AJHAS

https://albalqajournal.ammanu.edu.jo/SC.aspx
Vol.2 No.1 2023

Al-Balqa Journal
for Health & Applied Sciences

Formulation and Evaluation of Metformin-Vildagliptin Combination as Oral Dispersible Tablets

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Abstract

Oro-dispersible tablets (ODTs) are becoming more popular among innovative oral drug delivery systems since they have some extra benefits over existing formulations and can increase patient compliance. In the presence of saliva, ODTs dissolve within a minute in the mouth. It is an appropriate oral dose form for use in pediatric and geriatric patients who have difficulty swallowing.

The aim of this study was to formulate and evaluate ODTs containing 500 mg metformin (MTF) and 50 mg vildagliptin (VLD) using the direct compression method.

Three formulas were prepared using different types and concentrations of superdisintegrant with a fixed amount of diluents and additives to achieve a target weight of 1,000 mg/tablet. The fourth formula was prepared using cross povidone as a disintegrant but with a different ratio of avicel-mannitol to investigate the effect of avicel concentration on the parameters of the evaluation.

The prepared powder of the four formulations showed good flow properties with an angle of repose of 34–37o and a Carr's index of 11–13.5 with characteristics of free-flowing, according to the results. F1 demonstrated the quickest wetting (20 seconds) and disintegration (22 seconds) times, meeting both USP and EMA requirements.

The evaluation of formulas showed the effect of the type of disintegrant and diluent on both wetting and disintegration times. Drug release showed that F1 exhibited a very fast dissolution of both drugs where more than 85% of both drugs were released in less than 10 minutes. As a conclusion, the formulation design of MTF 500 mg – VLD 50 mg was successful as ODTs.

Keywords

Combination Therapy, Metformin, Oro dispersible Tablets, Superdisintegrant, Vildagliptin. Wetting.

Introduction

Tablets are the most popular solid dosage forms due to their ease of self-administration, compactness, and manufacture. The medication in tablets is in a distinctive quantity, allowing for proper dosing. Also, they are easy to store, distribute, and package (Gaikwad & Khirsagar, 2020). However, elderly and young patients might have trouble in swallowing the conventional tablets especially if they have a large size. To solve some of these problems, orodispersible tablets were developed (Ganesh & Deshpande, 2011; Habib et al., 2000). Orodispersible tablets are solid dosage forms that disintegrate in the mouth in less than a minute by the action of the saliva. They are especially designed to absorb water quickly and break down in a short time. They also offer the advantage of fast absorption due to fast disintegration (Comoglu & Dilek Ozyilmaz, 2019).

These ODTs have a number of benefits, including no swallowing compliance, quick onset of action, enhanced bioavailability, and good stability. The Superdisintegrant is the main component that must be present in an ODT. A superdisintegrant is primary function is to dissolve the tablet when it comes into contact with water (Sharma and Leel, 2022).

Several methods were reported in manufacturing ODTs such as Freeze drying (Iurian et al., 2016), Moulding (Dobetti, 2001), Spray drying, (Dey and Maiti, 2010) and Mass extrusion (Musazzi et al., 2018). However, direct compression is a known easy and quick method to prepare ODTs (Al-Ghabban et al., 2013).

Yet, manufacturing of ODTs has several challenges. These challenges include preserving good mechanical strength with short disintegration time, taste masking of unpleasant-taste drugs, use of aqueous soluble materials and maintaining minimum hygroscopicity (Al-Khattawi & Mohammed, 2014).

To produce good tablet integrity, several technologies are available such as Zydis technology introduced by R.P. Scherer (Roshan & & Keerthy, 2021), Orasolv technology and Durasolv technology invented by CIMA labs (Goshi et al., 2018), Wowtab technology which was patented by Yamanouchi Pharmaceutical Company (Reddy and Ghosh, 2002) and Flashtab technology by Prographarm laboratories (Beri and Sacher, 2013).

Excipients used in the formulation ODT are usually of high solubility to facilitate the dispersion in saliva. Fillers, superdisintegrants, glidants, colors and lubricant are carefully selected to fulfil the criteria of fast , good tasting mouth disintegration. Examples of excipients simple sugars like glucose and mannitol, aspartame ,and sorbitol (Panda et al., 2014). Crospovidone, croscarmellose sodium, sodium starch glycolate are examples of superdisintegrant proved for FDA (Ghourichay et al., 2021).

