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DEVELOPMENT OF A DISSOLUTION METHOD FOR DAPAGLIFLOZIN PROPANEDIOL MONOHYDRATE AND METFORMIN HYDROCHLORIDE TABLETS

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The purpose of this study was to develop and validate a method for dissolving film-coated tablets containing 5 mg dapagliflozin propanediol monohydrate (DAPA) and 850 mg metformin hydrochloride (MET). Four different types of dissolution media, two agitation speeds, and Apparatus 2 (paddle) were used. Analysis of the tablets was performed using HPLC at 223 nm for DAPA and 270 nm for MET. The ideal parameters included the use of an acetate buffer (0.05 M) at pH 4.5, an agitation speed of 50 rotations per minute (rpm), and a volume of 500 ml. The developed dissolution method has been validated according to USP46. In the validation studies, the method demonstrated specificity by showing no interference from other components, linearity within the range of 1.0 to 10.0 µg/ml with a correlation coefficient (r) of 0.9994 for DAPA and 0.17 to 1.70 mg/ml for MET with a correlation coefficient (r) of 0.9995. The precision, with Relative Standard Deviation (RSD %) values below 2%, was acceptable for both substances. The accuracy was confirmed by percent recovery values of 98.77%, 101.38%, and 104.57% for DAPA and 105.89%, 94.65%, and 98.37% for MET. The effect of the used filters on the concentrations of DAPA and MET was also evaluated, and the stability of the materials in the used dissolution medium was studied, with results that were acceptable. From the findings, it can be deduced that the established technique offers a viable option for conducting dissolution tests for DAPA and MET film-coated tablets in quality control laboratories.

***Keywords**: Dissolution test, Dapagliflozin, Metformin, Validation, HPLC*

INTRODUCTION

Diabetes mellitus is a chronic disease that affects metabolism and is characterized by high levels of glucose in the blood, which over time can lead to serious damage to the eyes, heart, kidneys, blood vessels, and nerves. The predominant form is type 2 diabetes, which usually appears in adults, where the body develops resistance to insulin or fails to produce enough of it[1].

Dapagliflozin, the first approved sodium-glucose cotransporter 2 (SGLT2) inhibitor, is indicated for the management of type 2 diabetes. It works by inhibiting glucose reabsorption in the proximal tubule of the nephron, helping to improve blood sugar control. It was FDA-approved in January 2014. Then, in April 2021, it received approval to reduce the risk of worsening kidney function, kidney failure, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease[2].

The chemical name of dapagliflozin propanediol monohydrate is (2S, 3R, 4R, 5S, 6R)-2-{4-chloro-3-[(4-ethoxyphenyl) methyl] phenyl}-6-(hydroxymethyl)oxane-3,4,5-triol; (2S)-propane-1, 2-diol; hydrate[3]. (**Fig.1**) Dapagliflozin is a white to off-white crystalline powder that can dissolve in methanol, ethanol, dimethylsulfoxide (DMSO), and dimethylformamide[4].

The solubility of dapagliflozin propanediol monohydrate is about 1.70 mg/ml in aqueous

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medium, 1.68 mg/ml in pH 1.2 acidic medium, 1.74 mg/ml in pH 4.0 medium, and 1.60 mg/ml in intestinal medium at pH 6.8[5].

Metformin hydrochloride (**Fig. 2**) is 1,1-dimethylbiguanide hydrochloride[6]. Belonging to the biguanide family, it has a wide range of uses and is the preferred first-line treatment for type 2 diabetes[7&8].

It is a white crystalline powder that is freely soluble in water, slightly soluble in alcohol, and practically insoluble in acetone and methylene chloride, depending on the substance's monograph in the British Pharmacopoeia 2023.

Metformin hydrochloride shows the following solubility at 25 °C in various media:
It is approximately 304.5 mg/ml in 0.1 N HCl (pH 1.2), 303.8 mg/ml in 0.05 M acetate buffer (pH 4.5), and 298.1 mg/ml in 0.05 M phosphate buffer (pH 6.8)[9].
As per the European Medicines Agency (EMA), dapagliflozin and metformin hydrochloride are categorized as Biopharmaceutics Classification System (BCS) Class 3 due to their high solubility and low permeability[10].

Dissolution testing has become a crucial tool in the generic pharmaceutical industry. It is extensively employed in pharmaceutical formulation development, overseeing the manufacturing process, and assessing drug quality control. Dissolution testing has also proven important in predicting the in vivo effectiveness of specific products[11]. To define dissolution parameters, we must consider the recommendations of the FDA for conducting dissolution tests on immediate-release oral solid pharmaceutical dosage forms and pharmacokinetic studies[12].

The selection of the apparatus should be determined by its ability to give consistent results and adapt a certain level of automation[13]. Typically, the basket apparatus (USP 1) is employed for capsules and products that tend to float, with agitation speeds of 50 or 100 rpm, while the paddle apparatus (USP 2) can be utilized for tablets and capsules at 50 or 75 rpm[14]. For testing immediate-release tablets, the paddle apparatus, also known as apparatus II, is the suggested equipment. (g)The aim of our work is to establish and validate a suitable dissolution method for combination tablets containing DAPA (5 mg) and MET (850 mg). To the best of our knowledge, there is no published information available in official compendiums or scientific journals regarding this specific formulation.

