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Formulation and in-vitro evaluation of metformin-tadalafil combination as oro-dispersible tablets

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Abstract— Diabetes Mellitus is one of the most common syndromes in the world. Many complications result from Diabetes including sexual impairment which highly affects the quality of life in men. The aim of this work is to formulate and evaluate oro-dispersible tablets (ODTs) containing 500 mg metformin and 5 mg Tadalafil. A successful, simple, valid method of analysis for simultaneous determination of metformin and tadalafil was developed using HPLC with UV detector. Acetonitrile-phosphate buffer pH 3.5 was used as a mobile phase and a successful separation and quantification were achieved. Linearity, precision, recovery, and robustness were all tested according to the ICH guideline of pharmaceutical analysis. Four formulas were prepared, using three types of disintegrants, cross povidone, sodium starch glycolate, and cross-linked alginic, and two types of diluents. The powder mix of each formula was tested for flowability and compressibility. Then, tablets were compressed by the direct compression method and evaluated according to the USP specifications of Oro-dispersible tablets. Results showed that the evaluation of all formulas showed an effect of type of disintegrant and diluent on wetting and disintegration times, where cross povidone gave the shortest disintegration time (52 ±2 seconds) Also, an increased concentration of Avicel resulted in an increase in disintegration time (from 46±2 to 52±2 seconds). The dissolution test of F4 in pH 1.2 and 6.8 showed very fast dissolution of both drugs where more than 85% of both drugs were released in less than 10 minutes.

Keywords: Metformin, Tadalafil, Orodispersible tablets, type 2 diabetes, combination therapy.

Introduction

Diabetes Mellitus is a chronic concern in many societies and is becoming more and more common in the rest of the world. It is not an illness, but a condition made up of many illnesses with common signs, symptoms, and complications, but with varying etiologies. The main types are; Type 1 Diabetes mellitus (T1DM) and Type2 Diabetes mellitus (T2DM). According to the World Health Organization (WHO), other classes were classified as “Hybrid classes”, “specific types” and “diabetes during pregnancy” [1,2]

The common denominator in all the diseases that make up diabetes syndrome is a deficiency of the hormone insulin. T1DM is immune-associated or immune-mediated destruction of β - cells in the

pancreas that secretes insulin resulting in lacking insulin. It is associated with the classical trio symptoms; Polydipsia, polyphagia, and polyuria with the disease onset [3,4].

In the case of T2DM, there is also a problem of resistance to the action of insulin. This results in a complex multifactorial disease that leads to serious health complications including high cardiovascular risks [5].
Diabetes mellitus is associated with sexual dysfunction in both men and ladies. While in women, the association between diabetes and sexual dysfunction is less conclusive, in men diabetes is associated with erectile dysfunction which is 3 folds above non-diabetic persons [6-8] The proposed mechanism of ED in diabetes is multifactorial. It is usually associated with poor glycemic control and high glycated hemoglobin. The proposed mechanisms of ED in diabetic patients are represented by vasculopathy, neuropathy, visceral adiposity, insulin resistance, and hypogonadism [9,10]. Macrovascular disease in diabetes resembles atherosclerotic damage in the blood vessels. This may limit blood flow to the penis. Several cardiovascular risk factors related to diabetes contribute to the genesis of penile arterial insufficiency: all of them converge on endothelial dysfunction, which represents the common denominator leading to vascular ED [11].

Metformin(MET) is the first-line pharmacologic treatment for T2DM and therefore the most prescribed drug for this condition worldwide, either alone or in combination with insulin or other glucose-lowering therapies[12,13].

Tadalafil (TAD) is a phosphodiesterase type 5 (PDE5) inhibitor that is used to improve erectile function by the volume of cGMP in the body. It is an effective treatment for sexual impotence caused by diabetes [14].
TAD therapy consistently improved erectile function, allowing patients to attain and sustain erections with greater ease. Tadalafil greatly improved erectile capacity and was well tolerated in men with diabetes and erectile dysfunction (ED) when taken as prescribed with no limits on food or alcohol consumption or the timing of dose administration relative to the start of sexual intercourse [15].

Orally disintegrating or so-called “Orodispersible tablets” (ODTs) are oral solid dosage forms that disintegrate rapidly in the mouth upon contact with saliva. It is a patient-centered dosage form that aim to increase compliance of pediatric, geriatric, psychiatric, and dysphagia patient. However, it gained wide acceptance by different age categories of patients [16].

Because they don’t need water and have good mouth taste, ODTs have many advantages over conventional tablets. They are suitable for elderly patients, stroke victims, bedridden patients, busy people, travelers, and pediatrics to whom parents suffer to convince them with therapy. They are also advantageous in psychiatric and paralyzed patients [17].