Various methods of preparations are used to manufacture ODTs. The methods that are mostly used are freeze drying, molding, direct compression, granulation, spray drying, cotton candy, phase transition, three-dimensional printing, and mass extrusion methods (Gulsun et al., 2018).

There are many medications available in the market like, ABILIFY (10 mg aripiprazole) , Niravam (Alprazolam), Aricept (Donepezil HCl), Cetar -100 DT(cefixime), Rybix (tramadol), Alvert (loratadine) and many others.

Type 2 Diabetes mellitus (T2DM) is a chronic disease that has become a worldwide pandemic (Cuschieri & Grech, 2021). Although the management of T2DM is expanding, changing a lifestyle remains the cornerstone of its control (Grammatiki et al., 2021). T2DM develops when insufficient insulin secretion is unable to raise to match insulin resistance (Freeman & Pennings, 2022), in addition to the inappropriate increase in glucagon levels which enhances the glucose output from the liver and increases the fasting glucose (Capozzi et al., 2019). Therefore, diabetes is a multi-effect disease which needs to be corrected. The impaired insulin secretion, insulin resistance, and hypersecretion of glucagon all need to be controlled (Davies et al., 2022). The rationale for combining MTF with DPP-4 inhibitors is the complimentary mechanism of the action of the two strategies. Thus, metformin (MTF) acts primarily by reducing hepatic glucose output and improving insulin sensitivity in liver and muscles whereas DPP-4 inhibitors such as vildagliptin (VLD) act by increasing GLP-1 levels and thereby stimulating insulin secretion and inhibiting glucagon secretion (Alshahrani, et al., 2021). The two strategies therefore have the potential to improve different mechanisms, which are defective in T2DM, so an additive or synergistic action when used in combination is anticipated. The European Medicines Agency (EMA) has also approved a combination of vildagliptin and metformin, vildagliptin/metformin (Eucreas by Novartis) as

an oral treatment for type-2 diabetes in 2008.

Both MTF and VLD are found as ODT each alone. But no combination of them has been introduced as ODT. The aim of this study is to prepare a combination ODTs containing 500 mg MTF and 50 mg VLD by a direct compression method using a simple design of different disintegrant-diluent ratios and to investigate different factors affecting the formula such as the effect of diluent and the type and the concentration of the superdisintegrant (SD).

Materials and Methods

Materials

Metformin (purity 99.1%), vildagliptin (purity 99.5%), cross povidone, sodium starch glycolate, alginic acid NF (crosslinked alginic acid), avicel (PH102), aspartame, mannitol, peppermint, strawberry and peach flavors, aerosil (hydrophilic grade), and Na stearate were all given as a gift from Dar Al Dawa pharmaceuticals/Jordan. Acetonitrile (Merck) HPLC grade, sodium dihydrogen phosphate (Sigma), and orthophosphoric acid (Sigma) were all purchased by Al-Ahliyya Amman University.

Methods

Formulation Design

The target was to prepare ODTs containing 500 mg MTF and 50 mg VLD. To optimize the characteristics of the ODTs, other excipients would complete the weight of each tablet to 1,000 mg. Mannitol is usually used in the formulation of ODTs for its good taste and mouth sensation beside high solubility in water (Omar et al., 2017), in addition to avicel (microcrystalline cellulose) which is a bulking agent beside disintegration agent which helps the quick absorption of water by capillary action (Dey & Maiti, 2010). Three types of disintegrants were used to get the best disintegration time. The design depends on the use of excipients that enhance disintegration and wettability of the tablet product to ensure minimum achievement with high active constituent. Table 1 shows the composition of the prepared formulas.

Preparation of the Powder Mixture

A batch of 500 tablets of each formula was prepared. All ingredients were weighed, and the mixing process was performed by a double cone mixer (capacity 2 Kg). First, all materials were sieved through a 1.5 mesh to avoid any particulate materials. Then all components except the lubricant were put in the mixer for 30 min in a rate of 30 rounds per min. After the mixing process, the powder was passed through a 1.5 mesh size manually for more homogenization of particles. After that, the powder was put back in the mixer and lubricant was added and mixed for 1-2 min. Then 50 g of a powder blend of each formula was taken to be used for the flowability and compressibility study.

