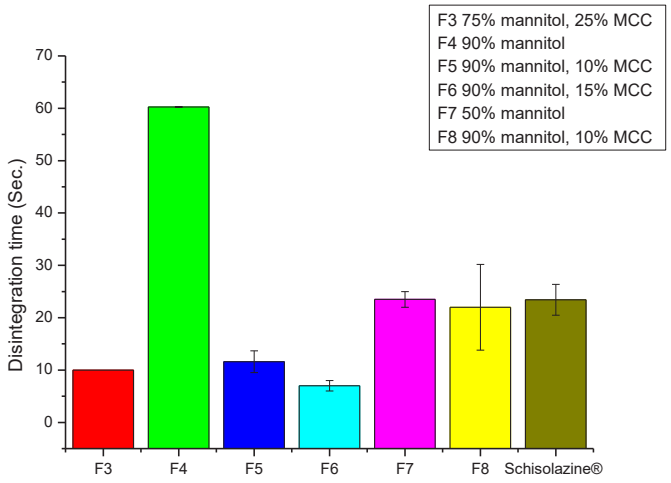


Figure 4: *Disintegration time of the different formulations of olanzapine oral lyophilisates*

taken at an acceleration voltage of 3 kV[25].

Fourier transform infrared spectroscopy (FTIR)

The test was performed for the pure drug, the drug-excipient physical mixtures including Olanzapine with mannitol, MCC, PVP, HPMC, and glycine in a ratio of 1:90, 1:10, 1:0.3,1:2, and 1:1 respectively, and for the succeeded formulations, to determine any possible interaction. It was carried out using an FTIR spectrophotometer (Bruker-FTIR, Germany), with a resolution of 4 cm and a scanning range of 400–4000 cm-1[17].

Statistical analysis

The experimental results were analyzed using the one-way Analysis of Variance (ANOVA) test using Origin software (version 8.0, OriginLab), and a p-value of less than 0.05 was considered significant (n = 3).

Results and discussion

Hardness

The hardness of all the produced tablets are expressed in Table 2 and Fig. 2. The hardness ranges from 3.33±1.15 to 14.33±2.68 Newton. There is a statistical significance difference in hardness among F3, F5 and F7 ($p<0.05$).

The general hardness is low, as one might anticipate. This is because there is no compression process used in the creation of lyophilised tablets; instead, they are made using a lyophilization procedure. However, tablets should be hard enough to be removed from the blister and being handled without any breakage. Nevertheless, there is no possibility for attrition during the transportation or handling, this is mainly due to the complete filling of the lyophilised tablets inside the blister and there is no extra space for tablets inside the blister as shown Fig. 3. As demonstrated in Table 2 only F3, F5 and F7 succeeded in producing tablets that can be handled. Other formulae were failed. The marketed oral dispersible product (Schisolazine)® differs from the made formulations, it exhibited high hardness ($p<0.05$), which is due to their different technique used during production. Remarkably, F7 showed higher hardness than F3 and F5 ($p<0.05$) and this may be explained by the existence of HPMC, which act as binding agent as illustrated in Fig. 1[26]. Comparing the formulations that contain different concentrations of mannitol (F1, F2, F4 and F5) reveals

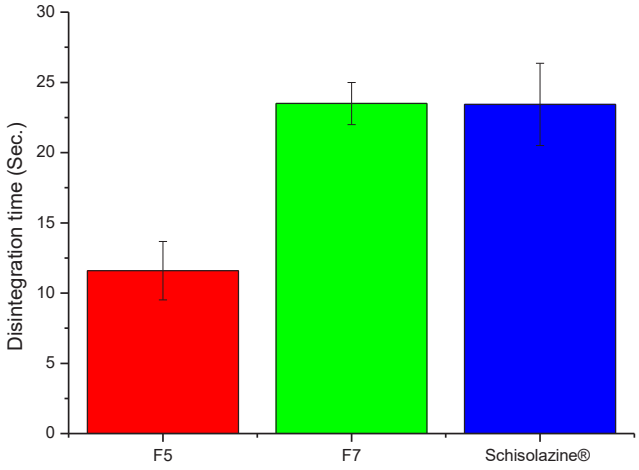


Figure 5: *Comparison of the disintegration time of the succeeded tablets from the formulations F5, F7, and Schisolazine® 5mg tablet*

that using mannitol alone cannot produce tablets with good mechanical properties without addition of suitable binding agent.

Weight variation

Weight variation of the resulting tablets is illustrated in Table 2, and it is in the range of 1.07%±0.008 to 6.43%±0.025. Indeed, according to USP requirement the acceptable weight variation for tablet weighing less than 130 mg is ± 10%. According to the results all the variations were within narrow limit and this indicates good uniformity of tablet production.

