Research Article

Formulation, characterization and evaluation of vildagliptin and metformin combined tablets

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Abstract

The current study was conducted to formulate and assess combined vildagliptin (VD) and metformin hydrochloride (MET) tablets. The formulations were developed by wet granulation to overwhelm the reduced compressibility of MET powder. Polymers like Kollidon K30 and K90 were used to prepare formulations. Micromeritics characteristics of blends were assessed. Subsequently, the tablets that had been manufactured were assessed for post-compression characteristics. The composition formula F7 was optimal due to having the best hardness, friability and good dissolution.

Keywords

Introduction

Amongst non-communicable diseases, diabetes mellitus (DM) is the most chronic and endemic on a global scale, with minimal and gradual eradication efforts and lifelong complications. In 2019, the Diabetes Atlas Ninth Edition of the International Diabetes Federation determined that around 463 million people are affected by diabetes. Effective management aims to achieve optimal glycaemic control and mitigate the risk of micro- and macrovascular complications. Although several additional considerations should be taken into account before commencing treatment, such as the efficacy profile, duration of treatment, adverse effects and associated complications, many more contribute to a more effective and secure therapeutic approach (Pheiffer et al. 2018)

Metformin, a biguanide oral antidiabetic, is often the primary type 2 diabetes treatment. Its complex process decreases blood glucose by lowering liver glucose production and release and boosting insulin sensitivity. There is a growing awareness that type 2 diabetes care should focus on lowering blood glucose and the consequences of severe adverse cardiovascular events (Dihoum et al. 2023). Vildagliptin inhibits DPP-4 selectively, reversibly and competitively, enhancing pancreatic sensitivity to glucose and inhibiting glucagon. Metformin reduces hepatic glucose synthesis without boosting insulin secretion. Therefore, vildagliptin and metformin synergistically enhance efficacy and have low adverse effects (Ding et al. 2022). The most often recommended combination of VD and MET is at 50/500, 50/850 and 50/1000 mg. Combining VD with MET significantly decreased the mean HbA1c levels by 1.34% (Das 2021).

The solubility of MET and VD is good in water (Polyakova et al. 2022; Yu et al. 2022). However, the most hindering step-facing formulation of MET is the lower compressibility

of metformin (Chaturvedi et al. 2023) due to its reduced bulk density, inadequate flow characteristics and reduced compressibility (Bhatt et al. 2020). Therefore, our study formulated eight VD and MET blends by wet granulation using Kollidon K 30, 90 to obtain compressible blends to have tablets with appropriate hardness and friability. The micromeritics characteristics were evaluated, assessed and characterised.

Materials and methods

Materials

Vildagliptin and metformin (Sigma-Aldrich, USA), Kollidon K30, K90 (BTC Europe GmbH/ BASF) and Avicel PH 101 (FMC BioPolymer, Ireland). Wadi Elrafideen for pharmaceuticals provided Explotab, magnesium stearate and potassium dihydrogen phosphate. Acetonitrile for HPLC (Merck, Darmstadt, Germany). Alcohol 96% was purchased from Fluka Chemika, Switzerland.

Chromatographic conditions

Column used: L 10 column (Nitrile groups chemically bonded to porous silica particles 25 cm in length, 5 μm in diameter).

Development of the HPLC method

Buffer solution preparations: 3 g potassium dihydrogen phosphate was dissolved into 900 ml purified water, adjusted to pH 3 with orthophosphoric acid, complete 1000 ml with the water and filter.

Mobile phase: 25% Acetonitrile: 75% Buffer pH (3.0)

The system comprised an Agilent HPLC apparatus. A L 10 or CN (5 μm, 25 cm × 4.6 mm) column with dual ultraviolet at 254 nm and 203 nm flow of 1.5 ml/min with 10.0 ml injection volume.

Standard solution preparation: Dissolve accurately weighed 50 mg VD and 500 mg MET into a 100 ml volumetric flask, add about 90 ml of water, sonicate for about 5 min, complete to volume, then dilute with the mobile phase as required.

Validation

The validation was conducted in adherence to the United States Pharmacopoeia (USP 2020) and the ICH Harmonization Guidance for validation of analytical procedures (ICH 2005).

