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The Influence of Excipients' Chemical Nature on the Degradation of Metformin and Vildagliptin

A. Demirović,[a*] *A. Uzunović*,[b] and *A. Veledar-Hamalukić*[a]

[a] Amsal Pharmaceuticals d. o. o. Sarajevo, Igmanska 38, 71 320 Vogošća, Bosnia and Herzegovina
[b] Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina, Maršala Tita 9, 71 000 Sarajevo, Bosnia and Herzegovina

Abstract

The influence of the chemical nature of excipients (magnesium stearate, povidone, microcrystalline cellulose, lactose, crospovidone, and talc) on the degradation of metformin and vildagliptin was tested by forced degradation, using acid hydrolysis, base hydrolysis, oxidation, and thermal degradation. The quantification of the content of metformin and vildagliptin before and after degradation was performed using the reversed-phase HPLC method. This method demonstrated good selectivity and specificity, with no interference from the peaks of degraded excipients on the peaks of metformin and vildagliptin, or excipient-excipient interaction. An alternative degradation pathway was discovered for vildagliptin with povidone and with magnesium stearate, as well as for metformin with povidone. Based on the results, recommendations were made regarding desirable and undesirable excipients. For vildagliptin, it is desirable to add lactose, while povidone and magnesium stearate should be avoided. Microcrystalline cellulose is recommended for metformin, whereas povidone should be avoided due to the impurities it introduces, which can lead to oxidative degradation of metformin. In the case of the combination of metformin and vildagliptin, lactose should not be included in the formulation, as it accelerates the degradation of the active substances. An exception is in the case of base hydrolysis, where lactose has a stabilising effect, absorbing moisture, thus reducing the degradation of both metformin and vildagliptin.

Keywords

Excipients, degradation, metformin, vildagliptin, HPLC

1 Introduction

Metformin hydrochloride and vildagliptin have for many years been produced as separate film-coated tablets. Over the past fifteen years, film-coated tablets containing a combination of these two antihyperglycaemic substances with complementary mechanisms of action have been developed to improve glycaemic control in patients with type 2 diabetes.[1] The key reactive group in vildagliptin is its **nitrile group** (−C≡N) (Fig. 1.), which is also sensitive to hydrolysis and can degrade vildagliptin into amides and carboxylic acid derivatives. Other functional groups, including a secondary amine and imidazolidine ring, contribute to the molecule's overall stability and reactivity in pharmacological environments.[2]

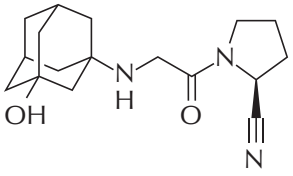

Fig. 1 – Structural formula of vildagliptin
Slika 1 – Strukturna formula vildagliptina

Metformin's structure (Fig. 2.) is comprised of a biguanide group (two linked guanidine units) and can undergo degradation in acidic or oxidative environments, possibly forming impurities like guanylurea.[3]

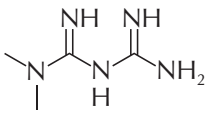

Fig. 2 – Structural formula of metformin
Slika 2 – Strukturna formula metformina

To examine whether alternative degradation pathways exist and whether additional degradation products occur, it was necessary to investigate the degradation of vildagliptin and metformin with excipients under frozen degradation conditions. This included studying the influence of the chemical nature of excipients and their potential degradation products on the degradation behaviour of vildagliptin and metformin.

A review of the available literature revealed that the effects of excipients on the degradation of vildagliptin and metformin have been studied separately.

* Corresponding author: Amra Demirović, M.Sc.
Email: a.demirovic@amsal.ba

In acidic conditions, lactose was found to stabilise vildagliptin, while the highest degradation occurred with microcrystalline cellulose. Under alkaline conditions, sucrose stabilised vildagliptin, whereas povidone provided stabilisation during forced hydrolytic degradation. No new degradation products were detected as a result of API excipient interaction.[4]

Excipients such as lactose, mannitol, magnesium stearate, and povidone have been identified as reactive when formulated with vildagliptin. Special attention must therefore be paid to selecting excipients for vildagliptin formulations.[5]

Hypromellose has been frequently used in metformin formulations. Dimethylamine, a starting material in metformin synthesis and a degradation product formed by oxidation, reacted with nitrite originating from excipients like hypromellose and povidone. As a result, N-nitroso dimethylamine (NDMA) was detected only in the final drug product and not in the active pharmaceutical ingredient (API).[6] However, no studies have been found that investigate the impact of excipients on the simultaneous degradation of vildagliptin and metformin.