In vitro Disintegration test

There was a statistically significant difference in the disintegration time of F4 when compared to other formulations ($p<0.05$), as shown in Fig. 4. The disintegration time of the tablets from various formulations was in the range of 7±1 sec to 60.26±0.09 sec, Fig. 4 demonstrated the significant difference in disintegration of F5 when compared with F7 and the investigated marketed product.

It is necessary to mention that not all the formulations were capable to produce lyophilised tablets. As demonstrated in Table 2, some of the formulations were failed including F9 and F10, which were prepared using poloxamer-188 as stabilizer. Indeed, Poloxamer-188 was used as stabilizer in preparation of meloxicam lyophylisate, however, the used concentration was higher than the concentrations we used in this study[5].Nonetheless, the disintegration time of the prepared formulations that were successful in producing tablets might be ordered in an ascending manner as follows: F6<F3<F5<F8< marketed product < F7 <F4 as shown in Fig. 4.

As shown in Fig. 5, there is a remarkable statistical difference between the disintegration times of the successful tablets from formulations F5, F7, and the marketed product ($p<0.05$). F5 demonstrated fast disintegration (11.6±2.08 sec) in comparison to F7 (23.5±1.5sec) and Schisolazine® (23.43±2.936 sec). This may be due to the presence of high percentage of mannitol as bulking agent in addition to the use of MCC[27]. However, the disintegration time for all of the successful formulations are in compliance with the specifications of USP, which revealed that orally

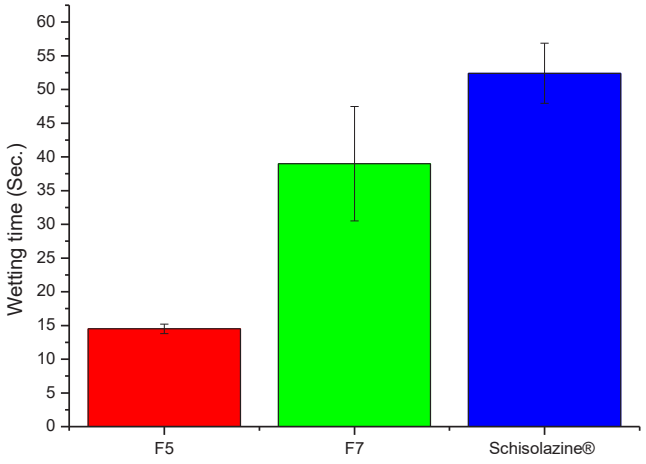


Figure 6: *Comparison of the wetting time of the successful tablets from the formulations F5, F7, and Schisolazine® 5mg tablet*

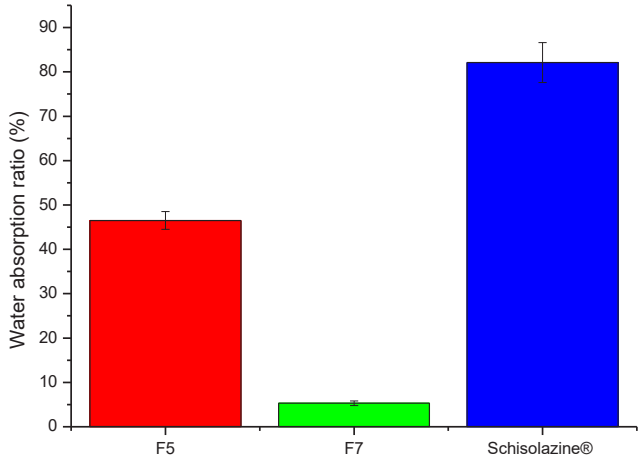


Figure 7: *Comparison of water absorption ratio of the successful tablets from the formulations F5, F7, and Schisolazine® 5mg tablet*

disintegrating tablets should be disintegrated within 30 seconds[20]. In addition, the results are in compliance with the European pharmacopeia requirement for orodispersible tablets disintegration time, which should be less than 3 min[20].

On the other hand, when comparing the formulations which contain the same amount of mannitol (F4 with F5 and F6), there were statistically significant differences ($p<0.05$) in the disintegration time and this could be attributed to the concentration of microcrystalline cellulose (MCC), which were used at 0, 10 and 15 % in F4, F5 and F6, respectively. Evidently, the speed of disintegration accelerated with higher MCC concentration as MCC act as a disintegrant and drain water into tablets and this lead to rapid disintegration[28].