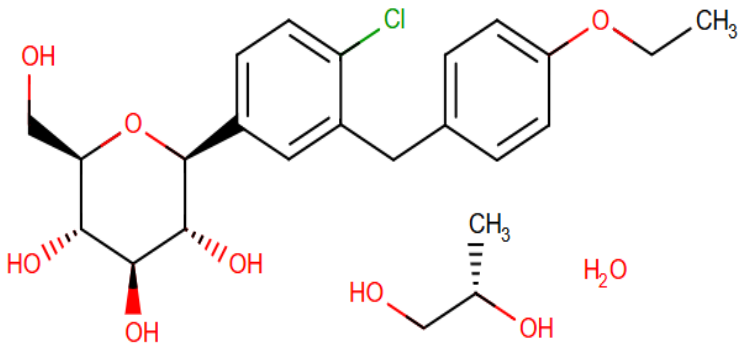

Fig. 1: Structure of Dapagliflozin propanediol monohydrate.

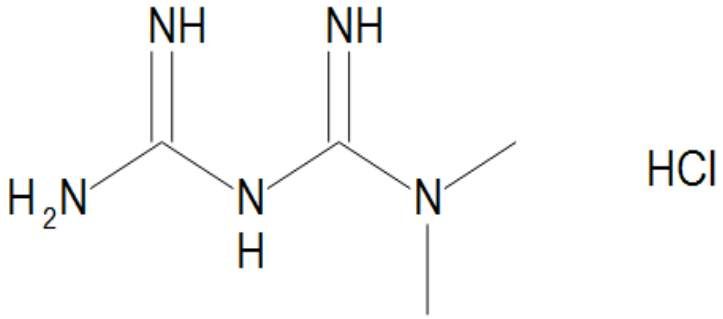

Fig. 2: Structure of Metformin hydrochloride**.**

MATERIALS AND METHODS

Materials and Reagents

The raw material of dapagliflozin propanediol monohydrate (purity 99.9%) was sourced from Hubei Derun Pharmaceutical (Hubei Sheng, China), and the raw material of metformin hydrochloride (purity 99.7%) was obtained from Aarti Drugs Limited (Mumbai, India). Commercially acquired film-coated tablets, which contain 5 mg of dapagliflozin propanediol monohydrate and 850 mg of metformin hydrochloride, were used for the dissolution testing. The excipients included in these tablets (hydroxypropyl cellulose, sodium starch glycolate type A, microcrystalline cellulose, magnesium stearate, polyethylene glycol 3350, polyvinyl alcohol, titanium dioxide, talc, and ferric oxides) were of pharmaceutical quality and were obtained from different suppliers for the formulation of a placebo.

Acetonitrile and methanol of HPLC grade were obtained from (MERCK, Supelco, Germany). Ultrapure water was sourced through reverse osmosis, and all standard aqueous buffer solutions were prepared in our laboratory in accordance with USP 35.

Instruments

The dissolution test was performed using an ERWEKA (Germany) type DT126 multi-bath (n = 6).

The quantification of the combination was performed in a high-performance liquid chromatograph (HPLC) Shimadzu LC-2050 C Photo Diode Array detector (PDA) (Kyoto, Japan). The LC-Solution Manager system software was used to control the equipment and to calculate data and responses from the HPLC system. A pH meter (Sartorius, Germany) was used, along with an ultrasonic bath (Power Sonic, model 405, Korea), an analytical balance ± 0.1 mg (Sartorius, Germany), and various types of filters (Membrane Solutions, China).

Chromatographic Conditions

A method for analysis using the HPLC Shimadzu system and PDA detector was developed and validated in our laboratories and will be published in another paper for the quantitative determination of DAPA and MET in combination at wavelengths of 223 nm for DAPA and 270 nm for MET. Chromatographic separations were conducted using a C18 reverse-phase column (4.6 mm × 150 mm, 3 µm). The mobile phase consisted of acetonitrile and 10 mM phosphate buffer adjusted to pH 3.0 with orthophosphoric acid 85% (v/v) at a ratio of 45:55 (v/v). The flow rate was 1 ml/min with gradient elution. An injection volume of 60 µL was employed, and the column temperature was controlled at 30 °C.

Physical and Chemical Test for Commercial Products

The tests for hardness, assay, average weight, and disintegration of the studied products (Product X and Product Y) were performed in accordance with USP 46[15].

Assay

Preparation of Stock Solution

A stock solution of DAPA (500 µg/ml) was prepared by weighing 10.1 mg of the raw material and transferring it to a 20 ml volumetric flask. It was then dissolved in 10 ml of methanol (solvent), placed in an ultrasonic bath for 10 min until complete dissolution, and the volume was completed with methanol.

An equivalent of 850 mg of MET (850.3 mg) was weighed and transferred to a 100 ml volumetric flask, dissolved in 70 ml of methanol (solvent), and sonicated for 15 min. The volume was then completed with the same solvent, resulting in a final concentration of 8.50 mg/ml.