The most common pharmaceutical dosage form is tablets, *i.e.,* film-coated tablets. Various excipients are added to tablets to make them acceptable and compatible with their therapeutic effect, enhance the manufacturing process, protect the active substance, increase the stability of the form, modulate bioavailability, or facilitate application to patient. The roles of excipients in tablets include diluents, binders, disintegrants, lubricants, glidants, and anti-caking agents.[7]

Although excipients were once considered pharmacologically inert, they can inject, spread, or participate in chemical or physical interactions with active substances, potentially compromising the stability and efficacy of the drug. This type of interaction occurs more often than the reaction of excipients with one another.[8] Excipients are not always of high purity, and even for the most commonly used excipients, it is necessary to understand the context of their production to identify potential interactions between active pharmaceutical ingredients with trace components. Chemical interactions can lead to degradation of the active ingredient, reducing the amount available for therapeutic effect. Physical interactions can affect dissolution rates, content uniformity, or ease of application. By selecting excipients in the pharmaceutical development of the finished product, their compatibility with the active substance/s is tested. The instability of a drug resulting from interactions between the active pharmaceutical ingredient (API) and excipients can be attributed to three factors. The first is related to the API itself, such as its physical and chemical properties, moisture content, impurities, specific surface area, and crystal form.[9] The second factor is related to formulation design, including the ratio of API to excipients, mixing method, granulation process, and packaging. The third factor involves environmental influences, such as temperature, humidity, and light. This study aimed to simulate external environmental conditions, particularly temperature, humidity, and oxidation. Table 1 shows the residues for different excipients.[10–16]

Table 1 – Residues of excipients
Tablica 1 – Ostaci pomoćnih tvari

Excipient	Residue
Povidone, crospovidone, polysorbates	Peroxides
Magnesium stearate, fixed oils, lipids	Antioxidants
Lactose	Aldehydes, reducing sugars
Microcrystalline cellulose	Lignin, hemicellulose, water
Talc	Heavy metals

2 Experimental

2.1 Excipients selection

It is known that in formulations containing metformin, it is necessary to avoid povidone (PVP) because the carbonyl group of PVP creates hydrogen bonds with the amino group of metformin, as well as mannitol, which is considered to affect the amino group of metformin.[5] It is of interest to select an excipient for which there is no information available in the literature regarding chemical and/or physical interactions with metformin or with vildagliptin. Microcrystalline cellulose (MCC) and lactose (LAC) were purchased from JRS Pharma, Germany, and DFE Pharma, Germany, respectively. Povidone was purchased from JRS Pharma, Germany, magnesium stearate (Mg-St) was obtained from Mallinckrodt Inc., USA, and crospovidone (PVPP) and talc (TAL) were purchased from JRS Pharma, Germany, and Imerys, Italy, respectively.

2.2 Other materials

Pure samples of metformin hydrochloride (99.8 %) and vildagliptin (99.7 %) were purchased from BOC Sciences, USA. Sodium phosphate dibasic anhydrous was purchased from Carlo Erba (Carlo Erba Reagents S.A.S., France), and orthophosphoric acid was obtained from Sigma Aldrich, Germany. For the mobile phase, HPLC-grade methanol was purchased from Merck, Germany. HPLC grade water was produced using a Milli-Q Advantage A10 purification system (Merck Millipore Co., USA) provided by Amsal Pharmaceuticals. Vildagliptin Cyclo Imidamide, Vildagliptin Amide, and Vildagliptin Impurity B certified standards were purchased from Clearsynth, India.

2.3 Instrumentation

High-pressure reverse-phase liquid chromatography (RP-HPLC) was used for testing. An Agilent 1260 Infinity HPLC System (Agilent, USA) was used for the analysis, a quadruple-channel gradient pump, an integrated degasser, an autosampler, a column compartment, and a diode array detector were also utilised. Data collection and further processing was conducted using Agilent OpenLAB CDS ChemStation Edition for LC System, Rev. C.01.09 [144].

Active ingredients and degradation products were separated on a Prodigy ODS 3, C18 reverse-phase (RP) column (5 µm, 250 × 4.6 mm, Phenomenex, USA).

2.4 Chromatographic conditions

Separation of analytes was achieved using gradient elution. Mobile phase A consisted of an 0.02 M sodium phosphate dibasic anhydrous buffer solution, adjusted to a pH of 7.5 using orthophosphoric acid and methanol (90 : 10). Mobile phase B consisted of methanol. The time programme was set as follows: *t*(min)/Mob A(%): 0/95; 5/95; 5.01/90; 20/50; 23/95; 30/95. The flow rate and injection volume were 1.0 ml min^{-1} and 30 µl, respectively. Experiments were performed at a temperature of 35 °C and detection was carried out at 208 nm. A nylon 0.45 um filter was used for the mobile phase and for filtering all prepared solutions.

2.5 Forced degradation study

The forced degradation study was conducted on an excipient mixture, vildagliptin with each excipient separately, metformin with each excipient separately, and the combination of vildagliptin and metformin with each excipient separately (Table 2). Degrading agents were adjusted to obtain an acceptable percentage of degradation. Forced degradation included acid hydrolysis (1 M HCl, 80 °C, 7 h, base hydrolysis (0.1 M NaOH, 80 °C, 30 min), oxidation (3 % H_2O_2, room temperature, 30 min), and thermal degradation (80 °C, 3 h).

To determine forced degradation, the following solutions were prepared:

Initial vildagliptin/metformin solution: Approximately 10 mg of vildagliptin/metformin was weighed into a 10 ml volumetric flask, 2 ml of methanol was added, and the solution was dissolved in an ultrasonic bath for 10 min, then brought to the mark with a buffer solution.