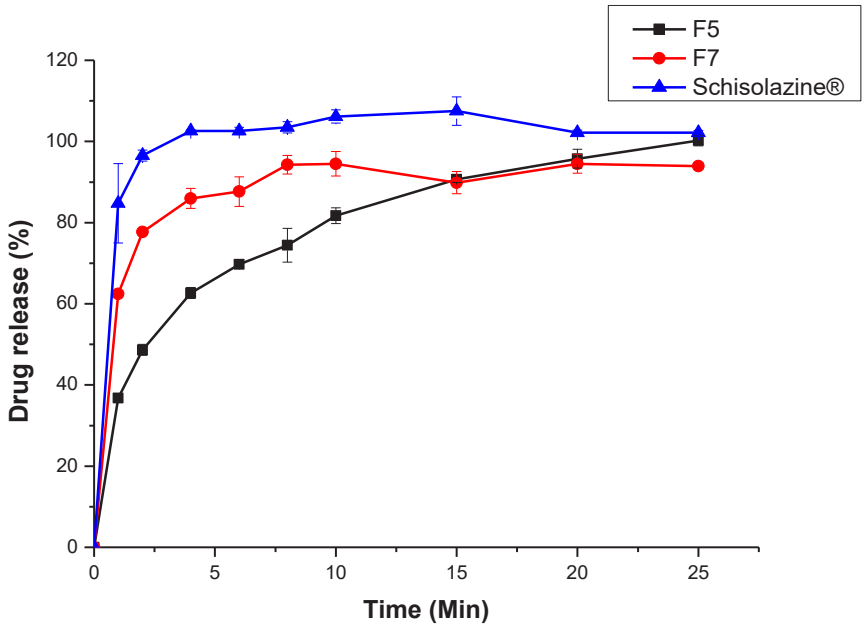


Figure 8: *Percentage of drug release from F5, F7 Olanzapine oral lyophilisates and from the marketed product.*

Table 3: The endothermic peaks of the investigated samples measured by DSC

Samples	Endothermic peak
Olanzapine alone	196°C
Mannitol alone	170.6°C
Physical mixture of Olanzapine with mannitol	196°C and 171°C
F5	167.48°C
F7	169.24°C

Wetting time and water absorption ratio

Wetting time for the succeeded formulations F5 and F7 was 14.5±0.707 sec and 39±8.485 sec, respectively. However, the marketed tablets exhibited longer wetting time (52.4±4.468 sec) and there was a statistical difference among them ($p<0.05$) as demonstrated in Fig. 6. The water absorption ratio for F5, and F7 was 46.5±2% and 5.3±0.54% respectively, and for the marketed tablets it was 82.1±4.52% ($p<0.05$) Fig.7.

The results of wetting time and water absorption ratio were directly related to the disintegration time as shown in Table 2, Fig. 6, and they were a function of the disintegration mechanism[29]. Microcrystalline cellulose in F5 has a good capillary ability, and it is a kind of porous granules with wicking property, in addition to that presence of PVP that has porous structure, and mannitol with its hydrophilic properties, enhance water penetration[30].

