Scientific paper

Chemical Stability and Dissolution of Paracetamol Tablets Formulated by Direct Compression and Granulation Process

Nemanja B. Todorović[1], Darija B. Sazdanić[1], Bojana G. Mamužić[1], Mladena N. Lalić-Popović[1,2], Milica T. Atanacković Krstonošić[1] and Mira P. Mikulić[1,2]

[1] *University of Novi Sad, Faculty of Medicine, Department of Pharmacy, Hajduk Veljkova 3, Novi Sad, Serbia*

[2] *University of Novi Sad, Faculty of Medicine, Center for Medical and Pharmaceutical Investigations and Quality Control, Hajduk Veljkova 3, Novi Sad, Serbia*

* *Corresponding author: E-mail: nemanja.todorovic@mf.uns.ac.rs*

Received: 06-19-2025

Abstract

The chemical stability of active substances affects the safety and efficacy of the drug products. The aim of this study was to investigate the stability and dissolution of paracetamol tablets produced by wet granulation (GS, GP) and direct compression (K). The highest percentage of loss was observed during alkaline hydrolysis (between 10.41% and 16.06%). Acidic conditions caused the highest degradation in sample K (5.3%). Oxidative conditions lead to the highest degradation in two formulations (K, GP). The loss was below 5% after thermal and photolytic degradation for all samples, with the highest decrease found in pure paracetamol after thermal degradation (2.63%). The dissolution profiles best fit to Korsmeyer-Peppas model, with the slowest release observed in formulation K. The study of different formulations revealed a significant influence of formulation factors (producing method, presence of excipients) on the stability and dissolution of paracetamol.

Keywords: HPLC; dissolution profiles; diluent; binder; mcc; lactose

1. Introduction

Paracetamol, acetaminophen or *N*-(4-hydroxyphenyl)-acetamide is an active pharmaceutical ingredient (API) with analgesic, antipyretic, and weak anti-inflammatory properties.[1,2] It is commercially available without a prescription (over-the-counter, OTC) and is therefore often used for self-treatment of headaches, body aches, arthritis, toothaches, and fevers in various dosage forms.[3] Among analgesics (ATC group N02), paracetamol is the most widely used. Its consumption is higher in countries with well-developed pharmacotherapeutic practices, such as the Kingdom of Norway and the Republic of Finland.[4] The Food and Drug Administration (FDA) approved paracetamol for the first time in 1951[5], and it is now available in multiple forms, including tablets, syrups, injections, and rectal suppositories.[6] The World Health Organization (WHO) includes it in its list of essential medicines.[7]

The tablet is the most widely used oral solid dosage form among all available forms due to its ease of administration, low manufacturing cost, stability, and patient acceptability.[8] It is traditionally produced by compressing a powder mixture. This mixture consists of various excipients and one or more APIs. However, in most cases, either wet or dry granulation precedes the compression step to ensure the desired characteristics of the finished pharmaceutical product.[9]

The stability of a pharmaceutical preparation is defined as its ability to retain the same properties and characteristics it possessed when produced, within the prescribed limits, over time and when stored in specific conditions. FDA and The International Council for Harmonisation (ICH) guidelines prescribe stability testing to assess changes in the quality of the drug substance and the finished drug product over time under the influence of various environmental factors. Five types of stability are defined: physical, chemical, microbiological, toxicological, and therapeutic.[10] Under various stressful conditions such as moisture, heat, pH, storage, and transportation, drug mol-

ecules can undergo degradation due to chemical instability. The chemical stability of medicinal substances affects the safety and effectiveness of the medicinal product; any change in stability can lead to a dose reduction or make the dosage form toxic.[11] Understanding the stability of molecules is essential for selecting the appropriate formulation and packaging, as well as providing proper storage conditions and defining the product's shelf life.[12]

Stability studies of pharmaceutical products are considered a prerequisite for their registration and are conducted in accordance with the guidelines of ICH, WHO, and other regulatory bodies.[10] Drug stability can be determined through forced degradation studies, also known as stress studies.[11] Forced degradation is a technique in which various stress conditions (such as acid and base hydrolysis, oxidation, thermal degradation, and photodegradation) are applied to medicinal substances or products. These studies provide insight into the degradation pathways of the API and the finished drug product, which can be used to assess compatibility with excipients and supporting the early stages of drug development.[13] Additionally, a carefully designed and conducted forced degradation study will generate a suitable sample for the development and validation of the stability-indicating method (SIM). The goal of forced degradation is to achieve the desired degree of degradation, typically 5–20%.[12]