Excipient mixture solution: Approximately 10 mg of each excipient was weighed into a 10 ml volumetric flask, and 2 ml of methanol was added, and the solution was dissolved in an ultrasonic bath for 10 min. Then, 3 ml of degradation agent was added, the mixture was treated under different stress conditions, and the volume was brought to the mark with a buffer solution. *Vildagliptin solution with individual excipients*: Approximately 10 mg of vildagliptin and each excipient were weighed individually into a 10 ml volumetric flask, 2 ml of methanol was added, and the mixture was dissolved in an ultrasonic bath for 10 min. Then, 3 ml of degradation agent was added, the mixture was treated under different stress conditions, and the volume was brought to the mark with a buffer solution. Note: Before filling the solution to the mark with buffer, the solution was first neutralised with 3 ml of 1 M NaOH in the case of acid hydrolysis, or with 3 ml of 0.1 M HCl in the case of basic hydrolysis. Metformin solutions with individual excipients, and metformin and vildagliptin solutions with individual excipients were prepared in the same manner.

Table 2 – Review of excipient and API combinations with types of degradation

Tablica 2 – Pregled kombinacija ekscipijensa i API-ja s tipovima razgradnje

Excipient and API combination	Type of forced degradation			
	1 M HCl 80 °C, 7 h	1 M HCl 80 °C, 7 h	1 M HCl 80 °C, 7 h	1 M HCl 80 °C, 7 h
Excipient mixture	√	√	√	√
Mg-St+VIL	√	√	√	√
Mg-St+MET	√	√	√	√
Mg-St +VIL+MET	√	√	√	√
PVP+VIL	√	√	√	√
PVP+MET	√	√	√	√
PVP+VIL+MET	√	√	√	√
MCC+VIL	√	√	√	√
MCC+MET	√	√	√	√
MCC+VIL+MET	√	√	√	√
LAC+VIL	√	√	√	√
LAC+MET	√	√	√	√
LAC+VIL+MET	√	√	√	√
PVPP+VIL	√	√	√	√
PVPP+MET	√	√	√	√
PVPP+VIL+MET	√	√	√	√
TAL+VIL	√	√	√	√
TAL+MET	√	√	√	√
TAL+VIL+MET	√	√	√	√

The recovery value (Rec) was calculated for all solutions according to Eq. (1).

$$\mathrm{Rec}(\%) = \frac{A_{\mathrm{deg}}}{A_{\mathrm{in}}} \cdot 100 \qquad (1)$$

A_{deg} is the area under the metformin/vildagliptin peak in degraded solutions, and A_{in} is the area under the metformin/vildagliptin peak in the initial vildagliptin/metformin solution.

2.6 Statistical processing of results

Minitab Statistical Software 22.1.0 (Minitab, LLC, Pennsylvania, SAD) was used to process the results statistically. One-way ANOVA was used to check whether there were statistically significant differences between the data group in which the active substance (metformin or vildagliptin) was treated with each degradation agent separately, with the group in which an excipient was added in addition to metformin or vildagliptin, and with the group in which, in addition to metformin and vildagliptin, an individual excipient was added, and then treated with an individual

degradation agent. For an excipient for which the ANOVA test showed a statistically significant difference compared to other excipients, it was necessary to perform a post-hoc test to detect which group within that excipient led to a significant difference. Dunnett's test was used to compare each group with the control group. The control group was metformin or vildagliptin, which was degraded without the addition of excipients and other active components.

3 Results and discussion

The HPLC method used for the simultaneous determination of vildagliptin, metformin, and their degradation products showed good specificity and selectivity.

3.1 Results of forced degradation study of excipient mixture

The chromatograms of excipient mixture solutions exposed to basic and acidic degradation, oxidation, and thermal degradation, exhibited no peaks interfering with the peaks of vildagliptin and metformin from the initial solution. The HPLC chromatograms are presented in the Fig. 3.

3.2 Results of forced degradation study of vildagliptin

The results of the forced degradation study of vildagliptin are presented in Table 3.