Several studies concluded that ODTs have improved bioavailability due to fast drug release and dissolution. Studies described possible absorption from the mouth pharynx, and esophagus during swallowing as described by “pre-gastric absorption” [18].

ODTs have a good mouth feeling and eliminate choking problems, especially in dysphagia patients or patients with obstructive problems in the esophagus [19].

The aim of this study is the formulation and in-vitro evaluation of MET (500 mg/TAD 5mg) ODTs.

2. Methodology

2.1 Materials

Metformin (purity 99.1%) , Tadalafil (purity 99.5%), Cross povidone, sodium starch glycolate, Alginic acid NF (crosslinked alginic acid), Avicel (PH102), aspartame, mannitol, peppermint, strawberry and peach flavors, aerosol (hydrophilic grade), Na stearate were all given as a gift from Dar Aldwa pharmaceutical/Jordan. Acetonitrile (Merck) HPLC grade, sodium dihydrogen phosphate (Sigma), Ortho phosphoric acid (Sigma).

2.2 Development and validation of method of simultaneous analysis of metformin and tadalafil

The chromatographic conditions of MTF and TAD analysis were as follows: The HPLC system: Server (LC-Thermo) with by LC Solution Software with UV detector, Windows 7, SP1; Data Management Software: Analyst 1.6.3; Mobile phase: ACN: phosphate buffer 15 mM pH=3.5(50:50%, v/v); Column : HypersilThermo Electron Corporation, C18 (250 X4.6, mm), particle size 5 µm; Flow Rate: 1 ml/min; Injection Volume: 15 µL; Total run time: wavelength was set on 270 nm.

The developed method was tested for linearity, precision, accuracy, recovery, and robustness.

Linearity of each drug was tested by 6 concentration points For MTF (6 , 12, 24, 48, 72, 150) µg /ml. and for TAD (5, 12, 24, 48, 72, 96 and 120) µg/ml. were used. Each concentration was measured in triplet and the correlation coefficient (R) was calculated.

The inter and intra-day precision of the method was determined by analysis of 6 samples (24 µg/ml) with three replicates, and CV%(s) were calculated.

The accuracy of the method was determined by comparing practical amounts recovered from the control samples with actual values present in the samples (theoretical values).
Recovery from all prepared formulas was tested and validated the method in this test. Conc. of MET used were (13, 18, and 26 µg/ml) and for TAD also, (35, 50, and 65 µg/ml).
Recovery was tested from parallel formulas containing 70 % APIs and 130 % APIs to test the ability of the method to measure drug concentration in higher and lower amounts in the formula.
The robustness of the method was done using several variations included (change in organic solvent ratio ± 10% of the mobile phase, changing the column, changing temperature (to 30^{o}C), and wavelength ± 5 nm). The chosen concentration (13 µg/ml metformin and 5µg/ml tadalafil) were then measured, and precision was calculated.

2.3 Compatibility of metformin -tadalafil

The compatibility of MET -TAD was studied by DSC. Mettler Toledo DCS instrument was used in this analysis. MET alone, TAD alone, and combination (physical mixture) 1:1 of MET -TAD were analyzed and the thermogram of each was obtained. 20 mg sample of each powder was used in the standard aluminum crucible of the instrument each time. The flow of heat was set on 10^{o}C/min.

2.4 Formulation of the tablet

The formulation design depended on the choice of active ingredients that are suitable for ODT specifications like fast disintegration and highwater absorbing capacity. To ensure minimum achievement with a high active constituent. The total weight of the tablet would be equal to 1000 mg. Table 1 shows the formulation design of 4 formulas with the different constituents of inactive ingredients per one table.

Table 1: The formulation design of the prepared ODTs

Ingredient	**Amount (mg) /tab.**	**Amount (mg) /tab.**	**Amount (mg) /tab.**	**Amount (mg) /tab.**
	F1	**F2**	**F3**	**F4**
MET HCl	500 mg	500 mg	500 mg	500 mg
TAD	5 mg	5 mg	5 mg	5 mg
Cross povidone	50 mg			50 mg
Sodium starch glycolate		50 mg		
Alginic acid NF			50mg	
Avicel	200 mg	200 mg	200 mg	300 mg
Mannitol	195 mg	195 mg	195 mg	95 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**

2.5 Powder mixing and precompression powder study

Five hundred (500) tablet batch 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 1.5 mesh to get rid of any particulate materials. Then all constituents except the

lubricant were put in a double cone mixer for 30 min at a rate of 30 rounds per min. After the mixing process powder was passed through 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.