Testing the dissolution rate of an API from a dosage form is another important test that provides key data on medicine characteristics. To conduct the test, it is necessary to set up controlled *in vitro* conditions, under which API release occurs. Dissolution test is one of the most important tests during the development and quality control of medicines. The results contribute to drawing conclusions about the quality, stability and biopharmaceutical characteristics of pharmaceutical preparations. Additionally, by applying the dissolution rate test, it is possible to detect similarities and differences between pharmaceutical formulations. Due to the possibility to predict the pharmacokinetic profiles of drugs based on the dissolution rate, this test is increasingly used in biowaiver studies under strictly controlled conditions.[14]

The aim of this study was to examine and compare the stability and dissolution rate of paracetamol in immediate-release tablets preparedusing different production methods (direct compression of powder and compression of granulate obtained by wet granulation) and with different excipients, through forced degradation studies.

2. Experimental

2. 1. Material

The following substances and solvents were used: distilled water (Department of Pharmacy, Faculty of Medicine, Novi Sad, Serbia), 35% hydrochloric acid (HCl, Lach-Ner, Czech Republic), sodium hydroxide granules (NaOH, Lach-Ner, Czech Republic), 30% hydrogen peroxide (H_2O_2, Lach-Ner, Czech Republic), 85% ortho-phosphoric acid (H_3PO_4, Poch, Poland), acetonitrile (J.T. Baker, USA), and a paracetamol standard substance with purity greater than 99% (Sigma-Aldrich, USA). The following substances were used to prepare the tested formulations: paracetamol (Alfa Aesar, Germany), microcrystalline cellulose (MCC, VIVAPUR® 101, JRS Pharma, Germany), anhydrous lactose (Sigma-Aldrich, Germany), polyvinylpyrrolidone K30 (PVP K30, Carl Roth, Germany), sucrose (Carl Roth, Germany), starch (Carl Roth, Germany), talc (Centrohem, Serbia), magnesium stearate (Centrohem, Serbia), and colloidal silicon dioxide (Merck, Germany).

2. 2. Instruments

The following devices were used in the work: technical balance (Denver Instruments, USA), analytical balance (Kern, Germany), magnetic stirrer (Welp Scientifica, Italy), centrifuge 2-5 (Sigma, Germany), laboratory oven (UNB 400, Memmert, Germany), pH meter (InoLab, Germany), NU-8 KL UV lamp (Konrad Benda, Germany), vibratory sieve shaker (AS200 control, Retsch, Germany), powder mixer (Pharmalabor, Italy), eccentric tablet press (EK0, Korsch, Germany), and a high-performance liquid chromatograph (Agilent 1100 series, USA) equipped with

Table 1: Formulation composition of the tested tablets

Component	Functional category	Formulation		
		GS wet granulation	GP wet granulation	K direct compression
paracetamol	API	30 mg	30 mg	37.5 mg
MCC	diluent	–	–	ad 100%
lactose	diluent	ad 100%	ad 100%	–
sucrose	binder	2%	–	–
PVP K30	binder	–	2%	–
starch	disintegrant	7%	7%	7%
talc	antiadhesive	3%	3%	3%
magnesium stearate	lubricant	0.5%	0.5%	0.5%
silicon dioxide	glidant	0.5%	0.5%	0.5%

a binary pump, degasser, autosampler, and UV/Vis DAD detector.

2. 3. Tablet Formulation

Three different groups of immediate-release paracetamol tablets, produced at the Faculty of Medicine, University of Novi Sad were tested. Tablets from the groups labeled GS and GP were produced by compressing granules obtained by wet granulation. Tablets from group K were produced by direct compression of powder blend. The composition of the tested tablets is shown in Table 1.

Before weighing and after mixing the powders, all components were sifted through a 355 sieve using a vibratory sieve shaker. The powders and granulates were mixed on a powder mixer for 20 minutes at the maximum mixing intensity (130 rpm). For the GS and GP formulations, wet granulation of the powder mixture containing all components except magnesium stearate and half of the starch was performed. An aqueous binder solutions were added, and the mixtures were then sieved through a 2000 sieve, dried in a laboratory oven at 60 °C for 3 hours, and then sieved again through an 800 sieve. The remaining starch was added to the mixtures and mixed thoroughly. Immediately before tableting, magnesium stearate was added and briefly mixed.