Preparation of Working Standard

To prepare the standard solution of the mixture (DAPA and MET), 0.2 ml and 2 ml of the stock solutions of DAPA and MET, respectively, were transferred to a 10 ml volumetric flask and made up to the mark with acetonitrile:phosphate buffer pH 3.0 (45:55 v/v) to get a final concentration of DAPA 10.00 µg/ml and MET 1.70 mg/ml.

Sample Preparation (Tablets)

20 tablets containing 5 mg DAPA and 850 mg MET were weighed and finely crushed in a mortar. Then, the equivalent of one tablet was accurately weighed, dissolved in 50 ml of methanol, and sonicated for 15 min. This solution was filtered to remove any undissolved excipients. Afterward, 1 ml of the filtered solution was transferred to a 10 ml volumetric flask, and dilution was performed using the mobile phase (acetonitrile:phosphate buffer pH 3.0 in a ratio of 45:55, v/v).

Development of Dissolution Method

Test conditions should be determined by considering the physicochemical characteristics of the drug substance and the environmental conditions to which the dosage form may be exposed following oral administration[14].

In this study, DAPA 5 mg and MET 850 mg film-coated tablets were used to develop the dissolution method under the specified conditions: 0.05 M potassium chloride buffer pH 1.2 (simulated gastric fluid without enzymes, SGF), 0.05 M acetate buffer pH 4.5, 0.05 M potassium phosphate buffer pH 6.8 (simulated intestinal fluid without enzymes, SIF), ultrapure water, using a paddle apparatus at stirring speeds of 50 and 75 rpm in 500 ml of medium (37 °C ± 0.5 °C). The test was conducted on a number of samples (n=12)[12&16]. To establish the dissolution profile, 5 ml aliquots were withdrawn at time intervals of 5, 10, 15, and 20 min with medium replacement. The samples were analyzed by HPLC at 223 nm and 270 nm for DAPA and MET, respectively, after filtering them through a Nylon filter (0.45 µm).

The dissolution profile was analyzed using factors $f1$ and $f2$, where $f1$ is the difference factor (1) and $f2$ is the similarity factor (2). The agitation speed of 50 rpm was chosen as the reference. These factors, introduced by Moore and Flanner in 1996, are specialized models for comparing dissolution profiles.

$$f1 = \left\{\frac{\sum_{t=1}^{n}|R_t - T_t|}{\sum_{t=1}^{n} R_t}\right\} \times 100, \qquad (1)$$

$$f2 = 50 \log\left\{\left[1 + \frac{1}{n}\sum_{t-1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}. \qquad (2)$$

The dissolution profiles are considered similar if the value of the difference factor ($f1$) is between $0 \leq f1 \leq 15$ and the similarity factor ($f2$) is between $50 \leq f2 \leq 100$[17&18]. The stability of the drug in the dissolution medium was assessed over a 24-hr period, and the usual acceptable range for solution stability is generally between 98% - 102%, in comparison to the initial analysis of these solutions. Additionally, the influence of filter compatibility on the concentrations of the studied active pharmaceutical substances was evaluated[19] using different types of filters: nylon filter 0.45 µm, polyvinylidene fluoride filter (PVDF) 0.45 µm, polytetrafluoroethylene filter (PTFE) 0.45 µm, glass filter (GF) 1 µm, and nylon filter 0.22 µm.

Sample Preparation

The impact of the types of filters used for sample filtration was evaluated by preparing raw materials of DAPA and MET solutions and as tablets in an acetate buffer pH 4.5. Subsequently, the samples were subjected to analysis using HPLC.

The stability of DAPA and MET in solution for the dissolution medium was evaluated by storing them as standard solutions and sample solutions (tablets) at 37 °C for 24 hr.

Validation of Dissolution Method[19,20]

The following mandatory parameters were conducted in the dissolution test validation: specificity, linearity, accuracy, precision, and robustness, according to the USP 46 and ICH recommendations.

In this validation procedure, a dissolution parameter was selected from a range of options tested, and the Paddle apparatus was set at 50 rpm with pH 4.5 using acetate buffer as the medium.

For the validation procedure, a product sample was prepared by weighing and crushing tablets containing 5 mg of DAPA and 850 mg of MET, respectively, to a fine powder. An amount of 1122.4 mg (equivalent to the average weight of one tablet) was transferred into vessels containing 500 ml of media. After specified collection times, the samples were analyzed using the HPLC method.