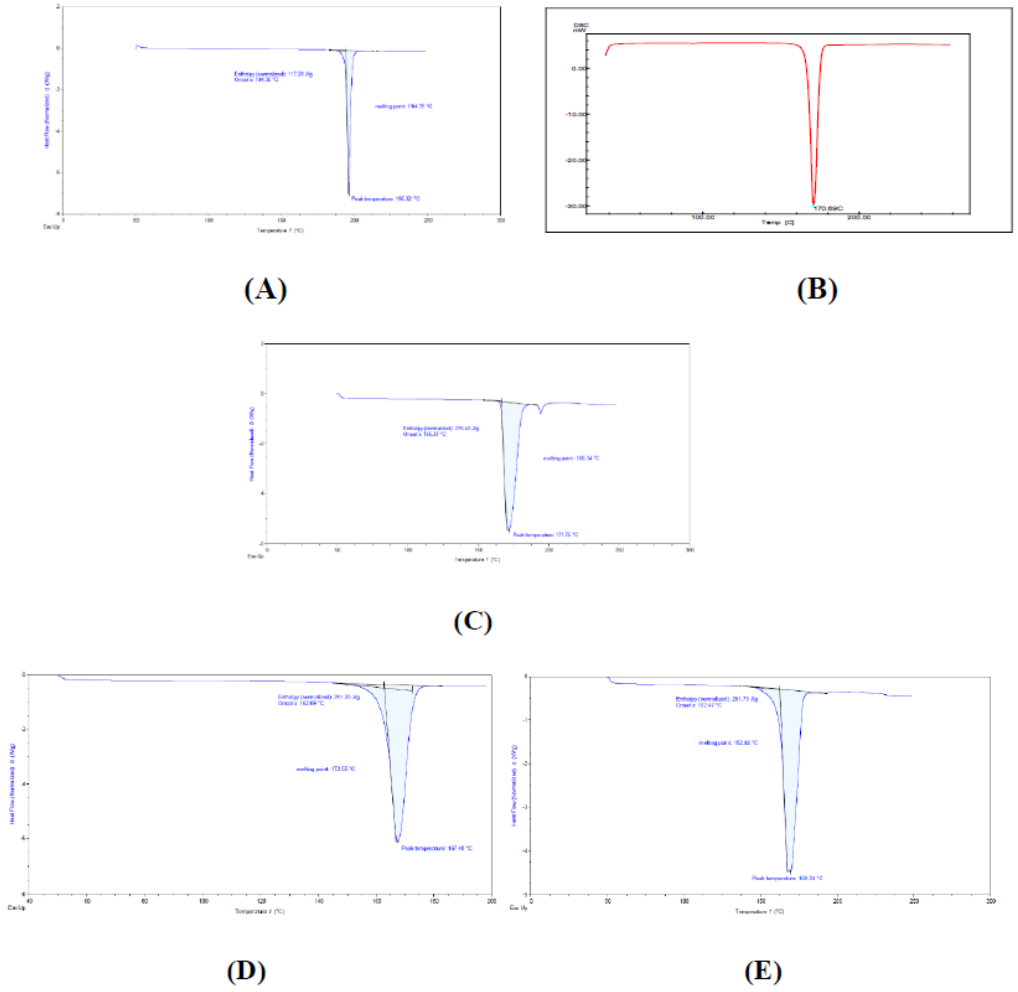


Figure 9: *DSC Thermogram of Olanzapine (A), Mannitol (B), Olanzapine and mannitol (C) , F5 (D) and F7 (E).*

The water absorption are presented in Table 2. When comparing the formulation that contains MCC (F5) with that without MCC (F7), there was a statistical significant difference between them ($p<0.05$), as illustrated in Fig. 7, which may be due to the combined effect of MCC that has a good wicking and absorbing capacity, and mannitol that has good wetting property and aqueous solubility in F5[30].

Dissolution test

The dissolution profiles of the produced tablets of formulations F5, F7, as well as the commercial product are illustrated in Fig. 8 . According to Table 2, the drug release at 2-minutes for F5 and F7 was 48.65±1.35 and 77.67±0.37 min, respectively and for the marketed product it was 96.55±1.35 %.