System suitability

The suitability of a standard solution with a one hundred percent strength was assessed using five injections utilising an Agilent HPLC apparatus. The evaluated parameters, including theoretical plates, tailing factor and resolution, are expected to satisfy the acceptance standards set by the FDA (Al Jamal et al. 2023).

Linearity

MET and VD were assessed in the range of 200–1750 and 20–175 μg/ml. Slope, y-intercept and coefficient (R^2) were assessed. Linearity refers to the capacity to achieve outcomes directly correlated to the strength. The average area was then graphed against the strength, where an R^2 value exceeding 0.998 is considered to be evidence of a suitable fit.

Accuracy

Accuracy refers to the degree of proximity between the predicted and observed values. The calculation determines the MET's and VD's recovery percentage (R%). Three sequential studies were performed using three different strengths (400, 500 and 600) μg/ml of MET. At the same time, the concentration of VD is 25 μg/ml, 50 μg/ml and 75 μg/ml. The acceptable average recuperation lies between 90% and 100%. The accuracy of the percent recovery was determined using three replicates of three distinct spike concentrations.

Precision

We examined the precision and repeatability of the HPLC method for MET and VD at the intermediate level. The repeatability was ascertained by performing six analyses on the test concentration. In order to highlight the intermediate level of accuracy, three distinct analysers measured six concentrations and the %RSD was computed. A test's precision is defined as the degree to which separate analyses of several duplicates, conducted over three days, yield results that are consistent with one another. In order to ascertain the intraday precision, six replicates containing varying concentrations of MET and VD were analysed on the same day. The inter-day precision was evaluated by assessing the MET and VD concentrations of six replicates over the course of three days.

Specificity

The specificity was intended to reveal the capacity to differentiate the main peaks from any other associated peaks and the placebo. The specificity was evaluated to verify that there was no interference.

LOD and LOQ

The limit of detection (LOD) refers to the minimum strength of a substance that may be detected, although it may not be accurately quantified. On the other hand, the limit of quantification (LOQ) is the minimum strength of a substance that can be measured with adequate accuracy. The LOD and LOQ were computed using LOD = 3.3 X SD/S and LOQ = 10 X SD/S, where SD represents the standard deviation and S represents the slope.

Robustness

Robustness is the ability to withstand minor changes and achieve reliable results. The evaluation of robustness involved changes in wavelength and flow rate.

Stressed degradation

Base hydrolysis: 500 mg MET and 50 mg VD were dissolved in 5 ml of 0.1 M sodium hydroxide (NaOH) in a 100 ml volumetric flask (VF) and then placed in a 90 °C water bath for 2 h. Cool, neutralised by adding 0.1 M hydrochloric acid (HCl), completed to 100 ml with water, diluted and analysed by HPLC.

Acid hydrolysis: 500 mg MET and 50 mg VD were dissolved in 15 ml of 1.0 M HCl in a 100 ml VF, then placed in a 90 °C water bath for about 3 h, cooled, neutralised by the addition of 1.0 M NaOH and complete to 100 ml with water then diluted and analysed by HPLC.

Oxidative Degradation: Weigh 500 mg MET and 50 mg VD accurately dissolved in 20 ml of solvent in a 100 ml VF. Add 0.5 ml of 50% hydrogen peroxide (H_2O_2), left for about 60 minutes and complete to 100 ml with water, diluted and inject the solution into HPLC.

Dry Heat Degradation: Weigh 500 mg MET and 50 mg VD accurately dissolved in 20 ml solvent. Agitate, then subject to thermal treatment in an 80 °C water bath for approximately 3 hours. After cooling, add water to the solution until it reaches a total volume of 100 ml. Then, diluted and finally, injected the resulting solution into the HPLC.

Photolytic Degradation: Weigh accurately 500 mg MET and 50 mg VD dissolve in 20 ml water, shake, then allow standing in a Photostability chamber (under the fluorescent lamp and UV lamp at 254 nm) for 24 h and then complete to 100 ml with water, diluted with the mobile phase and analysed by HPLC.