Table 1. Formulation Design of MTF-VLD ODTs

Ingredient	Amount in mg/tablet			
	F1	F2	F3	F4
Metformin HCl	500 mg	500 mg	500 mg	500 mg
Vildagliptin	50 mg	50 mg	50 mg	50 mg
Cross povidone	50 mg			50 mg
Sodium starch glycolate		50 mg		
Alginic acid NF (crosslinked alginic acid)			50mg	
Avicel	250 mg	250 mg	250 mg	175 mg
Mannitol	100 mg	100 mg	100 mg	175 mg
Aspartame	20 mg	20 mg	20 mg	20 mg
Flavor	10 mg	10 mg	10 mg	10 mg
Aerosil (hydrophilic grade)	10 mg (1%)	10 mg (1%)	10 mg (1%)	10 mg (1%)
Na stearate	10 mg (1%)	10 mg (1%)	10 mg (1%)	10 mg (1%)
Total weight	1000 mg	1000 mg	1000 mg	1000 mg

The angle of repose was used as a parameter to measure the flow properties of a powder (Loyed & Allen, 2018). The angle of repose (θ) was calculated from tan θ according to Equation 1.

$$\tan \theta = H/R \quad (1)$$

Where (H) is the height of the powder cone and (R) is the radius of the powder cone.

Bulk density was determined, according to USP 38 method I, by measuring the volume of 40 g of the powder mixture that was poured into a 100 ml graduated cylinder without compacting. Bulk density was calculated in gram per milliliter by Equation 2

$$P0 = M/V0 \quad (2)$$

Where P0 is the bulk density in g/ml, M is the mass of the powder in g, and V0 is the unsettled apparent volume of the powder in ml (USP, 2015).

Tapped density was measured by mechanically tapping the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight in an approximate rate of 200 drops per minute. Tapped density was calculated in gram per milliliter by Equation 3.

$$P_f = M/V_f \quad (3)$$

Where Pf is the tapped density in g/ml, M is the mass of the powder in grams, and Vf is the final tapped volume of the powder in milliliter. The Carr's compressibility index and Hausner ratio was calculated according to Equation 4 and Equation 5, respectively (USP, 2015).

$$\text{Carr's compressibility index} = 100(P_f - P_0) / P_f \quad (4)$$

$$\text{Hausner ratio} = P_f / P_0 \quad (5)$$

The tests above were performed to the four prepared formulas. Three readings were taken and average ± SD was calculated for each.

Preparation of Tablets by Direct Compression Method

The prepared powder blend was directly compressed into tablets on a rotary tablet press (Cadmach® compression machine, India) using an oval shaped upper punch and die The die measures 13 mm length and 5 mm width. The compression force used ranged between 15-20 kN and the in-process hardness was measured to optimize the final force used. The four formulas were compressed by the same method. A batch of 500 tablets of each formula were prepared.

Physical Evaluation of the Prepared ODT

The four prepared formulas were evaluated in terms of physical evaluation of ODTs. These tests included tablet appearance, uniformity of weight, tablet thickness, hardness and friability, disintegration time, content uniformity, and dissolution test in phosphate buffer pH 6.8 at 37 ± 0.5 °C as well as in pH 1.2 (HCl +NaCl). All tests were performed according to the USP specification of immediate release tablets (Gaikwad & Kshirsagar, 2020).

Appearance was examined visually for any defects like cracks, capping, lamination and irresgular edges. Uniformity of weight was performed according to the (USP, 2015). The test was performed by weighing, randomly selected, twenty tablets individually from each formula using electrical sensitive balance (Shimadzu, Japan) and the average weight ±SD was calculated (USP, 2009).

Thickness test was carried out using thickness caliper (Mitutoyo® CD-15B, England) for 10 randomly selected tablets from each formula. Average thickness ±SD were recorded

The breaking force (hardness) was measured using hardness taster (Dr. Schleuniger Pharmatron 8M, Switzerland). The test was performed on 10 tablets and average ± SD were recorded.

Friability of the tablets was determined using (Erweka® TA 100 friability tester, Germany). Twenty tablets were initially weighed (Wt1) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 mins. The tablets were weighed again (Wt2). The percentage (%) of friability was then calculated using equation (6):

$$\text{Percentage of friability} = \text{x } 100\ \% \quad (6)$$

Where Wt1 is weight of 20 tablets before placing in Friabilator and Wt2 is the weight of 20 tablets after taking out of Friabilator (USP, 2009).