Tableting was performed on an eccentric tablet press using 12-mm biconvex punches. The filling volume of the die (and consequently tablet mass) was defined by the position of the lower punch, while the position of the upper punch determined the final tablet mechanical properties. Resistance to crushing of tablets was determined using a hardness tester (Pharmalabor, Italy). Since the tablets demonstrated consistent resistance to crushing, this parameter was not expected to affect the dissolution profiles.

2. 4. Paracetamol Content Determination

For each tested formulation, a mass of tablet powder equivalent to the average tablet mass was measured and dissolved in 50 mL of distilled water. The solution was then diluted 1:1 with the same solvent. The resulting solutions were centrifuged for 10 minutes at 3500 rpm. The supernatants were filtered through a 0.45 μm membrane filter into vials for high-performance liquid chromatography (HPLC) analysis.

2. 5. Forced Degradation Study

The HPLC method was used to assess the extent of degradation of paracetamol in the prepared formulations and the standard substance, following acid and base hydrolysis, exposure to an oxidizing agent, and thermal and photolytic degradation. The percentage of paracetamol loss in samples exposed to stress conditions was calculated relative to the content in the control samples.

To perform acid and base hydrolysis, as well as oxidative degradation, solutions (samples) were prepared by pulverizing the tablets of each group into a fine powder. The mass of the tablet powder equivalent to the average tablet mass was measured, and the powder was then dissolved in distilled water with stirring on a magnetic stirrer. The resulting solution was quantitatively transferred into a standard 25 mL volumentric flask. After centrifugation at 3500 rpm for 10 minutes, the supernatants were used for further tests. For the standard substance, samples were prepared by dissolving an appropriate mass of paracetamol standard substance in distilled water to obtain solutions of equivalent concentration. To perform thermal (at 80 °C) and photolytic degradation (over 24 h), the tablet powder obtained after pulverizing the tablets was used (the average tablet mass was measured), as well as the equivalent mass of the paracetamol standard substance. The experimental stress conditions were achieved, and further analysis of the samples was performed as described in our previous work.[15]

2. 6. Dissolution Test

Dissolution testing of paracetamol from prepared tablets was performed on a dissolution tester (Erweka DT800, Germany). The paddle apparatus was used at a speed of 50 rpm and a temperature of 37 °C. The paddle speed of 50 rpm was chosen to maximize the influence of formulation factors on the dissolution profile, as well as in accordance with USP recommendations for fixed-dose combination tablets containing paracetamol and ibuprofen.[16] The test medium was 50 mM phosphate buffer pH 6.8 in a volume of 900 mL. Samples (5 mL) were withdrawn at 5, 15, 25, 35, 45 and 60 minute with replacement of fresh medium after each sampling. The samples were filtered through a 0.45 μm membrane filter (Sartorius Lab Instruments, Germany) and the concentration of paracetamol was determined using the HPLC method.

Statistical comparison of the dissolution profiles was performed by calculating the difference factor (f_1) and the similarity factor (f_2), as shown in Equations 1 and 2.

$$f_1 = \left[\frac{\sum_{t=1}^{n}|R_t - T_t|}{\sum_{t=1}^{n} R_t}\right] \times 100 \quad (1)$$

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t\right]^{-0.5} \times 100\right\} \quad (2)$$

where: n is the number of time points, R is the dissolution value of the reference, and T is the dissolution value of the test at time t.

According to established criteria, dissolution profiles are considered similar if the f_1 value is less than 15 and the f_2 value exceeds 50. Additionally, the dissolution data were fitted to selected mathematical models to evaluate the release kinetics: first-order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell, and Hopfenberg. Data analysis was per-

formed using DD Solver (Microsoft Excel add-in, Excel, 2016).

2. 7. HPLC Analysis

The content of paracetamol in tablet samples, as well as during the forced stability study, was determined using a previously validated and published HPLC method.[15] HPLC was performed on a Zorbax SB C18 reverse-phase column (4.6 × 150 mm, 5 µm) coupled with a Zorbax SB C18 guard column (12.5 × 4.6 mm, 5 µm). The elution was isocratic, with the mobile phase consisting of water acidified with phosphoric acid (pH 2) and acetonitrile in a 70:30 (v/v) ratio. The column temperature was maintained