Fifty (50)g of powder blend of each formula was taken to be used for the flowability and compressibility study.
The Flowability of the powder mixture was evaluated by measuring the "angle of repose" using the funnel method [20]. Bulk density and tapped density were measured according to USP 32 method I. Carr's Index, Hausner's ratio, and tablet porosity were calculated [21].

2.6 Physical evaluation of the ODTs prepared by direct compression

The obtained powder blend was directly compressed into tablets using tablet press (Erweka, single punch compression machine) using oval shape upper punch and die. The four formulas were compressed by the same method.

2.6.1 Appearance, Thickness and uniformity of weight

This test includes a visual examination of the tablets, checking the tablet's shape and excluding tablets with defects like capping or chipping.
The thickness test was carried out using a thickness caliper (Mitutoyo® CD-15B,England) for 10 randomly selected tablets from each formula. Average thicknesses ±SD were recorded.
Weight variation of ODT formulae was performed by weighing, randomly selected, twenty tablets individually from each formula using an electrical sensitive balance (Shimadzu, Japan) and the average weight ±SD was calculated [21].

2.6.2 Hardness and friability

The breaking force (hardness) was measured using a hardness taster (Dr. SchleunigerPharmatron 8M, Switzerland). The test was performed at the beginning, during, and at the end of the tablet production to ensure a fixed hardness over the production process.The Friability of the tablets was determined using (Erweka® TA 100 friability tester, Germany) following the USP 2009 method [22].

2.6.3 Wetting time and disintegration time

A piece of filter paper (Whatman filter paper 10.75 cm diameter) folded twice was placed in a small petri dish containing 6 ml of water to which a drop of Amaranth solution was added. A tablet was put on the paper and the time for complete wetting was measured [23,24].The test was performed 6 times by choosing randomly 6 tablets from each batch.
Also, the water absorption ratio was calculated for each formula using the method described by [25]

The disintegration test was performed by the method mentioned by Shinde, et al. One tablet was placed in a Petri dish (10 cm diameter) containing 6 ml of phosphate buffer pH 6.8 at 37 ± 1.0 °C.

The time required for complete defragmentation of the tablet was measured [26].

2.6.4 Assay and Content uniformity

Twenty tablets from each formula were randomly chosen and tested for MET and TADsimultaneously. An amount of powder equivalent to 50 mg MET and 5 mg TAD was dispersed in a 100 ml mobile phase. Then shake thoroughly for 15 min. to ensure solubility of both compounds. The dispersion was then, filtered and suitable dilution was then done by mobile phase and injected in the HPLC system. The area of each peak was then related to the concentration using a calibration curve and the total amount and percentage of each drug were calculated. The test would be considered passed if the amount of API was equal to 85%-115% of the labeled claims.

Ten tablets were chosen randomly from each formula and subjected to this test according to the USP specifications. Each tablet is assayed individually as described in the "assay" part. The accepted criterion is that 9 out of 10 should have both APIs amount 85% -115% of the labeled claim. If the test did not fulfill the criteria, other 30 tablets will be chosen according to the USP [21].

2.7 Drug release and dissolution

The dissolution test conditions were chosen according to the USP monographs and published works of both drugs. The USP recommends the use of 0.5 % SDS (sodium dodecyle sulfate) and 50 rpm to ensure solubilization and sink conditions for TAD (TAD tablets on USP, 2019 revision).

For this, the dissolution conditions were chosen as follows:Dissolution apparatus: USP app II (paddle),Media: Phosphate buffer, pH 6.8 (1000ml) contains 0.5% SDS,Temperature: 37±0.5 ^{o}C, Stirring rate = 50 rpm, Time points: 2 , 5, 10, 15, 20, 30, 45, 60 min.

Six (6) tablets were put each in a jar and 10 -ml samples were withdrawn and replaced by fresh media to keep sink condition, samples were suitably diluted by mobile phase and analyzed using the validated method developed, and data were reported as average conc. ±SD of each reading. Then percent of drug dissolved vs time was plotted to get the dissolution profile. The test was performed at pH 1.2 also with the same specifications. This test was performed on the formula that showed the best physical evaluation test results.

3. Results and discussion

3.1 Method Validation

Figure 1 shows the chromatogram of MET and TAD with RT of MET 3.2 min and for TAD 5.2 min.