Wetting time was performed as follows. A piece of filter paper (Whatman filter paper 10.75 cm diameter) was folded twice and placed in a small petri dish containing 6 ml of water. A tablet was put on the paper and the time for complete wetting was measured (Aly et al., 2010; Goudanavar et al., 2011). The test was performed 3 times by randomly choosing 3 tablets. The average time in seconds ± SD were recorded.

Also, the water absorption ratio was calculated for each formula. The tablet was weighed, and then after the wetting test,

it was reweighed again. The water absorption ratio is calculated by the formula by Goudanavar et al. (2011) as seen in Equation 7.

AR = (Wt of wet tablet-Wt of dry tablet)/(Wt of dry tablet)*100 **(7)**

The test was repeated 3 times and average AR ± SD was recorded.

The disintegration test for ODTs should mimic disintegration in the mouth within salivary contents. It was performed as by Bangale et al. (2011). One tablet was placed in a petridish (10 cm diameter) containing 10 ml of phosphate buffer pH 6.8 at 37 ± 0.5 °C. The time required for complete defragmentation of the tablet was measured. It was performed 3 times for each formula, and average ± SD time in seconds was recorded.

Dissolution Test

The dissolution test conditions were chosen according to the USP monographs and published works of both drugs. The dissolution conditions were type II dissolution apparatus (paddle), dissolution media, phosphate buffer pH 6.8, temp. at 37 ± °C, and 75 rpm. The test was also done in dissolution media pH 1.2 (HCl +NaCl).

Six tablets were put, each in a jar of the apparatus containing 900 ml dissolution media, and a 10 ml volume was withdrawn at each specified time point and replaced by fresh media. Time points of sampling were 5, 10, 15, 20, 30, 45, and 60 min. Samples withdrawn were analyzed in triplicate for the 6 tablets, and the average ± SD was calculated.

Method of Analysis of MTF and VLD

Simultaneous analysis of the MTF and VLD method was developed and validated. The chromatographic conditions were optimized as follows. Mobile phase composition was 40% acetonitrile and 60% phosphate buffer (pH 3.5), the flow rate was 1 ml/min, and the injection volume was 20µl. The column used was a Hypersil Thermo Electron C18 (250 X 4.6 mm) with column temp 24-26 °C and a HPLC system with UV detector (Servyor, Germany), and the lambda max was set on 215 nm.

The developed method was validated in terms of linearity, precision, accuracy, recovery, and robustness. All tests were performed according to the ICH guideline (ICH (Q2), EMA 2021).

Linearity was tested by analysis of six concentrations of MTF (6 , 12, 24, 48, 72, 150 µg/ml) ml prepared by suitable dilutions from a stock solution of 1 mg/ml using mobile phase. For VLD, (20, 40, 80 160, 240, 500 µg/ml) were prepared. To prove linearity, the samples were analysed and area was plotted against concentration and correlation coefficient (R^2) was calculated. The ICH guideline accept linearity if the $R^2 \geq 0.98$.

Precision was measured by analysis of calibration concentration of 50 µg/ml for MTF and 175 µg/ml for VLD six times as per the guideline. RSD was calculated in day 1 analysis (intraday) and day 2 (interday). Accuracy was calculated by percent ratio of measured concentration to the theoretical concentration prepared. Accepted values ranged between 95%-105%.

Recovery of both drugs was measured from the prepared formulation. Also, test formulation contain 70% and 130% of APIs. Recovery was measured at 3 levels of concentrations of MTF (13, 18, 25 µg/ml) and for VLD (35, 45, 60 µg/ml) using the following equation (8):

Reovery (%) = (Conc.measured) / (Theoretical conc.)*100 **(8)**

The ICH guideline defines the robustness of an analytical procedure as "a measure of its capacity to remain unaffected by small but deliberate variations in procedural parameters listed in the documentation, providing an indication of the method's or procedure's suitability and reliability during normal use".

Robustness of the method of MTF and VLD were done using no. of variations included (addition of organic solvent, changing pH, changing the column, changing temperature, and wavelength). The chosen concentration then measured, and precision was calculated.