Preparation of tablets

The wet granulation method is selected because it produces high-dose tablets that improve cohesion and flow characteristics (Kafedjiiski 2022). The ingredients are weighed and sieved via a pore size of 0.8 mm. MET, ½ Avicel PH 101, ½ Explotab kneading with a Kollidon K90 dissolved hydro-alcoholic solution (water: alcohol 50:50). The moist particles are passed through a USP sieve using a 2.0 mm mesh, then dried in an oven at temperatures of up to 50 °C, ensuring that the remaining moisture content is ≤ 3% and then sifted using a 1.2 mm filter. The remaining amount of Avicel PH 101 and Explotab were incorporated into the granules obtained and well blended. Subsequently, the lubricant was introduced and the micromeritics study was performed.

The blends were compressed using a single punch machine on an oblong punch 14 mm, resulting in tablets weighing 650 mg [Erweka, Germany]. The formulae are disclosed in Table 1. Punches: The punches are convex oblong with a diameter of 14 mm. Each tablet has an average mass of 650 mg ± 5.0% (ranging from 617.5 mg to 682.5 mg). The hardness should be at least 4 kg/cm³ and the friability should not exceed 1.0%.

Table 1. Formulations (each containing 500 mg MET, 50 mg VD, Explotab 20 mg, magnesium stearate 10 mg).

Composition*	Formulation							
	F1	F2	F3	F4	F5	F6	F7	F8
PVP K90	10		15		20		25	
PVP K30		10		15		20		25
Avicel PH 101	70	70	65	65	60	60	55	55
Ethanol 96%	10	10	10	10	10	10	10	10
Water	10	10	10	10	10	10	10	10

* Kollidon K 90, 30, Avicel PH 101 are in g; ethanol and water are in ml. Solvents were evaporated during the preparation.

Micromeritics characteristics

The compressibility index or Carr's index (CI) and Hausner ratio can be computed using the following equations, which use the initial volume (V_0) and the tapped volume (Vf):

$$CI = \frac{V_o - V_t}{V_o} \times 100 \qquad \text{(Equation 1)}$$

Results of 5–15% indicate excellent flow, 16–25% suggest good flow and ≥ 26% reveal poor flow (Sawafta et al. 2021).

$$\text{Hausner ratio} = V0/ Vf \qquad \text{(Equation 2)}$$

The angle of repose was found by assessing the inclination of the powder's top with the horizontal plane, using equation 3:

$$\text{Tan}(\alpha) = \text{Height} /0.5 \text{ base} \qquad \text{(Equation 3)}$$

The 2.5 cm height of the funnel was maintained throughout all the investigations. The diameters of the built base were measured precisely. Each formula's blend flowed down the funnel without any assistance. All of the cones created exhibited symmetry. The powder's flowability was evaluated by estimating the angle of repose. The angle of repose is a dependable indicator used to assess the flow characteristics of a substance. Values ranging from α = 25° to 30° represent a state of flow that is very effortless, α = 30° to 38° suggest a state of flow that is relatively easy and α > 38° indicates a state of flow that is of low quality (Darusman et al. 2023).

Characterisation of tablets

Hardness—Done using the United States Pharmacopoeia (USP).

Disintegration time—Done using the United States Pharmacopoeia (USP).

Friability—Done using the United States Pharmacopoeia (USP).

Drug content (*Assay*)—Twenty tablets of each formulation were weighed to determine the mean weight, then a known weight was taken and analysed by the developed HPLC method.

Dissolution testing—The USP dissolution tester [Dissolution Apparatus Veego, India] performed the release test in buffer phosphate at 37 °C at 5, 10, 15, 20, 30 and 45 min intervals. Aliquots, each 5 ml in size, were taken from Apparatus II (paddle), rotating at a speed of 50 rpm (USP 2020). The withdrawn samples were filtered, appropriately diluted and subjected to an established HPLC assay. In order to preserve sink conditions, comparable volumes of media were added to the dissolving media (Rahi et al. 2021).

Statistical analysis

To assess a reliable p-value for linearity, a one-way analysis of variance (ANOVA) was utilised.