In contrast to F7, where the matrix former was man-

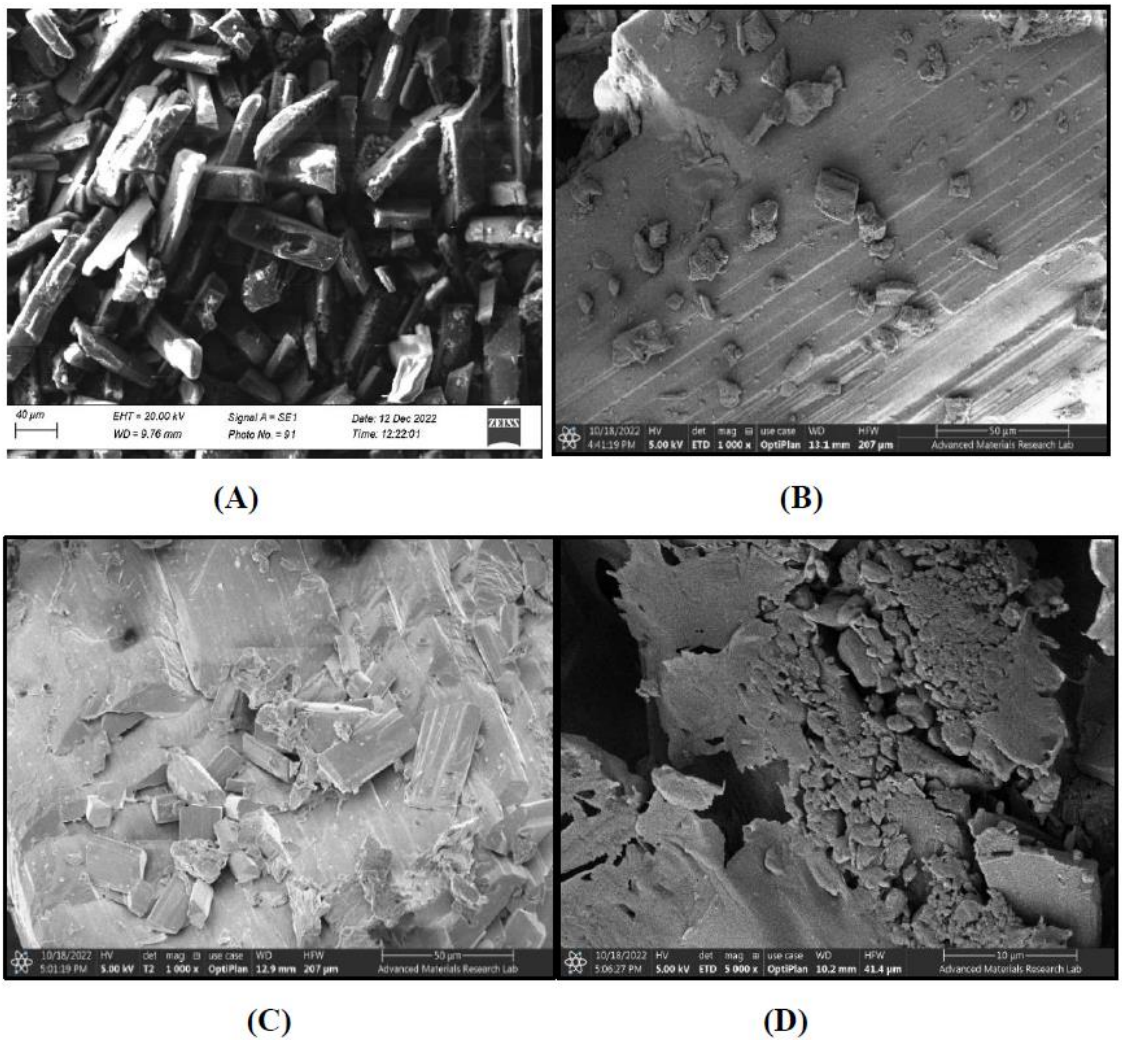


Figure 10: *Scanning electron micrographs of Olanzapine alone (A), Physical mixture of Olanzapine with mannitol (B), the successful formulation F5 (C) and the successful formulation F7 (D)*

nitol alone, F5, which is prepared with the mannitol and MCC, showed a slower Olanzapine dissolution profile as shown in Fig. 8. This is inconsistent with the results of the disintegration test, wetting time and water absorption ratio. The adsorption of such poorly soluble drug (Olanzapine) on MCC fiber may prolong its release and explain these contradiction[31]. However, it is interesting to note that the addition of MCC in F5 formulation did not have a significant effect on the dissolution rate when compared with that in F7 ($p>0.05$). Accordingly, F7 exhibited better dissolution profile than F5.

Differential scanning calorimetry

The DSC spectra of Olanzapine alone, mannitol alone, Olanzapine with mannitol as a physical mixture, the succeeded formulations, F5 and F7, are shown in