Results and discussion

Physical Evaluation of Powder Mixture

For each of the prepared formulas, the angle of repose was determined to evaluate the flow characteristics of the powder blend; the derived values are shown in Table 2. There was no need to modify the formulations because the values of the angle of repose of each formula (which contains 1% AerosilTM)

suggest that the powder combination flows freely during tablet compression regardless of the kind, quantity, or concentration of superdisintegrant (SD) utilized. Typically, powder is classified as extremely freely flowing if its value is less than 30°, freely flowing if it is between 30° and 38°, somewhat cohesive if it is between 45° and 55°, and very cohesive if it is greater than 55° (Al-Hashemi & Al-Amoudi, 2018). There were no amorphous powders employed in the formulation; all the ingredients were crystalline. (Al-Hashemi & Al-Amoudi, 2018). All the materials used in the formulation were crystalline, and no amorphous powder was used. In addition, sieving and homogenization of particles might help in showing good flow properties. Table 2 illustrates the results of the flow properties.

The density of the components of a powder mixture determine its bulk density. They can influence crucial traits like compaction behavior with tapping density. The more values of tapping density acquired, the more regular the particle shape. The quality of the tablet produced with the fewest issues will depend on the mechanical properties of the powder during compression. Statistically, there was no significant difference in the values of angle of repose ($p>0.05$)of the four formulations using ANOVA (CI0.05). The same result was obtained for CI and Hausner ratio.

The Carr's index (CI) with Hausner ration (HR) relate the two types of density to flow characteristics and ability of powder to be compressed. The excellent flow properties would have a Carr's index < 10 and Hausner ration 1-1.11. Free flow powder would have CI 11-15 and HR 1.12-1.18, a fair powder flow CI 16-20 and HR 1.19-1.25, passable CI 21-25 and HR 1.26-1.34, and poor flow CI 26-31 and HR 1.35-1.45 (Usman et al., 2018).

Physical Evaluation of the Prepared ODT

The compressed tablets of the four prepared formulas were evaluated as follows. The obtained tablets were inspected visually. Tablets were good shaped with sharp edges, shiny, smooth with bright white color with no cracks, and no capping or peeling were observed. Figure 1 shows the prepared tablets.

The average weight of ten tablets from each formula was measured individually. Since the tablets are of high weight (1,000 mg), the USP gives the limit of ± 5% as an allowed variation. Table 3 shows the weight uniformity test results. All tablet weights were within the specifications of USP, no tablet exceeded 1,050 mg, and RSD was less than 2 for all formulas.

Figure 1. The prepared ODTs

Table 2. Results of Flowability Study Showing Values of Angle of Repose and Flow Characteristics of the Four Prepared Formulas

Formula	Angle of repose (θ) ± SD (n = 3)	Po	P*f*	Compressibility index	Hausner ration	Flow properties
F1	36.5 ± 0.36	0.50 ± 0.01	0.578 ± 0.011	13.4 ± 1.56	1.156	Good, Free flowable
F2	35.7 ± 0.56	0.504 ± 0.009	0.580 ± 0.0085	13.10 ± 1.89	1.152	Good, Free flowable
F3	36.8 ± 0.45	0.51 ± 0.012	0.586 ± 0.0099	12.9 ± 1.3	1.149	Good, Free flowable
F4	34.5 ± 0.60	0.495 ± 0.014	0.558 ± 0.021	11.92 ± 1.9	1.128	Good, Free flowable

Table 3. Results of Tablet Weigh Uniformity Test, Hardness, Friability, Thickness, Wetting, Water Absorption, and Disintegration Tests

Formula	Average wt (mg) ± SD n = 10, RSD	Hardness (N) ± SD n = 3	% Friability (USP)	Wetting time (sec) n = 6	Water absorption ratio n =6	Disintegration time (sec) n = 6
F1	1,007 ± 6.0, 0.6	36.3 ± 0.57	0.7%	20 ± 2	3.0 ± 0.5	22 ± 1
F2	998.5 ± 5.2, 0.5	33.0 ± 3.06	0.45%	22 ± 1	3.2 ± 0.6	25 ± 0.5
F3	1,009 ± 5.0, 0.5	36.5 ± 2.3	0.54%	65 ± 4	4.5 ±1.2	70 ± 1
F4	1,002 ± 3.6, 0.4	37.6 ± 2.00	0.55%	35 ± 2	2.3 ± 0.6	40 ± 2

The hardness of ODTs should be kept minimum to facilitate in-mouth dispersion and disintegration through the absorption of saliva. That is why compression hardness was kept within the specifications of ODTs USP as shown in Table 3. Minimum hardness helps fast disintegration, but at the same time friability of ODTs exceeding 1% is unacceptable according to the USP which is similar to regular tablets. Results are shown in Table 3. Changing the diluent from avicel in F3 to mixture of avicel and mannitol did not affect the friability of the formula (0.54% and 0.55%), which means that the mannitol which has less compressibility than avicel did not affect this characteristic of the tablet, but it affected other specifications as described in table 3.