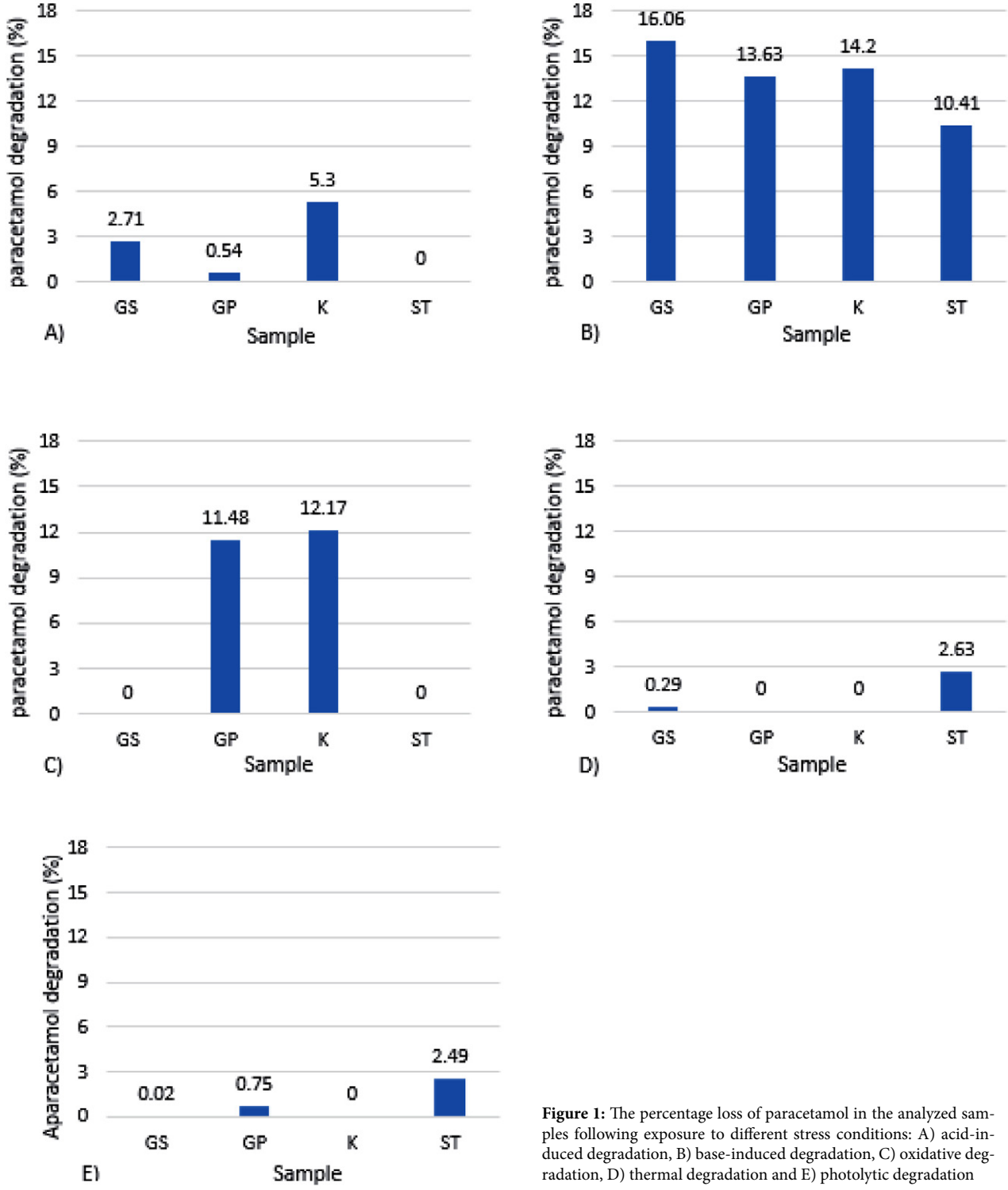

Figure 1: The percentage loss of paracetamol in the analyzed samples following exposure to different stress conditions: A) acid-induced degradation, B) base-induced degradation, C) oxidative degradation, D) thermal degradation and E) photolytic degradation

at 25 °C. The mobile phase flow rate was 1 mL/min, and the injection volume was 10 µL. Paracetamol detection was performed at a wavelength of 235 nm. All samples, including control and standard solutions, were filtered through 0.45 µm membrane filters (Agilent, USA) prior to analysis. Paracetamol was identified by comparing the retention times and UV spectra of the corresponding standard with the sample components. The external standard method was used for quantification. A series of standard solutions for the calibration curve was prepared by dissolving the paracetamol standard substance in distilled water and diluting to obtain a range of concentrations (10–300 µg/mL). The following calibration curve equation for paracetamol was obtained: $y = 33.2966x + 88.6291$ ($R^2 = 0.9996$).

3. Results and Discussion

The paracetamol content per average tablet mass was determined for each of the tested formulations. Tablets produced by direct compression (K) contained 7.52% paracetamol. In the formulations prepared by wet granulation, the paracetamol content was 5.75% in GS and 6.19% in GP.