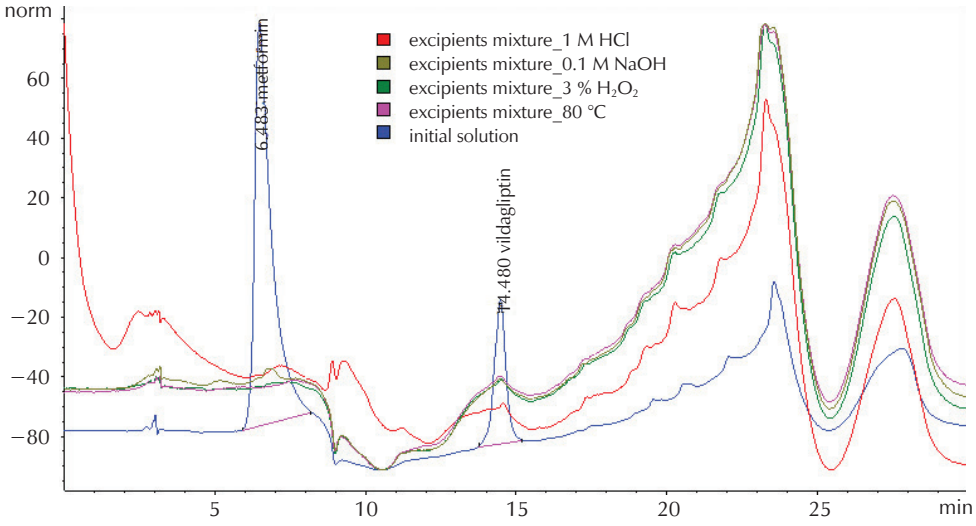

Fig. 3 – Overlay chromatograms of degraded excipient mixtures and initial solution
Slika 3 – Prekloplјeni kromatogrami razgrađenih mješavina pomoćnih tvari i početne otopine

Table 3 – Results of the forced degradation study of vildagliptin (VIL)
Tablica 3 – Rezultati prisilne razgradnje vildagliptina (VIL)

Stress condition	Recovery of vildagliptin / %												
	VIL without excipients	VIL with Mg-St	VIL with Mg-St and MET	VIL with PVP	VIL with PVP and MET	VIL with MCC	VIL with MCC and MET	VIL with LAC	VIL with LAC and MET	VIL with PVPP	VIL with PVPP and MET	VIL with TAL	VIL with TAL and MET
1 M HCl	76.01	78.82	61.13	76.47	58.73	73.39	67.25	100.99	46.64	70.34	56.40	87.80	48.41
0.1 M NaOH	13.99	16.21	6.83	17.20	12.95	17.05	14.31	18.59	15.50	17.55	13.16	17.09	14.04
3 % H_2O_2	64.70	59.89	68.94	62.76	54.95	64.75	56.91	64.95	58.34	48.33	50.74	64.54	49.72
80 °C	73.15	94.45	48.38	94.24	77.34	94.48	69.96	82.95	86.87	95.62	69.14	95.98	67.22
F-value		0.30		0.15		0.20		0.21		0.18		0.55	
p-value		0.747		0.860		0.826		0.815		0.839		0.595	

Critical *F*-value: 4.25

Table 4 – Results of the forced degradation study of metformin (MET)
Tablica 4 – Rezultati prisilne razgradnje metformina (MET)

Stress condition	Recovery of metformin / %												
	MET without excipients	MET with Mg-St	MET with Mg-St and VIL	MET with PVP	MET with PVP and VIL	MET with MCC	MET with MCC and VIL	MET with LAC	MET with LAC and VIL	MET with PVPP	MET with PVPP and VIL	MET with TAL	MET with TAL and VIL
1 M HCl	72.05	71.55	48.05	87.02	46.61	98.92	51.77	89.23	47.13	83.57	58.45	59.50	47.65
0.1 M NaOH	83.12	67.00	57.91	73.67	58.60	79.53	69.55	80.09	81.93	67.41	79.99	77.02	65.03
3 % H_2O_2	76.10	70.75	65.27	83.13	69.95	85.43	99.86	84.16	100.04	85.27	76.14	88.15	74.71
80 °C	87.13	93.85	57.24	61.04	58.27	76.38	60.63	53.45	63.89	70.85	67.09	93.04	67.29
F-value		3.38		5.77		1.12		0.79		0.95		2.50	
p-value		0.080		0.024		0.367		0.483		0.421		0.137	

Critical *F*-value: 4.25

3.3 Results of forced degradation study of metformin

The results of the forced degradation study of metformin are presented in Table 4.

For metformin with povidone and with the addition of vildagliptin, the ANOVA test showed a statistically significant difference compared to metformin without excipients (control group), so a *post hoc* Dunnett test was performed to determine which group of results is statistically significant (Fig. 4.).

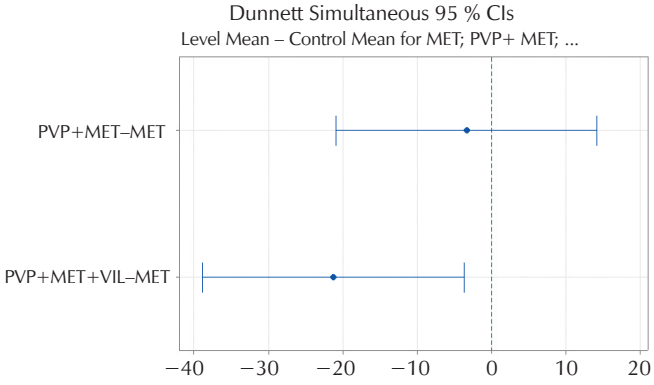

Fig. 4 – Dunnett multiple comparisons with the control
Slika 4 – Dunnettova višestruka usporedba s kontrolom

Dunnett's test indicated that the group with metformin, povidone, and vildagliptin (MET with PVP and VIL) was statistically significantly different from the group with metformin without excipients (MET without excipients) and metformin with povidone (MET with PVP).