Wetting, Water Absorption Ratio, and Disintegration Time

Wetting time is the time an ODT absorbs water until completely wetted. It gives an indication for the efficiency of water absorption which simulates saliva and the structure of tablet, porosity, and hydrophilicity of ingredients that permits the flow of water through. Wetting time of the four formulas was estimated as shown in Table 3. Water absorption ratio results are also presented in the same table.

The disintegration test was applied using the petri dish method with a 10 ml buffer pH 6.8. USP stated that disintegration time should be 30 sec and less while the EMA set it up to 3 min. Results of the four formulas are listed in Table 3. Usually, disintegration time is a bit longer than wetting time because complete fragmentation of a tablet should be achieved.

For ODT, disintegration should occur quickly to ensure short time residency in mouth and fast dissolution and absorption. Three disintegrators were used. In F1 cross povidone was used. This material acts by a swelling mechanism as well as wicking without gelling formation. Studies showed that increasing concentration in the formula above 7-8% will not give additional advantage of shortening wetting and disintegration (Gholve et al., 2018). Wetting and disintegration time of F1 was very convincing and fulfilled the criteria of ODT. The use of avicel as a diluent helped in creating channels in addition to those of the disintegrant which gave an additional path for water penetration inside the tablets, increasing hydrostatic pressure inside and breaking intraparticle bonds resulting in the disintegration of the tablet.

Results (Table 3) showed that F1 gave the shortest wetting and disintegration time . However, all formulas showed acceptable values according to EMA. Statistically, the difference was significant in both wetting and disintegration time ($p < 0.05$) between F1 and F3 and F1 and F4 and non-significant between F1 and F2. These results showed that using cross povidone and sodium starch glycolate gave almost the same results while using alginate as a disintegrant had significant (longer) wetting and disintegration time. Also, decreasing the amount of avicel (per tablet) in F4 had a significant (longer) effect on wetting and disintegration time of the tablet. Water absorption was the highest in F3 possibly due to the ability of cross-linked alginates to trap water like a gelled area around the tablet. Since the disintegration time is crucial in the design and evaluation of ODT, F1 was chosen to continue the evaluation of other parameters. Figure 2 shows the performance of the wetting and disintegration test.

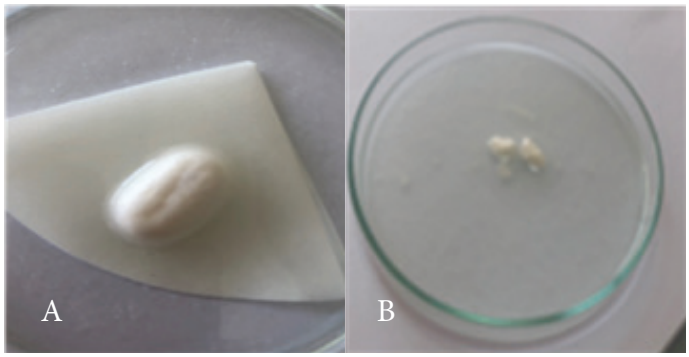

Figure 2. (A) wetting time test**, (B)** disintegration test.

Content uniformity test gave 98.66-101.5% of VLD and 100-102% of MTF in all formulas.

Drug Release and Dissolution

One important target of formulation of ODTs is to get rapid dissolution and then absorption. However, there are many factors affecting drug dissolution from tablet dosage form such as solubility of APIs, hydrophilicity of excipients, and the nature of binding forces between particles to get the drug released. The dissolution conditions were phosphate buffer 6.8 as a media, temp 37 ^{o}C, 75 RPM, and type II dissolution apparatus. Also, pH 2.1 simulated gastric fluid.

Figures 3 and 4 show the percent API released vs time in minutes of MTF and VLD in both pHs from F1 which gave the shortest wetting and disintegration time. In spite of its high concentration (50% of the tablet weight), MTF was released

very quickly achieving 90% in 20 min. MTF is highly water soluble and efficiently disintegrates the tablet to fine powder which helped to get such a high dissolution rate.