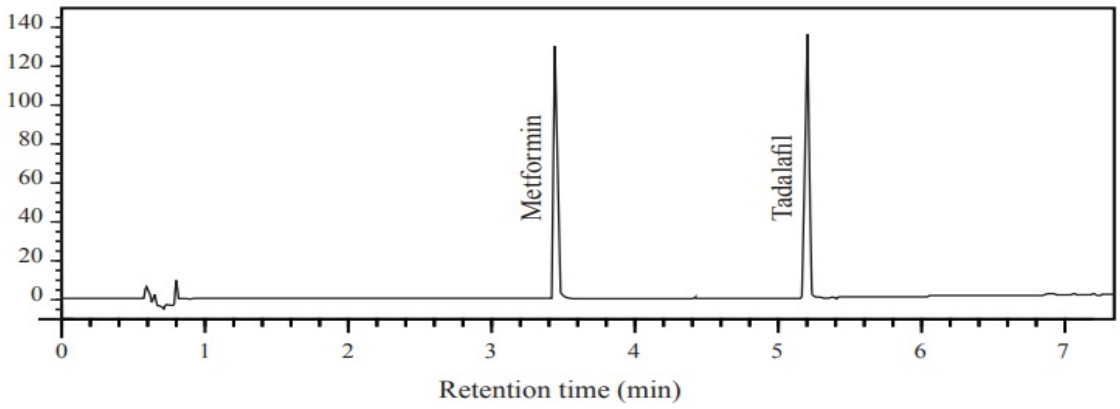
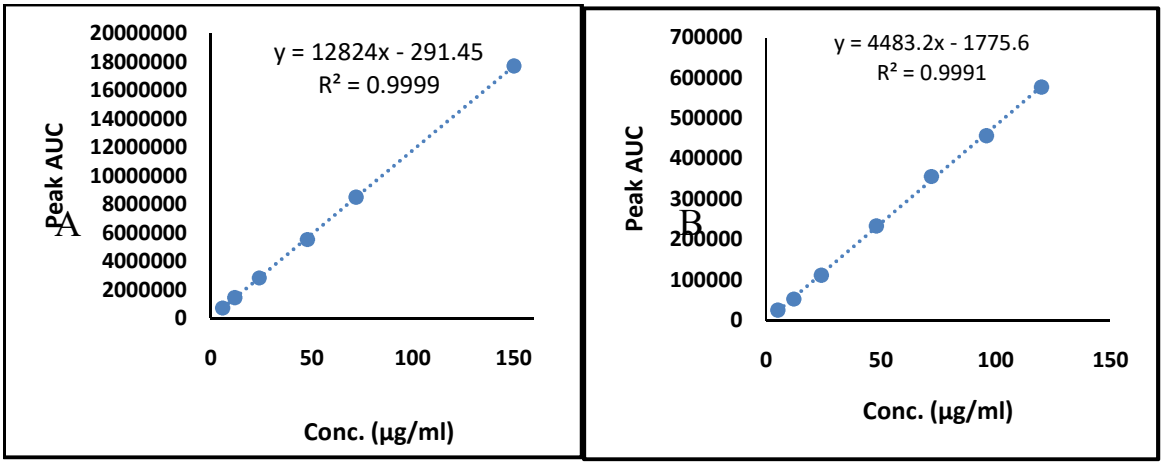


Figure 1: Chromatogram of MET (RT=3.2 min) and TAD (RT=5.2min)

Linearity of both APIs were expressed by R^2 which was >0.99 for both. Back calculations of the calibration concentrations gave RSD 0.1-0.65 for MET and 0.17-2.0 for TAD. Figure 2 shows the calibration curves for both APIs.



The precision of the method was measured by % RSD which was equal to 0.8 % for day1 and 0.9 % for day 2 while accuracy ranged between 98%-100% for day 1 and between 98%-101% for day 2 for MET. For TAD the precision was 0.8% day1 and 1.7% day2 and accuracy ranged between 98%-100% day1 and 98%-102% day 2. Precision was also calculated for 10 injections of the same sample for MET and TAD. Ten (10) injections were made of the same prepared sample of conc. 24 µg/ml for MET and 50 µg/ml for TAD. This is to ensure that each time the method measures

the concentration in the same precision. Percent RSD for MET was equal to 0.9 % and that of TAD 1.5% and the accuracy of MET ranged between 99%-102% and that of TAD 98%-103% of the 10 injections.

Recovery of MET and TAD from all prepared formulas and test formulas containing 70%-130% APIs showed %RSD 0.4-0.9% MET with accuracy 95%-98% and %RSD1.2%-3.1% and accuracy 96.6%-107%.

Robustness gave an accuracy range of 98.9% -101.3% for MET and 98% -105.5% for TAD, resolution between 5.69 and 5.72, theoretical plates 16547, and symmetry equals to 1 for all runs. All results comply with the ICH guideline and the method was ready to precede in measurements.