3.4 Acidic degradation of vildagliptin, metformin, and vildagliptin/metformin combination

In conditions of acid hydrolysis degradation of vildagliptin, the minimum content after degradation was recorded with crospovidone (70.34 %), as much as 30 % more vildagliptin was degraded in the presence of crospovidone, compared to lactose (100.99 %), as shown in Table 3. Lactose was also identified as a stabilising excipient by *Janicki et al.*, while no agreement exists regarding the excipient causing the highest degradation, as *Janicki et al.* did not work with crospovidone.[4] Lactose can help maintain the stability of vildagliptin by minimising moisture-induced degradation. Vildagliptin is sensitive to hydrolytic degradation, and the hygroscopic nature of excipients like lactose may mitigate moisture-induced breakdown by providing a protective matrix that limits moisture absorption.[17]

When metformin was added to vildagliptin (Table 3), the highest degradation was in the presence of lactose (46.64 %), and the lowest in the presence of microcrystalline cellulose (67.25 %). The addition of metformin generally increased the degradation of vildagliptin, and the content was the highest in the presence of povidone (58.73 %), and the lowest in the presence of lactose (46.64 %), as shown in Table 3. Lactose stabilized vildagliptin alone, but in combination with metformin, it had a destabilising effect. It is hypothesised that the −NH− group of vildagliptin interacts with lactose at high temperatures and humidity, making lactose a reactive excipient under such conditions.[17] The degradation of vildagliptin follows pseudo-first-order kinetics in oxidative, acidic, and basic environments, and its stability worsens when exposed to moisture over time,[15] while the combination of lactose and metformin, both of which are hygroscopic, further exacerbates the moisture. In formulations where metformin and vildagliptin are combined, this moisture release may exacerbate the degradation of vildagliptin, impacting the stability and efficacy of the drug over time.[18] The presence of vildagliptin and

lactose under conditions of acid hydrolysis (Table 4) did not lead to an increase in the degradation of metformin, but the lowest content was recorded after degradation with povidone (46.61 %) and the highest with crospovidone (58.45 %). When metformin is combined with povidone (polyvinylpyrrolidone, PVP) in formulations, there is a risk of degradation due to oxidative impurities present in povidone. These impurities, particularly organic peroxides, can lead to oxidative degradation of sensitive drugs, including metformin. This reaction is significant when povidone contains trace levels of these reactive by-products, which can accelerate the breakdown of the drug, affecting its stability and potency.[19] Povidone can promote hydrolytic degradation by facilitating moisture absorption, which interacts with the amino group of vildagliptin, contributing to its breakdown.[20] Acidic degradation of vildagliptin in the presence of povidone resulted in a peak at relative retention time (RRT) 0.30 in accordance to vildagliptin. This peak did not appear on the chromatogram of the forced degradation study of the excipient mixture, nor the chromatograms of the forced degradation study of vildagliptin without the presence of excipients, which means that it appeared due to the chemical interaction of povidone and vildagliptin. The peak with RRT 0.45 showed on the chromatogram as a result of the interaction of vildagliptin with magnesium stearate (Fig 5).

3.5 Basic degradation of vildagliptin, metformin, and the vildagliptin/metformin combination

Under conditions of base hydrolysis degradation of vildagliptin (Table 3), the lowest vildagliptin content was recorded with magnesium stearate (16.21 %), and the highest with lactose (18.59 %). The same situation applies to metformin, where the lowest content was 67.00 %, and the highest 80.09 %, as shown in Table 4. *Janicki et al.* identified sucrose as a stabilising excipient, with lactose also serving as a secondary stabiliser. In this paper, lactose was also identified as the most potent stabiliser, which agrees with the previous paper.[4] It is known from the literature that magnesium stearate, often present in formulations, can elevate the pH of their microenvironments due to magnesium oxide impurities, consequently, accelerating the hydrolysis of some labile drugs.[21] In the situation of base hydrolysis of lactose, both vildagliptin and metformin were stabilised, while the addition of metformin increased the degradation of vildagliptin (Table 3), and the content was the highest in the presence of lactose (15.50 %), and the lowest in the presence of magnesium stearate (6.83 %). With the addition of vildagliptin (Table 4), the highest content for metformin was in the presence of lactose (81.93 %), and the lowest in the presence of magnesium stearate (57.91 %). In the case of base hydrolysis, lactose stabilised both individually and in combination with metformin and vildagliptin. Lactose plays a key role in stabilising both metformin and vildagliptin by absorbing moisture, acting as a diluent and binder, and providing a neutral environment that protects the active pharmaceutical ingredients from degradation. Base degradation of metformin/vildagliptin in the presence of povidone resulted in a peak at RRT 0.69, in accordance to metformin (*i.e.,* to RRT 0.30 counting vildagliptin). This peak did not appear on the chromatogram of the forced degradation study of excipient mixture, nor the chromatograms of the forced degradation study of metformin/vildagliptin without excipients, which means that it appeared due to the chemical interaction of metformin and povidone, or vildagliptin and povidone (Fig. 6.). Vildagliptin with magnesium stearate behaved the same in both acid and base hydrolysis, a peak appeared at RRT 0.45, where hydrolysis of the nitrile group probably