Specificity

A simulated mixture of the formulation excipient was prepared and used for the specificity assessment of the method. An amount of mixture equivalent to the average weight of one tablet was transferred to vessels of the paddle apparatus (n=3) containing 500 ml of acetate buffer medium pH 4.5 at 37 ± 0.5 °C. After 30 min at 150 rpm, 5 ml samples were taken, filtered, and analyzed by HPLC. Comparing the sample to a standard solution at concentrations of 1.70 mg/ml for MET and 10 .00 µg/ml for DAPA, the result can be calculated using the formula:

$$\text{Result} = (AP/AS) \times CS \times (V/L) \times 100 \qquad (3)$$

Where:

- AP = response of the placebo blend
- AS = response of the standard solution

- CS = concentration of the standard solution (mg/ml)
- V = volume of the dissolution medium (ml)
- L = label claim (mg)

Linearity

Linearity is assessed by creating a series of DAPA and MET solutions with concentrations spanning from below the minimum anticipated concentration to above the maximum expected concentration at release. Dilutions were made from stock solutions of DAPA (500 µg/ml) and MET (8.50 mg/ml) with 0.05 M acetate buffer pH 4.5 to obtain concentrations of 1.00, 2.20, 4.75, 7.50, and 10.00 µg/ml for DAPA and 0.17, 0.35, 0.80, 1.20, and 1.7 mg/ml for MET. Each of the above concentrations was injected three times.

Linearity was assessed by linear regression analysis calculated using the least squares method.

Accuracy

To establish accuracy/recovery, multiple sample solutions containing the drug substance and other constituents present in the dosage form were prepared in a range of concentrations from below the lowest expected concentration to above the highest concentration during release. Therefore, it was assessed by adding known quantities of powdered DAPA and MET tablets pool, equivalent to 25%, 100%, and 125% of the labeled amount, to an average tablet weight in acetate buffer pH 4.5. The dissolution test was conducted for 30 min using 500 ml of the medium in the paddle at 50 rpm. This approach was chosen due to the limited availability of the DAPA and MET reference standard.

Precision

Method precision was evaluated using repeatability and intermediate precision. Repeatability was assessed by adding known amounts of the powdered DAPA and MET tablets pool, corresponding to a drug level of 100% (the labeled amount in an average tablet weight). RSD% was then calculated based on the results obtained from this procedure. The dissolution test was conducted for 30 min using 500 ml of acetate buffer medium at 50 rpm, spanning two following days with a sample size of n = 6.

Robustness

The evaluation of robustness involves making small deliberate changes to the dissolution conditions and observing the impact on the dissolution results, such as pH (4.5 ± 0.2) and agitation speed (50 ± 5 rpm). Robustness can be quantified by calculating the percentage difference in dissolution results between the different conditions tested. The dissolution test was conducted for 30 min at 37 ± 0.5 °C using 500 ml of medium at 50 rpm. Three vessels were utilized for each modification to assess the suggested alterations.

RESULTS AND DISCUSSION

The physical controls, in addition to the assay of the analyzed products, facilitate a more thorough evaluation. Key information that addresses any uncertainties during the comparison of the dissolution profiles of the drugs under investigation **(Table 1)** includes the results for all the above-mentioned parameters.

Table 1: Quality control of tablets: Product X and Product Y in terms of physical attributes (mean ± SD*)

	Description	Average weight (g)	Thickness (mm)	Hardness (Kp)	Disintegration time(min.)	Assay % ± (RSD %)	
						DAPA	DAPA
Product X	Oblonged	1.13 ± 0.9	5.80 ± 0.04	29 ± 0.81	7 ± 0.58	102.02 ± (0.10)	99.71 ± (0.06)
Product Y	Oval	1.10 ± 1.02	6.50 ± 0.07	25 ± 0.78	15 ± 0.38	101.6 ± (0.08)	99.7 ± (0.12)

*SD: Standard deviation

In selecting a dissolution method for analyzing tablets, various criteria were considered, including the requirement for the method to be accurate, robust, discriminatory, and adequate for detecting any alterations made during the manufacturing process[21]. The dissolution test was conducted under moderate test conditions, using a USP apparatus 2 (paddle) at 50 rpm and 75 rpm, with a medium volume of 500 ml (the 900 ml volume was not used as there was no suitable justification) and at intervals of 15-20 min, to generate a dissolution profile. To achieve an appropriate dissolution profile for rapidly dissolving products, it may be essential to sample at intervals of 5 or 10 min[12].

The outcomes of the filtration tests indicated negligible interference, as 5 types of filters were used with the assay percentages for samples **(Table 2)**. The results were evaluated using Analysis of Variance (ANOVA), which demonstrated a significant statistical difference ($p < 0.05$, F = 4.78) for DAPA, and through Post Hoc Tests (Tukey), it was found that the difference was only between the GF filter (1 µm) and the nylon filter (0.45 µm), probably due to the difference in dimensions between the two filters. As for MET, the results of ANOVA showed no significant statistical difference between the filter types ($p > 0.05$, F = 2.359). The nylon filter (0.45 µm) was chosen for its cost-effectiveness.

The dissolution profiles **(Fig. 3)** depict the results obtained from various media using paddles at 50 rpm. All tested media achieved sink conditions. Among the tested media, the simulated gastric fluid without enzymes (pH 1.2) resulted in a slower drug release, where approximately 50% and 55% of DAPA and MET were dissolved, respectively, within 20 min. Meanwhile, the pH 4.5 acetate buffer medium led to a faster drug release profile. The results were similar in both pH 4.5 and pH 6.8 media, where an average of 100% was released within 20 min.

Table 2: Filters results of DAPA and MET. (mean ± SD).