Results and discussion

Validation

System suitability

A newly-developed and verified high-performance liquid chromatography (HPLC) technique for analysing MET and VD was used. The validation process adhered to the parameters outlined in the International Council for Harmonization (ICH) and United States Pharmacopeia (USP). Before analysing the samples, an evaluation of the system's suitability was performed. In this evaluation, the resolution was assessed to be larger than 2, the tailing factor (T) was assessed to ensure it did not exceed a value of 2, the capacity factor (k') was found to be greater than 2 and the plates were verified to be greater than 2000 (Sangani et al. 2024). The observed attributes comply with the specified limitations (Table 2). Fig. 1 illustrates the chromatogram of MET and VD.

Linearity

The regression analysis yielded results that indicated a strong linear relationship, as evidenced by R^2 values > 0.999, which was statistically significant at $p < 0.05$.

Table 2. Validation characteristics.

	Criteria	MET	VD
Linearity	Correlation coefficient $R^2 \geq 0.98$	0.9998	0.9989
	Slope	2.93	7.44
	Intercept	41.14	19.52
	Regression equation	2.93x + 41.14	7.44x + 19.52
System suitability	Tailing factor < 2	0.95	0.87
	Plates > 2000	6000	
	capacity factor (k') > 2	6.2	
	Resolution > 2	2.2	
Accuracy	Mean% recovery (95% to 105%)	99.9%	99.85%
	RSD ≤ 2%	0.36%	0.29%
Precision	Repeatability (RSD% ≤ 5%)	0.12%	0.06%
	Intermediate precision (RSD% ≤ 10%)	0.19%	0.25%
Sensitivity	LOD (µg/ml)	12.26	4.78
	LOQ (µg/ml)	37.17	14.49
Forced degradation	1 M HCl	84.92%	98%
	1 M NaOH	89.85%	89.8%
	10% H_2O_2	51.89%	80%
	Dry heat	89.3%	95%
	Photolytic	84.1%	94%
Robustness	RSD% at 253 nm	0.31%	–
	RSD% at 252 nm	0.29%	–
	RSD% at 204 nm	–	0.24%
	RSD% at 202 nm	–	0.18%
	RSD% at pH 2.8	0.12%	0.15%
	RSD% at pH 3.2	0.29%	0.25%

Furthermore, the linear equations for the relationship between MET and VD are as follows: y = 2.934x + 41.141 and y = 7.440x + 19.52, respectively, where y refers to the area and x indicates the concentration, as shown in Table 2 and Figs 2, 3. The intercept was 41.14 and 19.52 for MET and VD and the p-values were 0.005 and 0.005. The parameters satisfied the constraints outlined in Table 2. Fig. 1 depicts the MET and VD chromatogram.

Specificity

Examining a placebo and a reference solution verified the specificity. The remarkable specificity was confirmed by the observation of zero peaks around the retention periods of MET and VD.
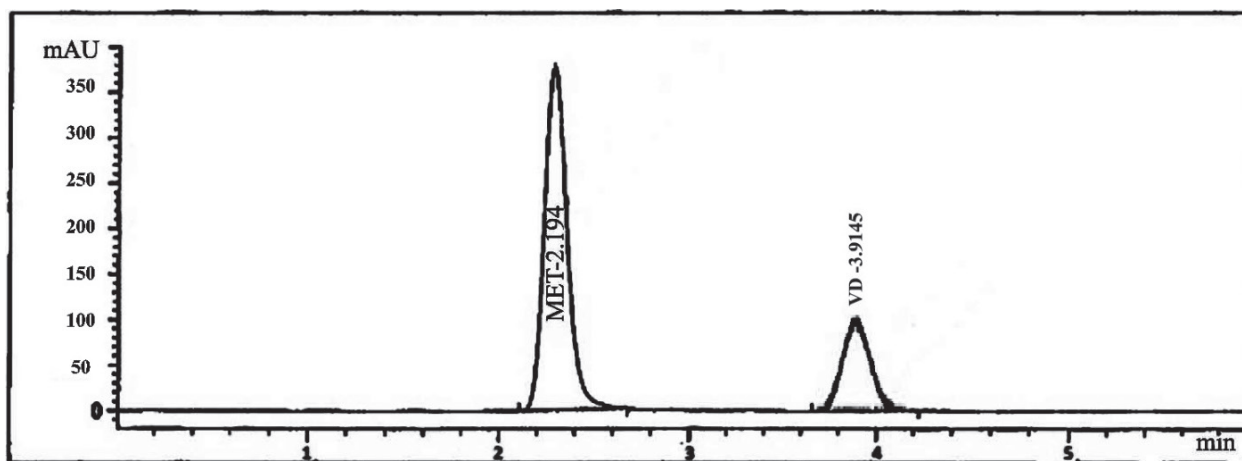
Figure 1. HPLC of MET and VD at a retention time of 2.194 and 3.945 min, respectively, for 500 µg/ml and 50 µg/ml. Conditions: a CN (5 µm, 25 cm × 4.6 mm) column and 25% Acetonitrile: 75% Buffer pH (3.0) as the mobile phase were detected at 254 and 203 nm.