3.2 Differential scanning calorimetry (DSC)

Figure3 shows Thermograms of MET (A), TAD (B) and the physical combination of them (C) respectively as (mW vs. ^{o}C). MET has a melting point of 223-226^{o}C the chart shows a clear endothermic sharp peak at 250^{o}C indicating the melting point of MET. This agrees with many studies in which DSC of MET was performed [26]. TAD has a melting point of around 300^{o}C. A clear sharp endothermic peak is shown in the thermogram of TAD (B) alone refers to the melting point of the drug. Many studies in which TAD was subjected to DSC analysis show the endothermic peak in the same range [27].

Figure 3 (C) shows two endothermic distinctive peaks at 220 ^{o}C and 300^{o}C which indicates the presence of the two compounds in the sample intact and each one gives its own melting point which means no interaction occurred between them.

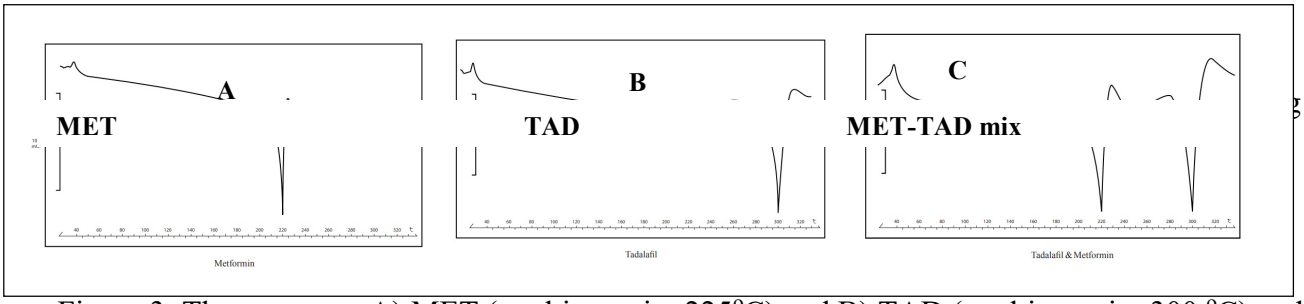


Figure 3: Thermograms A) MET (melting point 225^{o}C) and B) TAD (melting point 300 ^{o}C) and C) shows two peaks at (225^{o}C and 300^{o}C) for the mixture of them.

3.3 Physical evaluation of powder mixture

The powder mix of each formula was evaluated before the compression process. The evaluation involvedflowability, compressibility, and porosity.

Studying the flow properties of a powder mix is important for the compression step. Powders of

poor flowability characters create a problem in compression and in many times segregation of powder occurs during compression which might result in poor tablet quality, non-uniformity of content, and a variable amount of API from tablet to tablet.

The angle of repose was calculated to estimate the flow properties of the powder blend for each of the prepared formulas; these calculated values are presented in table 2.Values of the angle of repose Carr's Index and Hausner ratio indicate the flow properties and compressibility of the powder blend [28].

The values of angle of repose of each formula contain 1% of Aerosil™) indicate a free flow of the powder mixture during tablet compression regardless of the type, the concentration of super disintegrant (SD) or the diluents used; therefore, there was no need for modification of the formulas. Carr's index and Hausner ratio also gave acceptable results with the best characteristics from F2.

The porosity € of powder is defined as the ratio of void volume to the bulk volume of the packaging. Usually, the powder with high porosity would be able to absorb a larger amount of water, in addition to other characteristics of the powder blend and type of disintegrant used. Other methods of production like lyophilization give high porosity which is considered as an advantage [29].

During compression the void volume will be decreased but, the powder with higher porosity would give a tablet of higher porosity. Table …also shows the porosity as a percentage of each formula and also F2 had the highest value.

Table 2: Results of flowability, compressibility and porosity of the powder of the four suggested formulas.

Formula	Angle of repose (θ) ±SD (n=3)	Compressibility index (CI)	Hausner Ration	Porosity € (%)	Flow property
F1	34.2± 0.25	9.83±0.95	1.12	9.8%	Good/free flow
F2	35.3±0.40	11.1±1.05	1.13	11.2 %	Excellent/free flow
F3	35.6±0.26	10.00±0.96	1.125	10 %	Good/free flow
F4	33.4±0.70	12.12±1.08	1.15	12 %	Good/free flow

3.4 Physical evaluation of the prepared ODT

3.4.1 Tablet appearance, thickness, and weight uniformity

The obtained tablets were inspected visually. Tablets were well shaped with sharp edges, shiny,

smooth with bright white color that smelledof peppermint, peach, and strawberry. No cracks, no capping, or peeling were observed. Figure 4 shows the prepared tablets.