	Nylon filter (0.45 µm)	PVDF (0.45 µm)	PTFE (0.45 µm)	GF (1 µm)	Nylon filter (0.22 µm)
*Assay percentage of DAPA (%)	97.51	99.10	98.2	99.90	98.69
*Assay percentage of MET (%)	103.65	103.28	103.16	103	102.46

* Average of three determination.

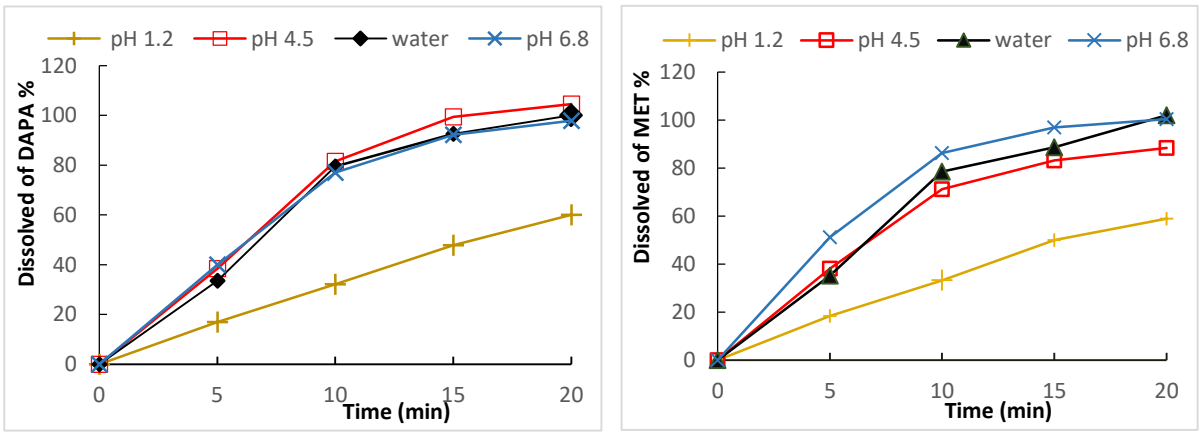

Fig. 3: Dissolution profile of DAPA and MET tablets in each medium: 0.05 M potassium chloride buffer pH 1.2, 0.05 M acetate buffer pH 4.5, water, and 0.05 M potassium phosphate buffer pH 6.8, 500 ml of media, 50 rpm.

The ultrapure water demonstrated good results; however, it is not included in the list of media recommended by the United States Pharmacopeia (USP). This is because the quality of water may differ between laboratories, leading to less stringent control of pH levels compared to buffer solutions. Furthermore, pH can fluctuate daily and may also change throughout the process, depending on the drug substance and excipients involved.

The results demonstrated that the in vitro dissolution test for the acidic medium (pH 1.2) did not meet the requirement, as less than 85% of the drug dissolved within 15 min. Even though DAPA and MET are classified as BCS Class 3, the crystalline form or particle size of both active pharmaceutical substances may be the reason for the observed solubility differences in the pH 1.2 medium.

The choice of a lower agitation speed (50 rpm) was made to facilitate the initial dissolution process, enabling better observation of the profile and yielding more discriminative results.

High dissolution rates were observed at agitation speeds of 50 and 75 rpm in the acetate buffer medium, which was confirmed by statistical analysis of data $f1$, $f2$, comparing the lower rotational speed of 50 rpm with the rotational speed of 75 rpm. At 75 rpm, the difference factor ($f1$) was 7%, and the similarity factor ($f2$) was 62% for DAPA. The same applies to MET, where ($f1$) was 10% and ($f2$) was 53%, compared to 50 rpm. This indicates that there is no significant difference between the two agitation speeds. Nonetheless, a reduced rotational speed also provides the benefit of more readily identifying any discrepancies in quality during industrial manufacturing. In the steps validating subsequent dissolution to identify potential lot-to-lot variations during routine quality control analyses, the selected condition involved using an acetate buffer at pH 4.5 with the Paddle apparatus set to 50 rpm, as shown in **Table 3**.

Finally, the stability results of the solution and tablets within the dissolution medium after 24 hr at 37 °C were between 99.74% and 98.90% for both DAPA and MET, indicating that the sample is stable in acetate buffer medium.

Comparative Study Between Products

The evaluation comparing Product X and Product Y in their tablet forms was carried out through quality control measures. Distinct variations were observed in the dissolution profiles of the products under comparison **(Fig. 4)** and **(Fig. 5)**.

Table 3: Summary of the parameters selected in developing the dissolution method.