The solubility of MTF is 300 mg/ml in the pH range 1.2-6.8. However, some studies reported slower dissolution in acidic media. However, more than 80% of it dissolved in 30 min. The volume of dissolution media (900 ml) kept a high sink condition and helped metformin to dissolve quickly.

VLD has a good water solubility (10 mg/ml at pH 7). In the formula in a concentration of 5%, it fulfills the sink condition . Also, very fast dissolution was achieved with 88% dissolution in 20 min. Both drugs had more than 90% dissolved in 30 min where many studies took a minimum time for more than 75% of the API to be dissolved.

The dissolution profile in pH 1.2 showed a very slight difference in the percent drug release of both drugs over the time period of the test. In general, very similar profiles were obtained in both pHs.

When ingested, the prepared ODT (F1) is expected to have fast dissolution in stomach and in intestine. This facilitates their absorption and action in blood simultaneously to give the combined action as aimed from this combination.

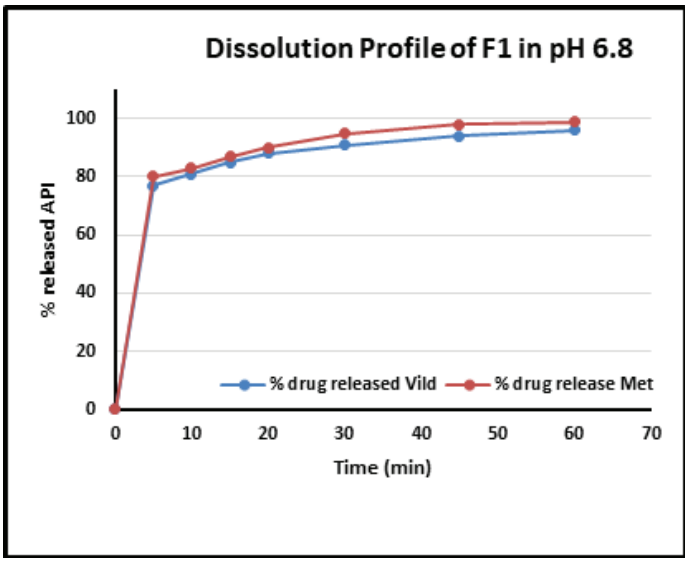

Figure 3. Dissolution profile of F1 at pH 6.8, 37 °C, and 75 rpm.

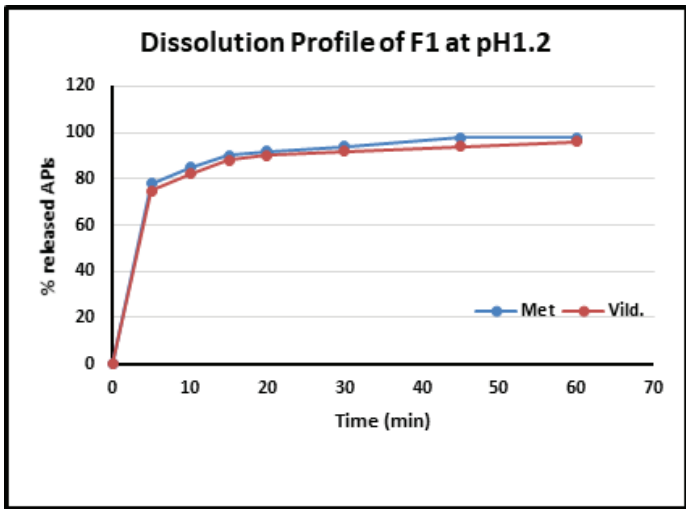

Figure 4. Dissolution profile of F1 at pH 1.2, 37 °C, and 75 rpm.

Method of Analysis

The chromatographic conditions resulted in good separation of the two compounds. MTF retention time (RT) was equal to 2.5 min while that of VLD was equal to 5.1 min. Figure 5 shows the chromatogram of both drugs. Results in figure 1 are for working solution contained 12 µg/ml MTF and 36 µg/ml prepared by suitable dilution of a stock solution contained 1 mg MTF and 3 mg VLD in 50 ml D.W.