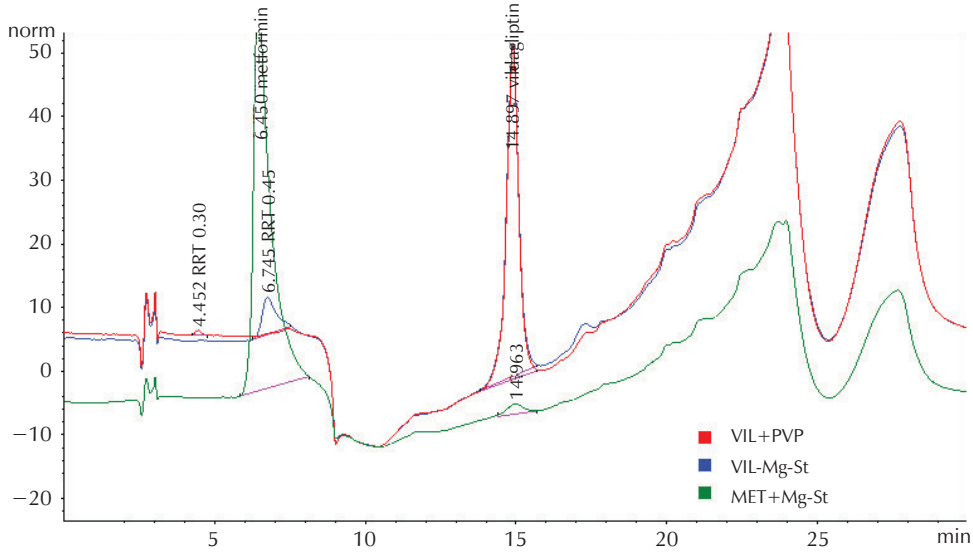

Fig. 5 – Overlay chromatograms of vildagliptin with magnesium stearate/povidone and metformin with magnesium stearate degraded with 1 M HCl

Slika 5 – Prekloplјeni kromatogrami vildagliptina s magnezijevim stearatom/povidonom i metformina s magnezijevim stearatom razgrađeni s 1 M HCl

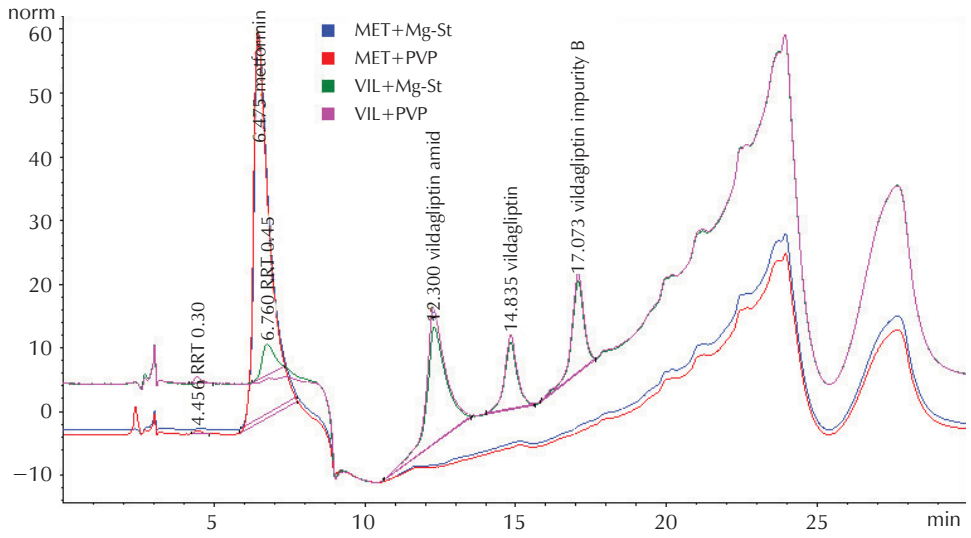

Fig. 6 – Overlay chromatograms of vildagliptin/metformin with magnesium stearate/povidone degraded with 0.1 M NaOH

Slika 6 – Prekloplјeni kromatogrami vildagliptina/metformina s magnezijevim stearatom/povidonom razgrađeni s 0,1 M NaOH