Ideal test parameters			
The studied product		Product X	Product Y
Apparatus		Paddle	
Agitation speed (rpm)		50	
Medium		Acetate buffer pH 4.5	
Temperature		37 ºC	
Time interval (min.)		5- 10- 15- 20	
Detection		HPLC (223 nm, 270 nm)	
Dissolved percentage %	DAPA	104	91
	MET	89	79.4

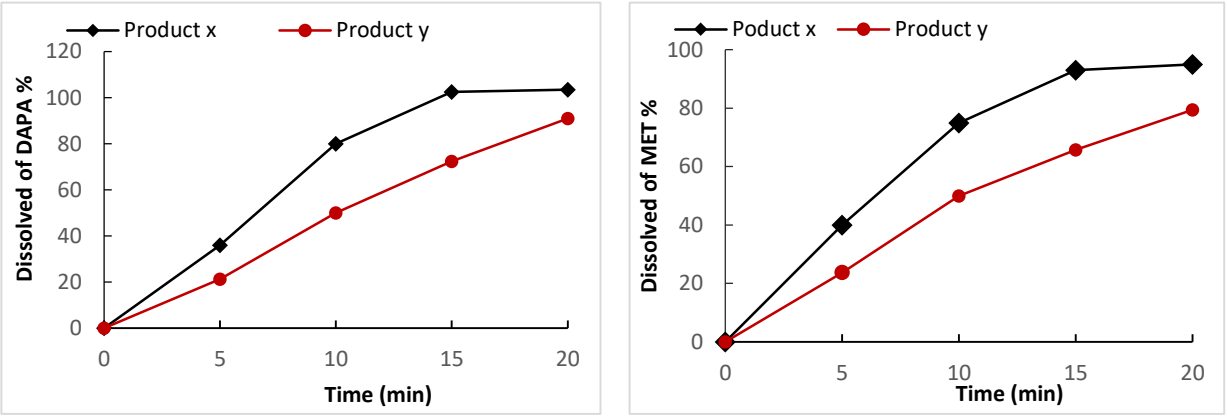

Fig. 4: Comparative dissolution profile between Product X and Product Y, using acetate buffer pH 4.5, 50 rpm, 500 ml of media.

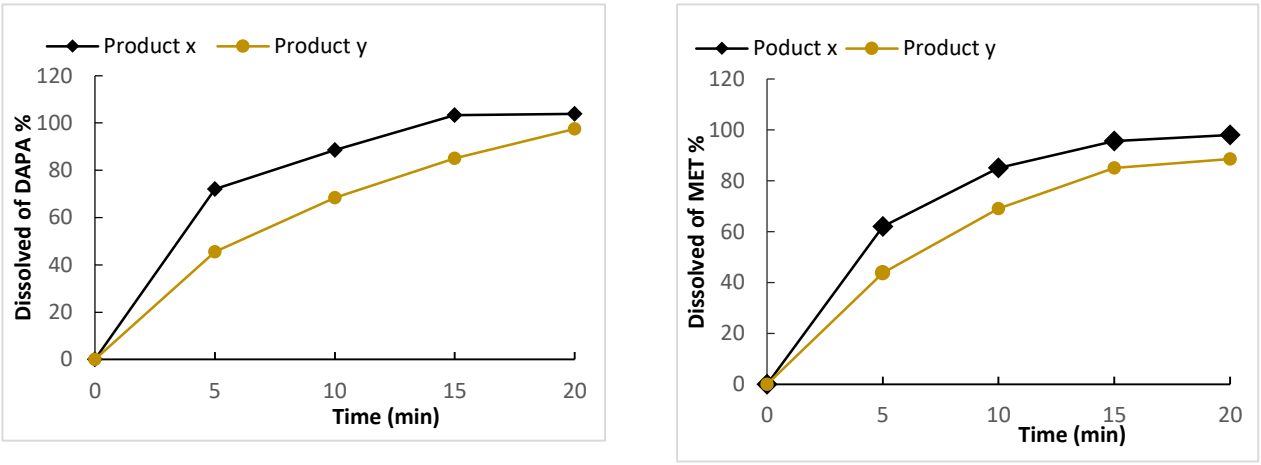

Fig. 5: Comparative dissolution profile between Product X and Product Y, using acetate buffer pH 4.5, 75 rpm, 500 ml of media.

It can be noted from the previous curves that Product X and Product Y do not exhibit similar in vitro dissolution profiles. The results of of f1 and f2 for MET were 28% and 33%, respectively, while for DAPA, the values of the value of f1 was 27% and f2 was 32%, respectively. Moreover, the results were statistically evaluated using a one-way analysis of variance (ANOVA) which demonstrated a statistically significant difference ($p < 0.05$). So, these two products differ statistically significantly, corroborating with the test of similarity factor f2 and difference factor f1 that was performed.

Results of a comparative study between Product X and Product Y were showed in **Table 4** and **Table 5**.

The difference observed is not related to the assay of the active ingredients (as shown in **Table 1**), but may instead be attributed to differences in the spatial shape, surface area of the two tablets, variations in the applied compressive force, or differences in the amount of disintegrating agent used between the two products.

Once the dissolution conditions for combination tablets were established, the method underwent validation according to the United States Pharmacopeia.

Validation of Dissolution Method

During validation, the method demonstrated specificity **(Fig. 6)**. The interference of excipients was calculated based on the relationship (No.3), which yielded a value of 0.6%, below the 2% limit, at the chosen wavelengths of 223 and 270 nm relative to a standard solution of the MET and DAPA mixture.

Table 4: Results of a comparative study between Product X and Product Y for DAPA

Time interval (min.)	Dissolved of Product X % (RSD%)	Dissolved of Product Y % (RSD%)
5	36.00 (1.8)	21.30 (2.4)
10	80.00 (3.6)	50.00 (3.3)
15	102.60 (0.8)	72.35 (3.7)
20	103.10 (2.7)	91.00 (0.7)

Table 5: Results of a comparative study between Product X and Product Y for MET.