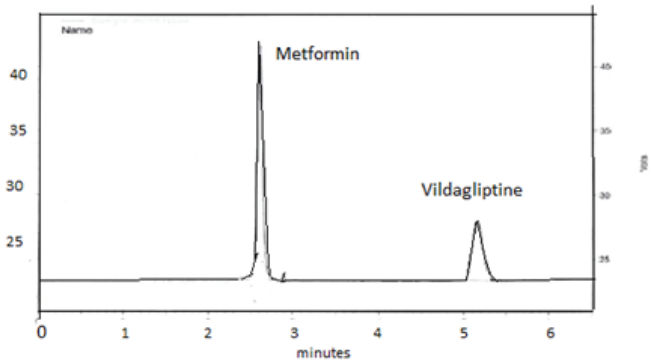

Figure 5. Chromatogram showing the peaks of MTF with RT (2.57 min) and VLD with RT (5.1 min) at 215 nm.

Linearity was achieved for MTF in the concentration range 6-125 µg/ml with R^2 = 0.9999 and 20-500 µg/ml for VLD with R^2 = 0.9999. Figure 6 shows the linearity curves of MTF and VLD.

The results of precision and accuracy were in compliance with ICH guideline where RSD ranged between 0.9-1.0 for MTF with accuracy between 99.0-101.5% and 0.7-1.4 for VLD with accuracy between 96.6-101.1%. Recovery results ranged between 98.6-99.0% for MTF for formulas containing 70%,

130%, and 100% MTF (RSD 0.4-1.0) and 99.0-101.5% for VLD using the same criterion (RSD 0.1-1.7).

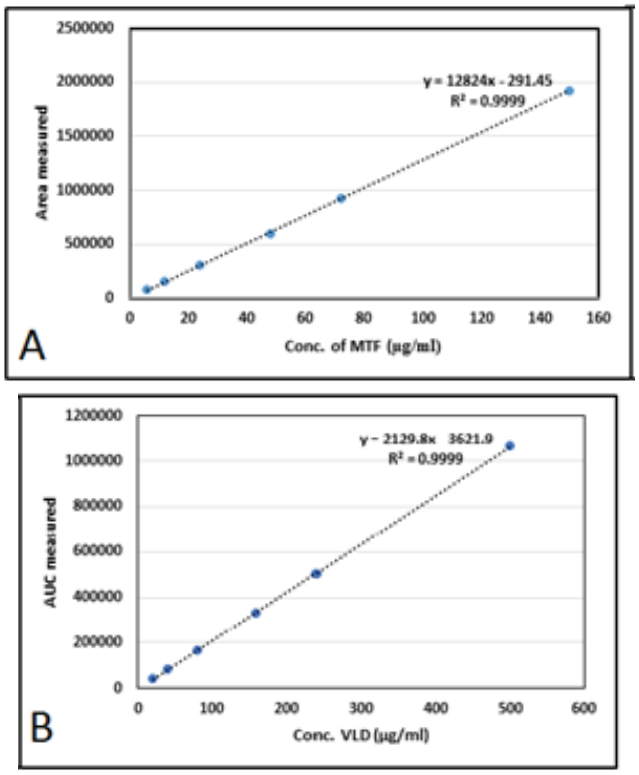

Figure 6. Linearity plot of MTF (A) and VLD (B) showing the straight-line equation and correlation coefficient of each.

Conclusion

The metformin-vildagliptin combination was successfully formulated as ODTs by the direct compression method using sodium starch glycolate, cross povidone, and crossed linked algenic acid as disintegrants, avicel, and mannitol as diluents.

The formula (F1) gave the best evaluation results with the shortest wetting and disintegration time over the other tests. Weight variation, content uniformity, and friability are all within the specification of USP. The in vitro DT of the best selected formula (F1) at pH 2.1 and 6.8 gave very fast drug release and dissolution where at both pHs more than 80% of both drugs were released in 10 min and more than 95% in 30 min. In conclusion, MTF-VLP can be successfully formulated as ODTs with good quality.

Conflict of interest

The authors declare that there is no conflict of interest.

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Mustafa Ayesh , data curation.

Israa Al-Ani, project administration , conceptualization

Fatima Tawfiq, conceptualization.

Naeem Shalan, resources

Sina Matalqah, writing-original draft, resources

Enas Daoud , methodology

Randa Atwan, methodology

Bayan Abdul Majeed, writing, reviewing & editing

Rolla Alshalabi , writing, reviewing & editing

Wael Abu Dayyih, validation, formal analysis.

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