LOD and LOQ

Sensitivity was demonstrated by revealing that the MET and VD LOD and LOQ were 12.26, 37.17, 4.78 and 14.49 µg/ml, respectively. A placebo was injected and MET and VD retention durations showed no peaks. Degradation in 1M NaOH, 1M HCl and 10% H_2O_2, dry heat and photolytic was 10.2%, 15.1%, 48.11%, 10.7% and 15.9% for MET, while for VD was 15.2%, 2%, 20%, 5% and 6%, respectively. In addition, the approach demonstrated robustness, as the relative standard deviation (RSD) remained below 0.4% despite minor variations and the results are shown in Table 2.
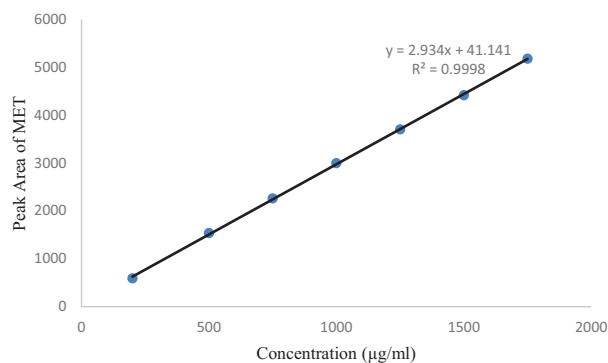

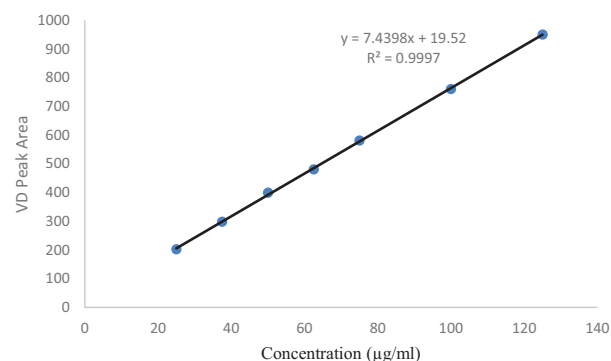**Figure 2.** MET Calibration curve.

Figure 3. VD Calibration curve.

Micromeritics of blends

According to the findings presented in Table 3, the blends' flowability was improved in formulations containing Kollidon K 90. Additionally, the flowability of powders was found to improve when the proportion of Kollidon K 90 in the kneading process was raised. The results may be attributed to the greater binding capacity of Kollidon K 90 compared to K30 (Sawafta et al. 2021).