Time interval (min.)	Dissolved of Product X % (RSD%)	Dissolved of Product Y % (RSD%)
5	40.00 (2.9)	21.30 (2.4)
10	75.00 (3.4)	50.00 (3.3)
15	93.01 (0.8)	72.35 (3.7)
20	95.67 (1.1)	91.00 (0.7)

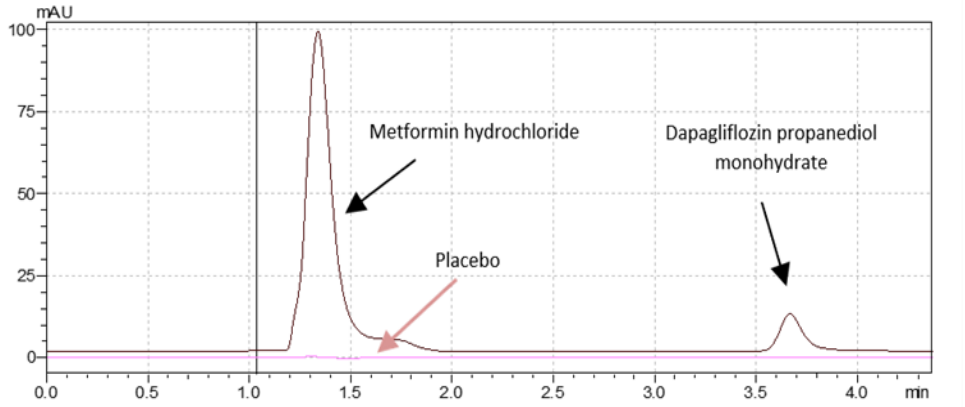

Fig. 6: Represents the chromatogram obtained for the solutions of the tablets and the formulation excipients.

The linearity of the data was assessed over the range of 1 to 10 µg/ml for DAPA and 0.17 to 1.7 mg/ml for MET, yielding the equation of the calibration curve:

- For DAPA: y = 121009x − 31894, with a correlation coefficient (r) of 0.9994.
- For MET: y = 530315x + 12910, with (r) of 0.9995.

This indicates a good correlation between the drug and response. The representative line showing the relationship between the areas under the curve (AUC) and the corresponding concentrations (C) for both DAPA and MET was plotted. Regression lines for DAPA and MET, with their correlation coefficients (r), are shown in (**Fig. 7)**.

To demonstrate accuracy, the recovery of known amounts of DAPA and MET from the tablet pool into the dissolution vessels was evaluated at three levels: low, medium, and high. The results, presented in **Table 6**, show percentage recoveries within a satisfactory range (95-105%) of the amount added, indicating the method's accuracy.

The RSD% values recorded were below 2% for repeatability and below 5 % for intermediate precision, indicating the dissolution process's high level of precision. The method's precision results are outlined in **Tables 7 and 8**.

The dissolution process remained unaffected by any of the modifications made, with RSD values below 5%. The robustness of the method was confirmed (**Table 9**).

Finally, summary of validation parameters was shown in (**Table 10**).

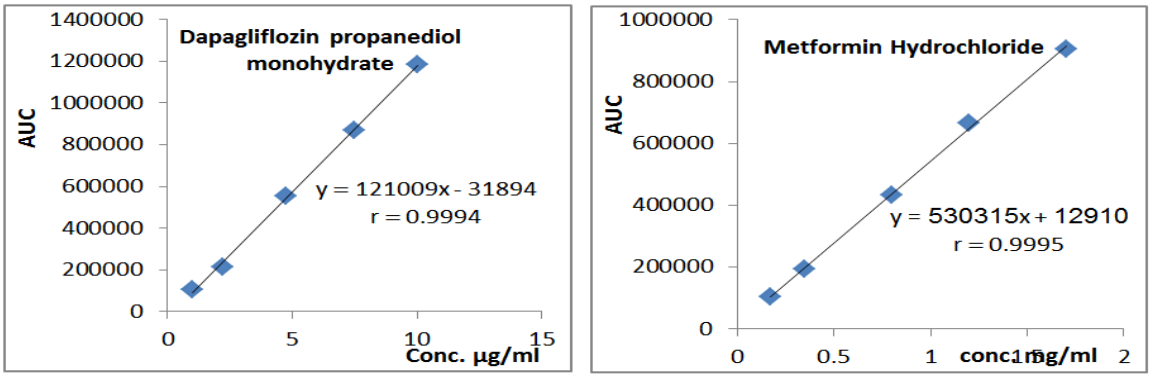

Fig. 7: Linearity of DAPA, and MET.

Table 6: Accuracy Results.

Level (%)	Added DAPA (mg)	Added MET (mg)	Added tablets "pool" (mg)	Mean recovery for DAPA ± RSD (%)	Mean recovery for MET ± RSD (%)
25	1.25	212.5	280.605	98.77 ± 1.65	105.89 ± 0.99
100	5	850	1122.42	101.38 ± 1.20	94.65 ± 0.06
125	6.25	1062.5	1403.03	104.57 ± 0.24	98.37 ± 0.33

Table 7: Precision Results for DAPA.