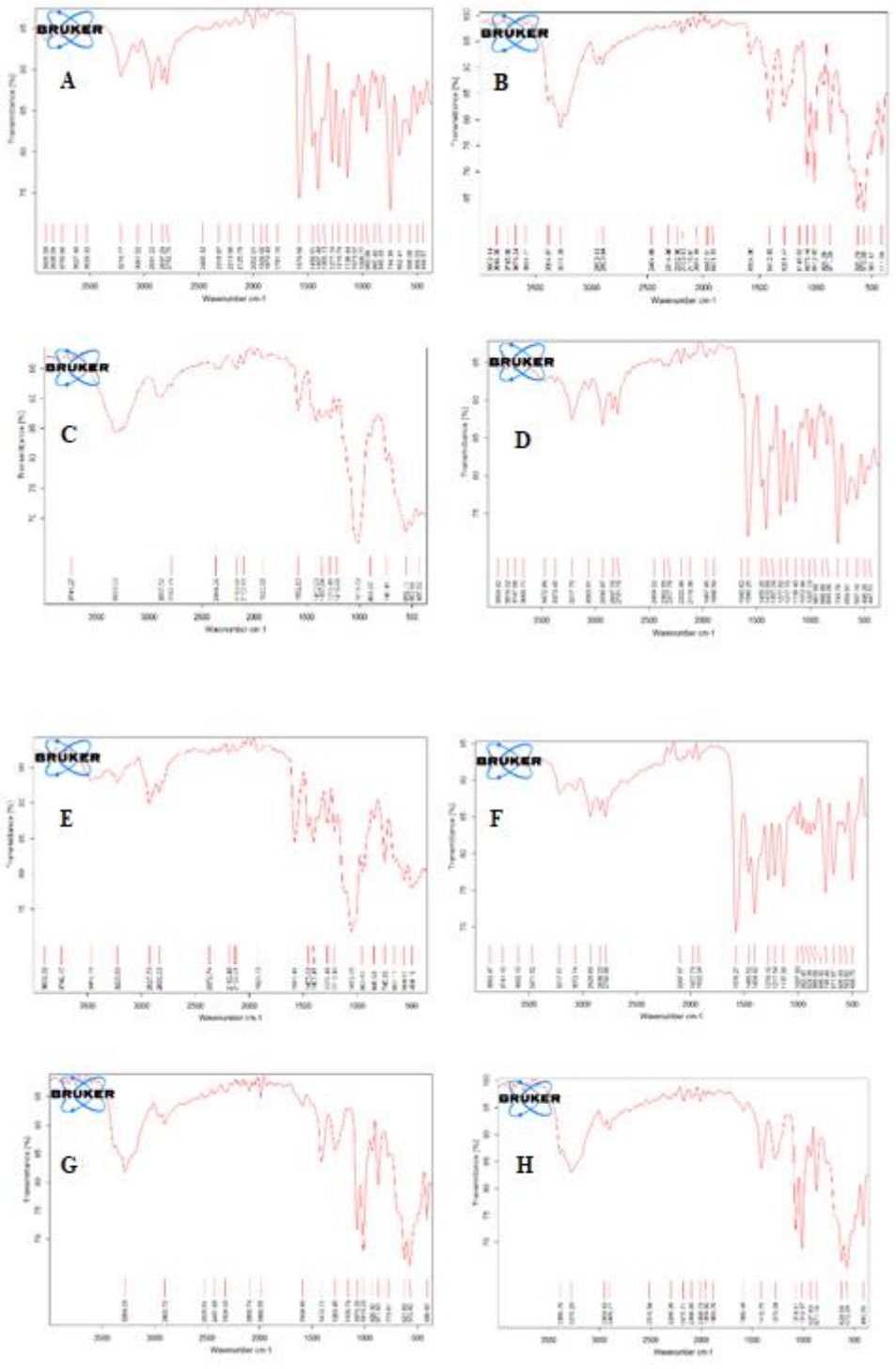


Figure (11): *FTIR spectra of Olanzapine (A), Olanzapine and mannitol (B), Olanzapine and MCC (C), Olanzapine and PVP (D), Olanzapine and HPMC (E), Olanzapine and glycine (F) , Formula 5 (G) and Formula 7 (H)*

Fig. 9 as A,B,C,D and E, respectively. The DSC scan of the pure Olanzapine sample presented a single, sharp endothermic peak at 196.32°C, which was similar to the melting point of the pure drug and this confirmed both the purity and high crystallinity of the drug[32].

As illustrated in table 3, the DSC scan for the physical combination of mannitol and Olanzapine displayed a small endothermic peak associated with Olanzapine at 196°C and a sharp peak at 171°C, which is very near to the melting point of mannitol stated at 168.5°C[33]. However, in F5 and F7, a boarder one peak was appeared in both while the peak of Olanzapine disappeared suggesting that Olanzapine might be changed (upon lyophilization) to an amorphous state.

Scanning Electron Microscopy

The images of scanning electron micrographs of Olanzapine alone, a physical mixture of Olanzapine and mannitol, and the successful prepared Olanzapine oral lyophilisates (F5 and F7 formulations) are illustrated in Fig 10.

The results demonstrated that Olanzapine crystals were very clear in the pure drug and the physical mixture, however, the micrograph of Olanzapine oral lyophilisates F5 displays a matrix in which Olanzapine crystals are embedded or dispersed in comparison to no-crystals were seen with the lyophilisate formula coded F7[3,25].

Fourier transform infrared spectroscopy

The obtained FTIR spectra of Olanzapine alone, and its physical mixture with mannitol, MCC, PVP, HPMC, and glycine, and of the successful formulations (F5, and F7) are shown in Fig. 11. FTIR analysis of Olanzapine alone showed the following characteristic peaks: 3216 cm-1 corresponding to the secondary amine, 3061 cm-1 belong to aromatic C-H group, 2931cm-1 for the aliphatic C-H, 2792 cm-1 for C=N group, 2465 cm-1 for C=C aromatic and 744 cm-1 related to C-S aromatic.

These characteristic peaks appear also in the physical blending of the drug with other ingredients, and in the successful formulations, F5 and F7 which shows there is no proof of an interaction between the Olanzapine drug and the excipients[20,27].