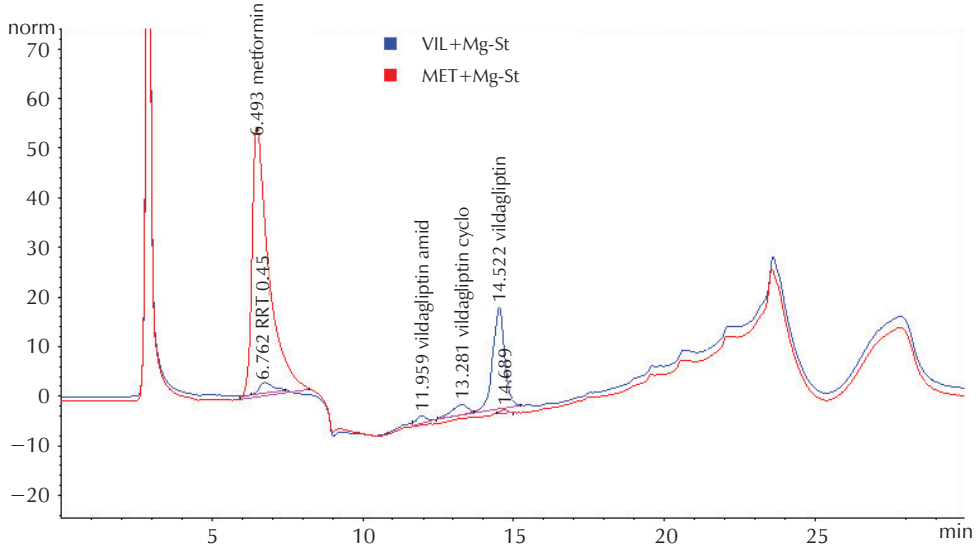

Fig. 7 – Overlay chromatograms of vildagliptin/metformin with magnesium stearate degraded with 3 % H_2O_2

Slika 7 – Prekloplјeni kromatogrami vildagliptina/metformina s Mg-St razgrađenim s 3 % H_2O_2

occurred (Fig. 6).[22] Vildagliptin Amid, Vildagliptin Cyclo and Vildagliptin Impurity B peaks were identified using standard substances.

3.6 Oxidative degradation of vildagliptin, metformin, and the vildagliptin/metformin combination

Metformin (76.10%, Table 4) showed slightly higher stability compared to vildagliptin (64.70 %, Table 3) under conditions of oxidative degradation with hydrogen peroxide (Fig. 7). The only excipient that increased metformin degradation was magnesium stearate (70.75 %, Table 4), while all other excipients had a stabilising effect on metformin degradation. Magnesium stearate in a formulation can induce an oxidation reaction.[23] The addition of vildagliptin to metformin and magnesium stearate increased the degradation of metformin (65.27 %), as shown in Table 4. An increase in degradation with the addition of vildagliptin of 13 % was observed only with povidone (69.95 %, Table 4). The povidone can contribute to the degradation of metformin under oxidative conditions. The explanation for the increase in degradation in the presence of povidone is that the amino group of metformin reacts with the carbon-

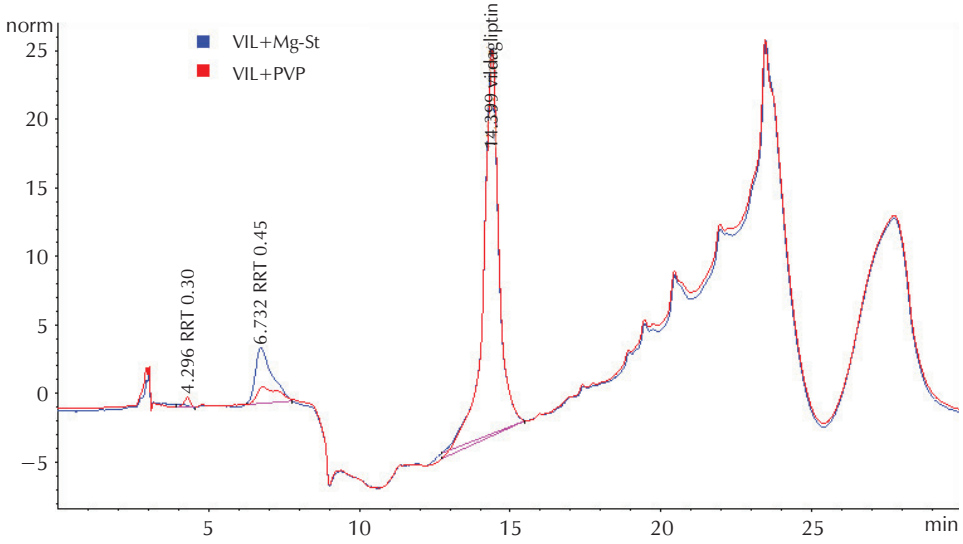

Fig. 8 – Overlay chromatograms of vildagliptin with magnesium stearate/povidone degraded at 80 °C

Slika 8 – Kromatogrami vildagliptina s magnezijevim stearatom i povidonom razgrađenim pri 80 °C

yl group of PVP, as well as the amino group of vildagliptin.[14] As with acidic degradation, the minimum content of vildagliptin after oxidative degradation was recorded with crospovidone (48.33 %), while with the addition of metformin, it increased by only 2.41 % (Table 3). In the case of other excipients, no significant difference was observed when only the vildagliptin excipient was added, and when metformin was also added, in relation to the degree of degradation of vildagliptin itself.

3.7 Thermal degradation of vildagliptin, metformin, and the vildagliptin/metformin combination

By thermal degradation of vildagliptin itself, the percentage of content after degradation was 73.15 %, while with the addition of certain excipients, this percentage increased to 95.98 % for talc, and 82.95 % for lactose. The addition of metformin increased the degradation of vildagliptin with magnesium stearate (48.38 %), while it stabilised it in lactose (86.87 %), as shown in Table 3. Contrary to the degradation of vildagliptin, with metformin (Table 4), the lowest degradation was recorded with magnesium stearate (93.85 %), and the highest with lactose (53.45 %). When metformin and vildagliptin were combined with individual excipients, magnesium stearate increased the degradation of both components, while lactose stabilised vildagliptin and talc metformin. As with acid and base hydrolysis, the chromatogram of vildagliptin with povidone elutes a peak at RRT 0.30, as with magnesium stearate at RRT 0.45 (Fig. 8).