Sample	Day 1	Day 2
1	10.59	10.24
2	10.40	10.16
3	10.47	10.22
Average content (µg/ml)	10.49	10.35
Intraday RSD (%)	0.9	0.40
Interday RSD (%)	1.60	

Table 8: Precision Results for MET

Sample	Day 1	Day 2
1	1.62	1.67
2	1.64	1.63
3	1.62	1.64
Average content (mg/ml)	1.63	1.64
Intraday RSD (%)	0.84	1.14
Interday RSD (%)	1.15	

Table 9: Robustness results

pH	rpm	Average content of DAPA ± RSD (%)	Average content of MET ± RSD (%)
4.3	50	100.11 ± 0.21	101.66 ± 0.38
4.7	50	103.50 ± 0.08	102.13 ± 0.24
4.5	45	102.24 ± 0.01	97.26 ± 0.20
4.5	55	98.80 ± 0.1	99.49 ± 0.25

Table 10: Summary of Validation Parameters.

Parameter		MET	DAPA
Selected wavelength (nm)		270	223
Retention time (min.)		1.366	3.678
Calibration range		0.17 – 1.7 mg/ml	1 – 10 µg/ml
Correlation coefficient (r)		0.9995	0.9994
Recovery %	Low (25 %)	105.98	98.77
	Medium (50 %)	94.65	101.38
	High (100 %)	98.73	104.75
Precision	RSD % Intraday (n=3)	0.84 (Day 1), 1.14 (Day 2)	0.9 (Day 1), 0.40 (Day 2)
	RSD % Interday (n=6)	1.15	1.60

Conclusions

The creation of assays for in vitro dissolution testing of medications is essential. The absence of a specific method for DAPA and MET tablets in official compendia and scientific literature underscores the importance of developing such tests to establish a dedicated approach for this purpose. By using apparatus 2 (paddle) at an agitation speed of 50 rpm, a medium volume of 500 ml, acetate buffer pH 4.5 as the dissolution medium, and an experimental duration of 20 min, the dissolution test results were validated to demonstrate the method's specificity, linearity, accuracy, precision, and robustness. The validation process confirms that both the HPLC analytical method and the in vitro dissolution test are valid and suitable for evaluating the release profile of DAPA and MET from film-coated tablets. Therefore, these methods can be employed as routine analytical tools in quality control laboratories.

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تطوير طريقة انحلال مضغوطات داباغليفلوزين بروبان ديول أحادي الماء مع الميتفورمين هيدروكلورايد

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كان الهدف من هذه الدراسة تطوير والتحقق من صحة طريقة انحلال المضغوطات الملبسة بالفيلم الحاوية على داباجليفلوزين بروبان ديول أحادي الماء (٥ ملغ) وميتفورمين هيدروكلورايد (٨٥٠ ملغ). تم استخدام أربعة أنواع مختلفة من أوساط الانحلال وسرعتين تحريك وجهاز ٢ (المجداف). تم إجراء تحليل الكمية المنحلة من المضغوطات باستخدام الكروماتوغرافيا السائلة عالية الأداء (HPLC) عند ٢٢٣ نانومتر للداباغليفوزين و٢٧٠ نانومتر للميتفورمين. تضمنت المعلمات المثالية استخدام وقاء الخلات (بتركيز 0.05 M) عند درجة حموضة ٤,٥ وسرعة تحريك ٥٠ دورة في الدقيقة (rpm) وحجم وسط ٥٠٠ مل. تم التحقق من صحة طريقة الانحلال المطورة وفقًا لـ USP46. وفي دراسات التحقق، أظهرت الطريقة نوعية، وخطية ضمن مجال تراكيز من ١,٠– ١٠,٠ مكغ/مل مع معامل ارتباط (r) 0.9994 للداباغليفلوزين و٠,١٧– ١,٧٠ ملغ/مل من أجل الميتفورمين مع معامل ارتباط 0.9995 (r). وكانت الدقة، مع قيم الانحراف المعياري النسبي (RSD %) أقل من ٢%، مقبولة لكلا المادتين. وتم تأكيد الصحة من خلال قيم النسبة المئوية للاسترداد والتي بلغت ٩٨,٧٧% و١٠١,٣٨% و١٠٤,٥٧% للداباغليفوزين و١٠٥,٨٩% و٩٤,٦٥% و٩٨,٣٧% للميتفورمين. كما تم تقييم تأثير الفلاتر المستخدمة على تراكيز الداباغليفلوزين والميتفورمين، وتمت دراسة ثبات المواد الدوائية السابقة في وسط الانحلال المستخدم (محلول الخلات بدرجة حموضة ٤,٥)، وكانت النتائج مقبولة. ومن خلال النتائج، يمكن استنتاج أن التقنية المتبعة تقدم خيارًا قابلاً للتطبيق لإجراء اختبار انحلال مضغوطات الداباغليفلوزين مع الميتفورمين الملبسة بالفيلم في مخابر مراقبة الجودة.