Conclusion

It is clear that rapid Olanzapine disintegration and dissolution were made possible by developing Olanzapine oral lyophilisates by lyophilization technology and employing mannitol as matrix formers. However, not all the formulations were able to produce lyophilised tablets; for example, mannitol by itself cannot create tablets with high mechanical qualities without the inclusion of an appropriate binding agent. High-hardness tablets are made with the binding agent HPMC, while tablets with a quicker rate of disintegration are made with the diluent MCC. The F7 Olanzapine oral lyophilisate with mannitol (50%), PVP (0.2%), and HPMC (2%), was considered successful formulation. F7 exhibited the best mechanical properties, fast disintegration times and fast drug releases.

It is possible to conclude that this method represents a promising manufacturing process for the formulation of Olanzapine orodispersible tablets, which are rapidly dissolve inside the mouth without the need for water, improving patient compliance and lowering the anticipated side effects associated with the conventional tablet dosage form.

Acknowledgement

The authors express their thanks to the College of Pharmacy at Mosul University as well as to the College of Pharmacy at Al-sharjah University, United Arab Emirates for supplying the essential machinery and equipment. Additionally, thanks to the Assistant Prof Dr. Ahmed A. J. Mahmood, Assistant Prof Dr. Moath Bashir and Assistant Lecturer Zahraa Hussain at College of Pharmacy, University of Mosul, for their crucial roles in facilitating the tests required to finish this research. □

References

1. Anup N., Thakkar S., Misra M. Formulation of olanzapine nanosuspension based orally disintegrating tablets (ODT); comparative evaluation of lyophilization and electrospraying process as solidification techniques. *Adv. Powder Technol*. 29(8),1913–24, 2018.
2. Montgomery B., Treuer., Karagianis., Ascher-Svanum H., Harrison. Orally disintegrating olanzapine review: effectiveness, patient preference, adherence, and other properties. *Patient Prefer. Adherence*. 6.109-125, 2012.
3. Ravi S., Rudrangi S., Trivedi V., Mitchell JC., Wicks SR., Alexander BD. Preparation of olanzapine and methyl- b -cyclodextrin complexes using a single-step , organic solvent-free supercritical fl uid process : An approach to enhance the solubility and dissolution properties. *Int. J. Pharm*. 494(1), 408–16, 2015.
4. Hooper P., Lasher J., Alexander KS., Baki G. Journal of Pharmaceutical and Biomedical Analysis A new modified wetting test and an alternative disintegration test for orally disintegrating tablets. *J. Pharm. Biomed. Anal*. 120, 391–6, 2016.
5. Iurian S., Tomu I., Szabó-révész P., Chvatal A., Leucu SE., Moldovan M., et al. European Journal of Pharmaceutical Sciences Development of oral lyophilisates containing meloxicam nanocrystals using QbD approach. 104, 356–65, 2017.
6. de Haan L., van Amelsvoort T., Rosien K., Linszen D. Weight loss after switching from conventional olanzapine tablets to orally disintegrating olanzapine tablets. *Psychopharmacology (Berl)*. 175, 389–90, 2004.
7. Girault E.M., Alkemade A., Foppen E., Ackermans M. T., Fliers. E., Kalsbeek A. Acute peripheral but not central administration of olanzapine induces hyperglycemia associated with hepatic and extra-hepatic insulin resistance. *PLOS ONE*. 7(8), 43244, 2012.
8. Abed K.K., Hussein A.A., Ghareeb M.M., Abdulrasool A.A. Formulation and Optimization of Orodispersible Tablets of Diazepam. *AAPS PharmSciTech*. 11(1), 356–61, 2010.
9. Mahajan H.S., Kelkar Y.V. Journal of Drug Delivery Science and Technology Pregelatinized hydroxypropyl pea starch as matrix forming material for lyophilized orodispersible tablets of tadala fi l. *J. Drug Deliv. Sci. Technol*. 41, 310–6, 2017.
10. Al Ashmawy A.G, Eissa N.G., Nahas H.M. El., Balata G.F. Journal of Drug Delivery Science and Technology Fast disintegrating tablet of Doxazosin Mesylate nanosuspension : Preparation and characterization. *J. Drug Deliv. Sci. Technol*. 61,102210, 2021.
11. Salama A.H., Basha M., El S. Experimentally designed lyophilized dry emulsion tablets for enhancing the antihyperlipidemic activity of atorvastatin calcium : Preparation , in-vitro evaluation and in-vivo assessment. *Eur. J .Pharm Sci*. 112,52–62, 2018.
12. Vanbillemont B., De Beer T. Model-based optimization of the primary drying phase of oral lyophilizates. *Int. J. Pharm. X*. 2, 100057, Dec; 2020.
13. Stange U., Führling C., Gieseler H. Formulation, Preparation, and Evaluation of Novel Orally Disintegrating Tablets Containing Taste-Masked Naproxen Sodium Granules and Naratriptan Hydrochloride. *J. Pharm. Sci*. 103(4), 1233–45, 2014.
14. Nasser S.J., Sameen L.H,. Ghareeb M.M. Preparation and Evaluation of Oral Disintegrating Tablets of Ketoprofen by Dirct Compression. *Iraqi J. Pharm. Sci* .P-. 21(2), 63–8, 2017.
15. Rowe R.C. editor (2009) Handbook of pharmaceutical excipients. 6. ed. London: APhA, (PhP) Pharmaceutical Press.
16. Rus L.M. Development Of Meloxicam Oral Lyophilisates: Role Of Thermal Analysis And Complementary Techniques. *FARMACIA*. 67(1), 56–67,2019.
17. Rus L.M., Iurian S., Kacso I., Borodi G., Porav S. Hegheş S,C. Iuga C.A., Tomuţă I. Development of meloxicam oral lyophilisates : Role opf thermal analysis complementary techniques. *Farmacia.* 67(1), 57, 2019.
18. Dhahir R.K., Al-kotaji M. Preparation of Cinnarizine Oral Lyophilizates. *Irq. J. Pharm*. 18(1), 35, 2021.