The average weight of ten tablets from each formula was measuredindividually. Since the tablets are of high weight (1000 mg), the USP gives the limit of ± 5% as an allowed variation. Table3 shows the weight uniformity test results. All tablets' weights were within the specifications of USP and no tablet exceeded 1050 mg and RSD was less than 2 for all formulas. The thickness of an average of 10 tablets of each formula is also presented in table 3.

3.4.2 Hardness and friability

The hardness of ODTs should be kept minimum to facilitate in-mouth dispersion and disintegration through the absorption of saliva. That's why compression hardness was tried to be 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 unaccepted according to the USP which is similar to regular tablets. After several trials in compression of each formula, the hardness was controlled to give friability below1%.

Table 3: Results of Tablet Weigh Uniformity Test, Hardness, Friability and Thickness Evaluation.

Formula no.	**Average wt (mg)±SD n= 10, RSD**	**Hardness (N) ±SD n= 3**	**% Friability (USP)**	**Thickness (mm) ±SD n=10**
F1	1002 ± 2.0, 0.5	35.5±2.42	0.6%	4.00 ±0.01
F2	1001±5.2, 0.5	34.2±3.20	0.5%	4.06±0.0.02
F3	1007±3.0, 0.4	36.6±3.3	0.5%	4.10±0.08
F4	995 ±3.6, 0.4	33.2±1.06	0.9 %	4.00±0.020

3.4.3 Wetting time, water absorption ratio, and disintegration time

Wetting time indicates 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. The

wetting time of the four formulas was estimated as shown in 4, water absorption ratios results are also presented in the same table.

The disintegration time is reported to be 30 sec up to 1 min (USP), while the EMA set it up to 3 min. The results of the four formulas are listed in table 4. Usually, disintegration time is a bit longer than wetting time because complete fragmentation of the tablet should be achieved. Figure 5-A shows the wetting test and 5-B shows the steps of disintegration time.

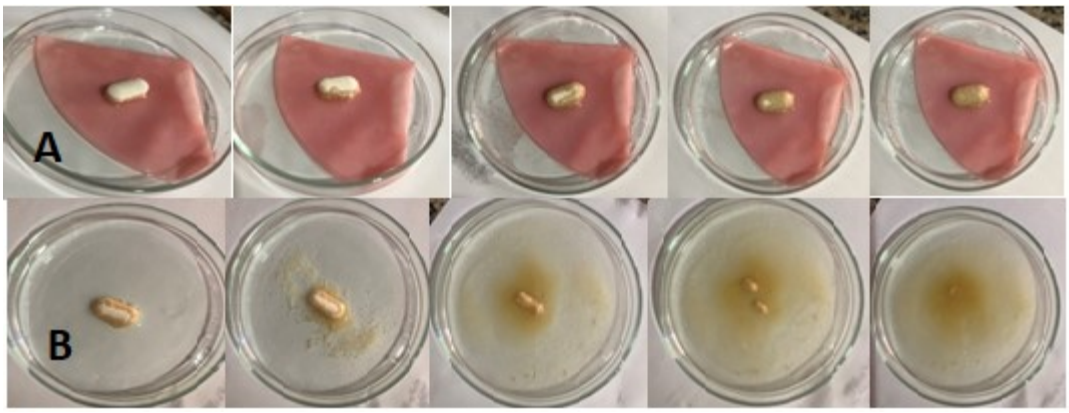


Figure 4: A) Wetting test (of F4) showing how water is absorbed to cover the surface of the tablet. B) Disintegration steps of F4.

Table 4: Results of wetting time, water absorption ratio and disintegration time of the four prepared formulas.

Formula	Wetting time (sec) n= 6	Water absorption ratio n=6	Disintegration time (sec), n= 6
F1	28 ±2	3.5±0.8	52±2
F2	30±2	3.0±0.2	54±2
F3	42 ±3	3.8 ±0.6	70 ±3
F4	25 ± 2	3.5±0.9	46±2

The action of the disintegrating agent is basic to ensure tablet fragmentation. For ODT, this should occur quickly to ensure short-time residency in the mouth and fast dissolution and absorption. Three disintegrators were used, in formula 1, cross povidone was used. This material acts by swelling mechanism as well as wicking without gelling formation. Studies showed that increasing concentration in the formula above 7-8% will not give an additional advantage of shortening wetting and disintegration[30]. That's why 5% of it was used. The use of Avicel as diluent helps 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 disintegrating the tablet. Formula 3 which used alginic acid as disintegrant showed a longer disintegration time than other formulas.