4 Conclusion

The forced degradation studies of excipients with vildagliptin and metformin revealed alternative degradation pathways. Vildagliptin and metformin exhibit chemical interactions with povidone, resulting in the elution of an additional peak with a retention time of 4.4 min. In addition to povidone, vildagliptin also interacts chemically with magnesium stearate, producing a peak at a retention time of 6.7 min. Notably, *Janicki et al.* did not record the formation of additional degradation peaks resulting from interactions between excipients and the treated active substances.[4] This study confirms the chemical reactivity of povidone and magnesium stearate, aligning with previous findings by *Gumieniczek et al.*[5] Structural characterisation of the newly formed degradation products was not undertaken in this study and should be addressed in future research. The results, along with the possible reasons for degradation, evaluated in the discussion, confirmed the reactive groups mentioned in the introduction of this paper. Analysis of the recovery values for the monitored analytes allows for conclusions regarding the suitability of specific excipients from a stability perspective. For formulations containing vildagliptin alone, lactose is recommended, while magnesium stearate and povidone are not advised. For metformin formulations, microcrystalline cellulose is the preferred excipient, whereas povidone is not recommended due to its impurities that lead to oxidative degradation of metformin. Only in the case of povidone, the ANOVA test showed statistically significant differences for metformin, although povidone does not degrade vildagliptin. For for-

mulations combining vildagliptin and metformin, lactose is not recommended due to its significant degradation effect on vildagliptin, which could adversely impact the therapeutic efficacy of the formulation. The results indicate that metformin is more sensitive to moisture and vildagliptin is more susceptible to hydrolysis. An unresolved question remains regarding how lactose stabilises both metformin and vildagliptin in combination under conditions of base hydrolysis. When selecting excipients, it is essential to consider that metformin and vildagliptin are produced in the form of film-coated tablets, and that the film itself has a protective role, which additionally stabilises the active ingredients.

List of symbols and abbreviations
Popis simbola i kratica

API – active pharmaceutical ingredient
– aktivni farmaceutski sastojak

HPLC – high-performance liquid chromatography
– tekućinska kromatografija visoke učinkovitosti

PVP – povidone
– povidon

VIL – vildagliptin
– vildagliptin

MET – metformin
– metformin

MCC – microcrystalline cellulose
– mikrokristalna celuloza

LAC – lactose
– laktoza

Mg-St – magnesium stearate
– magnezijev stearat

PVPP – crospovidone
– krospovidon

TAL – talc
– talk

RRT – relative retention time
– relativno vrijeme zadržavanja

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SAŽETAK

Utjecaj kemijske prirode pomoćnih tvari na degradaciju metformina i vildagliptina

Amra Demirović,[a] *Alija Uzunović*[b] i *Anisa Veledar-Hamalukić*[a]

Utjecaj kemijske prirode pomoćnih tvari (magnezijev stearat, povidon, mikrikristalna celuloza, laktoza, krospovidon i talk) na razgradnju metformina i vildagliptina ispitan je prisilnom razgradnjom, uz primjenu kiselinske i bazne hidrolize, oksidacije i termalne razgradnje. Kvantifikacija sadržaja metformina i vildagliptina prije i nakon razgradnje rađena je HPLC metodom obrnutih faza. Primijenjena metoda pokazala je dobru selektivnost i specifičnost. Nije zabilježena interferencija nastala od pikova degradiranih ekscipijensa na pikove metformina i vildagliptina, kao ni interakcija ekscipijens-ekscipijens. Za vildagliptin s povidonom te s magnezijevim stearatom otkriven je alternativni put razgradnje, kao i kod metformina s povidonom. Pregledom rezultata dane su preporuke za poželjne i nepoželjne pomoćne tvari, pa je za sam vildagliptin poželjno dodati laktozu, a nije poželjno dodati povidon i magnezijev stearat. Za metformin se preporučuje mikrokristalna celuloza, dok je povidon potrebno izbjegavati zbog onečišćenja koja vode do oksidativne razgradnje metformina. U slučaju kombinacije metformina i vildagliptina ne treba upotrebljavati laktozu u formulaciji, jer povećava razgradnju aktivnih tvari. Iznimka je kod bazne hidrolize kad laktoza djeluje stabilizirajuće, apsorbirajući vlagu čime se smanjuje razgradnja metformina i vildagliptina.

Ključne riječi
Pomoćne tvari, razgradnja, metformin, vildagliptin, HPLC

[a] *Amsal Pharmaceuticals d. o. o. Sarajevo, Igmanska 38, 71 320 Vogošća, Bosna i Hercegovina*
[b] *Agencija za lijekove i medicinska sredstva Bosne i Hercegovine, Maršala Tita 9, 71 000 Sarajevo, Bosna i Hercegovina*

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