19. Nikam V.K., Shete S.K., Khapare J.P. Most promising solid dispersion technique of oral dispersible tablet. *Beni-Suef Univ. J. Basic Appl. Sci. Rev*. 9(62),14, 2020.
20. Conseil de L'Europe European Pharmacopoeia. 10th ed. 2020.
21. USP 33-NF 28. United States Pharmacopeial Convention. Rockville MD, USA; 2010.
22. Patel V. First and second derivative spectrophotometric method for determination of olanzapine in pharmaceutical formulation. *Int. J. Chem. Tech. Res*. 2(1),756–61, 2010.
23. Ibrahim A.H., Rosqvist E., Smått J.-H., Ibrahim H.M., Ismael H.R., Afouna M.I., Samy A.M., Rosenholm J. Formulation and optimization of lyophilized nanosuspension tablets to improve the physicochemical properties and provide immediate release of silymarin. *Int. J Pharm*. 563, 217–27, 2019.
24. Shahi S. Formul;ation and evaluation of quick dispersible tablet of olanzapine. *IJPRD*. 7(0974 – 9446):3, 2009.
25. Dixit M., Kini A.G., Kulkarni P.K. Enhancing the aqueous solubility and dissolution of olanzapine using freeze-drying. *Braz.J. Pharm. Sci*. 47(4), 743-749, 2011.
26. Liew K.B.., Peh.,K.K.. Investigation on the effect of polymer and starch on the tablet properties of lyophilized orally disintegrating tablet. *Arch. Pharm. Res*. 817–26, 2021.
27. Alalaiwe A., Fayed M.H., Alshahrani S.M., Alsulays B.B., Alshetaili A.S., Tawfeek H.M., et al. Application of design of experiment approach for investigating the effect of partially pre-gelatinized starch on critical quality attributes of rapid orally disintegrating tablets. *J. Drug Deliv. Sci. Technol*. 49, 227–34, 2019.
28. Desai P.M., Er P.X., Liew C.V., Heng P.W. Functionality of Disintegrants and Their Mixtures in Enabling Fast Disintegration of Tablets by a Quality by Design Approach. *AAPS PharmSciTech.* 15(5), 1094-104, 2014.
29. Pabari R.M., Ramtoola Z. Effect of a Disintegration Mechanism on Wetting, Water Absorption, and Disintegration Time of Orodispersible Tablets. *J Young Pharm*. 4(3), 157–63, 2012.
30. Yang B., Wei C., Yang Y., Wang Q., Li S. Evaluation about wettability, water absorption or swelling of excipients through various methods and the correlation between these parameters and tablet disintegration. *Drug Dev. Ind. Pharm*. 44(9),1417–25, 2018.
31. Dukić-Ott A., Thommes M., Remon J.P., Kleinebudde P., Vervaet C. Production of pellets via extrusion–spheronisation without the incorporation of microcrystalline cellulose: a critical review. *Eur. J. Pharm. Biopharm*. 71(1),38–46, 2009.
32. Anup N., Thakkar S., Misra M. Formulation of olanzapine nanosuspension based orally disintegrating tablets (ODT); comparative evaluation of lyophilization and electrospraying process as solidification techniques. *Adv. Powder Technol*. 29(8), 1913–24, 2018.
33. Iurian S., Tomuta I., Bogdan C., Rus L., Tokes T., Barbu-Tudoran L., et al. Defining the design space for freeze-dried orodispersible tablets with meloxicam. *Drug Dev. Ind. Pharm*. 42(12),1977–89, 2016.