Formula 2 included sodium starch glycolate (SSG) as a disintegrant in the same concentration of Cross povidone in F1 and the same combination of diluents was also used. So, any differences would be attributed to the type of disintegrant used. SSG is the sodium salt of cross-linked carboxymethyl starch. Cross-linking of SSG to reduces solubility and gel formation upon contact with water) SSG acts as a superdisintegrant through rapid swelling because of the adsorption of large amounts of water leading to faster disintegration.F3 which used alginic acid as disintegrant gave the longest wetting and disintegration parameters. The usual concertation used as superdisintegrant is 1-5% . In this study, 5% of the total tablet weight was used taking in consideration the high weight of the tablet. But the wetting and disintegration times were longer than F1, F2, and F4 although it is still acceptable as ODT according to EMA. The long disintegration time obtained might be attributed to the gelled layer formed around the tablet in the wetting and dispersion test which might hinder further penetration of water.

F4 gave the shortest wetting and disintegration time. Since it has the same concentration and type of disintegrant as F1 but a higher amount of Avicel, the shorter wetting and disintegration time might be attributed to the high capacity of Avicel to absorb water and enhances the action of the disintegrator. This formula might show less improved taste due to less amount of mannitol, but this could be overcome by the sweetener and flavor added and the short disintegration time is favored.
Since F4 gave the shortest wetting and disintegration time, other formulas were compared to its parameters statistically using t-test and 0.05 as CI. Results presented in table 4 showed close values, yet statistical differences in wetting and disintegration time. Comparing of F1, F2, and F3 each to F4, the three parameters gave a significant difference ($p<0.05$) for all. This means that F4 gave significantly shorter wetting and disintegration time and a higher water absorption ratio.

If the criterion of USP is followed, then F3 is not accepted. But if the EMA criterion was followed, F3 could be accepted as a successful formulation for MET-TAD combination ODTs. F1, F2, and F4 are all accepted according to both USP and EMA.

Several studies related the wetting time with disintegration time like Pabari, &Ramtoola [31].. F1,F2, and F3 which used different types with the same concentration of disintegrant gave linear regression between wetting time and disintegration time which means that this relation depends on the percentage weight disintegrant in the formula rather than the type and mechanism. This linearity is shown in figure 5.

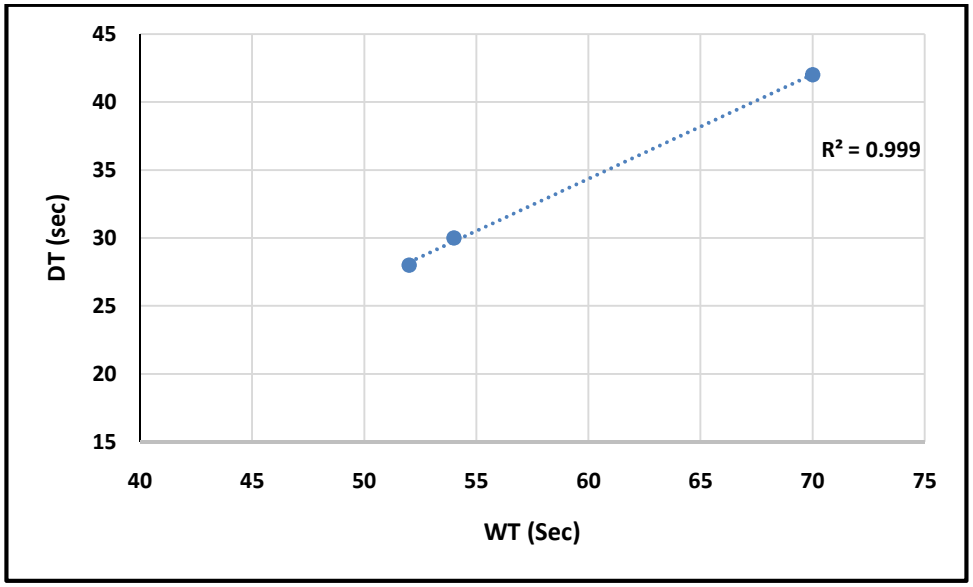


Figure 5 : linear regression of the relation between wetting time and disintegration time in F1, F2 and F3 with different types and the same concentration of disintegrants.

3.4.4 Assay of tablets and content uniformity

The concentration of MET and TAD obtained after dilution was analyzed in triplicates for each formula. Three samples were taken for each formula and then measured in triplicate and an average of nine readings were calculated. Then. percent amount of drug was calculated for each formula. F1 assay results gave MET (97.6%) and TAD 98.5%. F2 gave 103.6% and 98.0% , F3 103.5% and 101.4% , F4 102.6% and 101.6% for Met and Tad respectively. These results comply with the USP specification of API content.