Physical characteristics of tablets

The average weight was within the limit and there was acceptable variation. Disintegration was within 1 min, while Galvus Met disintegrated within 10 min. The hardness of tablets prepared with Kollidon K30 was ≤ 4 and broke with capping on the hardness tester (Erweka, Germany) (Table 4). Moreover, on the friability testing, they fractured into parts, while the tablets prepared by Kollidon K90, such as F3, F5 and F7, had good friability and hardness in comparison to other formulations (Njega et al. 2018)
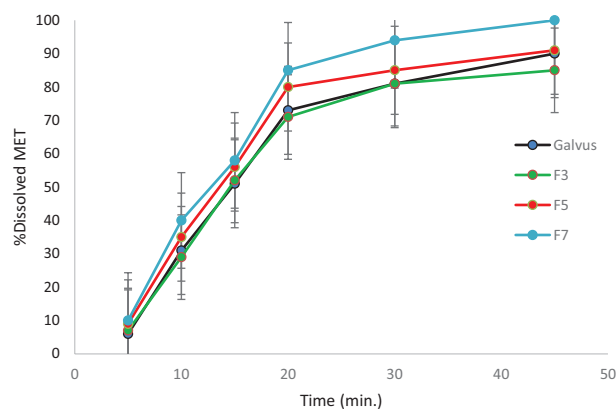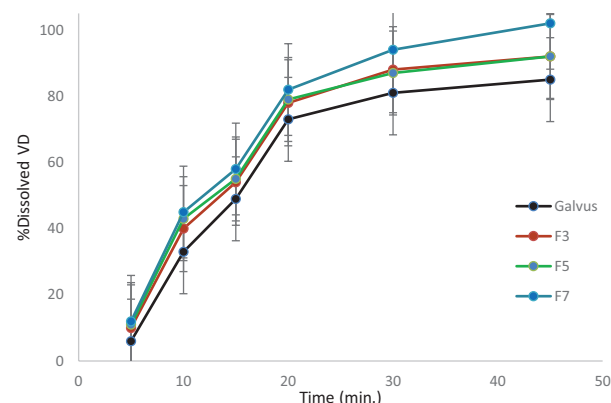

Figure 4. Release of MET from tablets.

Figure 5. Release of VD from tablets.

Table 3. Rheology of blends.

	F1	F2	F3	F4	F5	F6	F7	F8
Angle of repose (°)	38	42	32	39	28.5	40	25.1	39.2
Carr' s index (%)	37.5	43.7	31.25	33	25	28.75	13.75	12.5
Hausner index	1.6	2	1.45	1.70	1.33	1.33	1.4	1.14

In vitro release

The in vitro system was performed by dissolving the innovator (Galvus Met 50/500 mg tablets) and preparing formulations. Formulations containing Kollidon K90 showed dissolving more than 80%. However, the fastest release was F7, which released > 90% of both drugs within 30 minutes; moreover, F7 released more MET and VD compared to the innovator (Galvus Met 50/500) which released only about 80% of both drugs (Figs 4, 5).

In this study, all the prepared formulations exhibited rapid disintegration when compared to the innovator (Galvus Met 50/500) and dissolved faster than Galvus Met 50/500, except F3. Many scholars, such as Chaturvedi et al. (2023) performed co-processing MET with hydroxypropyl cellulose (HPC-L) to improve its compressibility compared to pure MET without alteration of the solubility of MET. Moreover, Srinivasan et al. (2023) prepared MET by direct compression employing Explotab, croscarmellose and mannitol. The pre-compression studies reveal that the medicinal

Table 4. Characteristics of tablets.

Formula	Galvus Met	F1	F2	F3	F4	F5	F6	F7	F8
Average weight (mg)*	–	651 ± 0.5%	649 ± 2.9%	652 ± 1.5%	648 ± 2.6%	651 ± 0.7%	645 ± 3.5%	652 ± 1.1%	657 ± 3%
Drug content (%)	99.3	99.5	101.4	99.9	101.1	99.8	99.6	100.7	99.8
Disintegration time (s)	600	50	91	65	85	57	70	45	60
Hardness (kg/cm³)	–	5	3	8	3.1	11	3.3	13	4
Friability(%)	–	1	–	0.9	–	0.2%	–	0.1%	3

*Values are stated as mean ± SD.

excipients perform well together and compress effectively. F7 demonstrated the fastest disintegration (45 s) and >95% release of MET and VD in 30 minutes.

hanced micromeritic characteristics and, after compression, the tablets produced have lower friability, good hardness and good dissolution.

Conclusion

Incorporating MET and VD into tablets using Kollidon K 90 and wet granulation could produce blends with en-

Acknowledgements

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