Content uniformity testResults show that all formulas fulfilled the USP criteria of this test. Content uniformity of the dosage form reflects the efficiency of mixing and compression processes which preserved the uniformity of the powder and that no segregation of ingredients occurred. The concentration analyzed for both MET and TAD was equal to 50 µg/ml. API content ranged between 95.2-102.6% for MET and 93.6-102.6% for TAD.

3.5 Drug release and dissolution (F4)

One important target of formulation of ODT 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, the hydrophilicity of excipients, nature of binding forces between particles to get the drug released.

Figure 6-A shows the dissolution profile of MET and TAD at pH 6.8. The results showed that 92% MET and 90% TAD were released at 10 minutes which indicated a very fast dissolution of both APIs occurred in the first 10 minutes. Although TAD has lower solubility than MET, the size of the dose, the high hydrophilicity of the tablet content, and the fast disintegration all helped the fast release of TAD and this would help the fast absorption. Results of dissolution at pH 1.2 also

showed a high release of MET (87%) and TAD (85%) at 10 minutes. These results suggested that the absorption might be fast which is a major aim of ODTs.

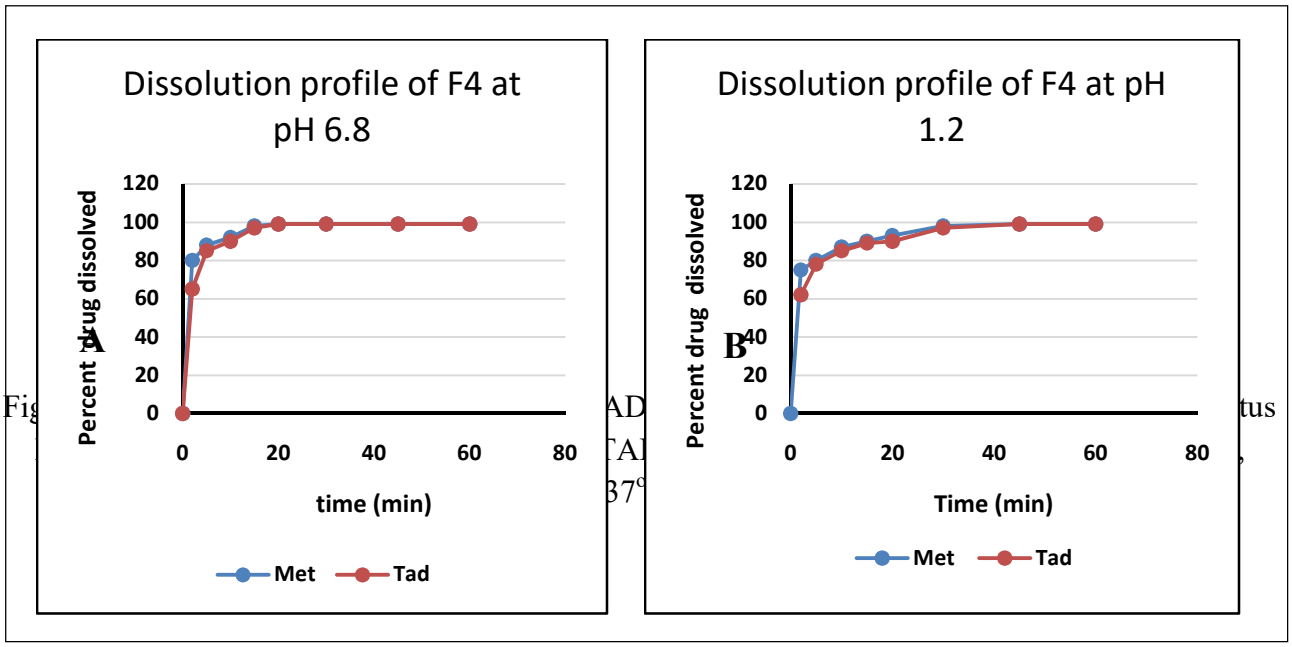


Fig AD tus
TA
37°

4. Conclusion

A successful method of analysis for simultaneous determination of MET and TAD using HPLC was developed and validated in terms of linearity, accuracy, precision, recovery, and robustness and was found to comply with the ICH guideline specifications.

MET-TAD combination was successfully formulated using sodium starch glycolate as disintegrants, Avicel and mannitol as diluents and the best formula (F4) gave the shortest wetting and disintegration time with other tests; weight variation, content uniformity, and friability all within the specification of USP.

Dissolution of F4 at pH 1.2 and 6.8 gave very fast drug release and dissolution where at both pHs more than 85% of both drugs were released in 10 min. These findings suggest the successful formulation of MET-TAD combination as ODTs.

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