To examine and compare the stability of paracetamol as the API in different immediate-release tablet formulations, forced degradation studies were conducted using acid, base, oxidizing agents, elevated temperature and exposure to UV light and daylight. The stress conditions to which the paracetamol formulations and the standard were subjected were selected based on established guidelines[17] and data from the literature. In our study, the deg-

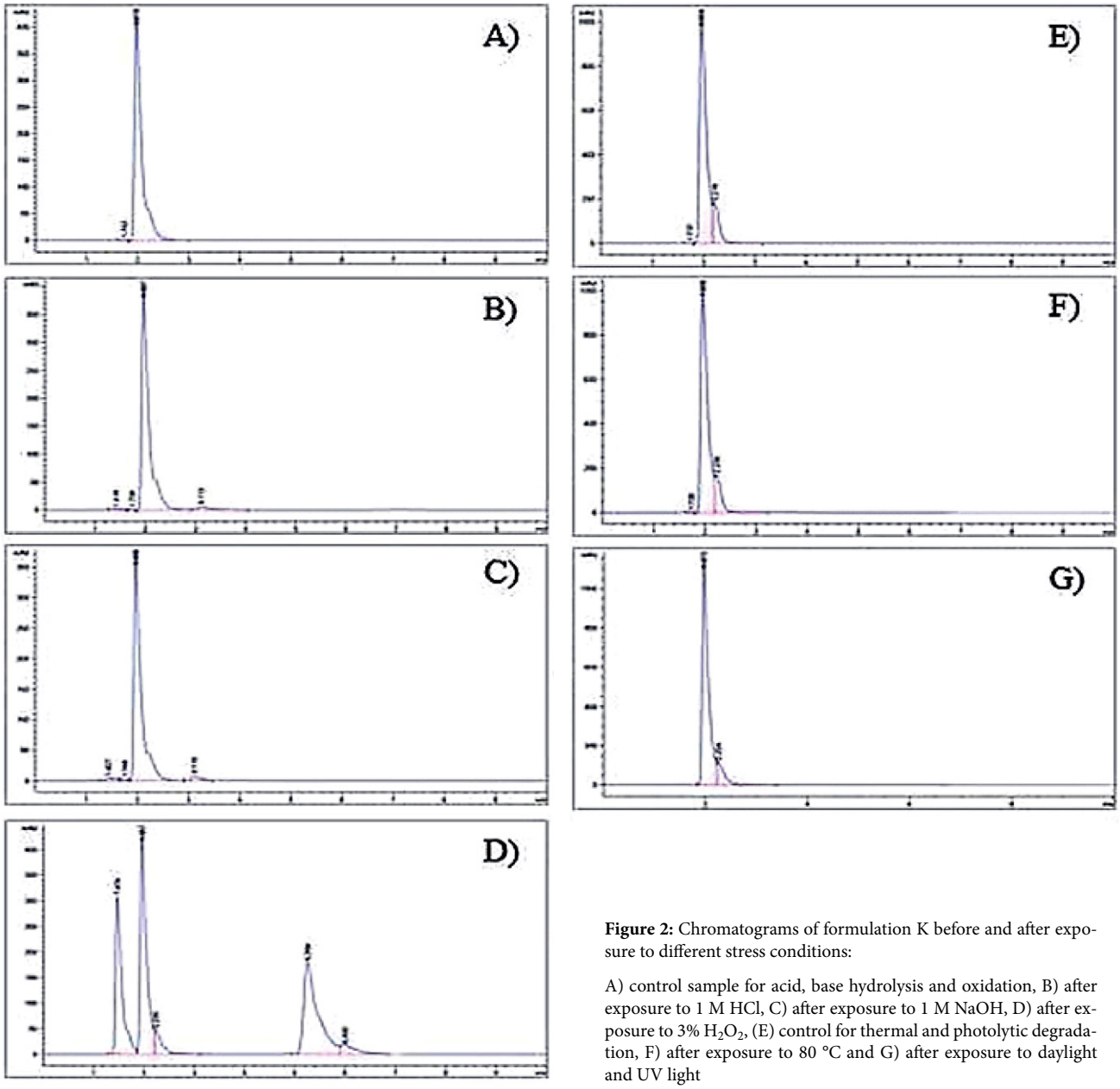

Figure 2: Chromatograms of formulation K before and after exposure to different stress conditions:

A) control sample for acid, base hydrolysis and oxidation, B) after exposure to 1 M HCl, C) after exposure to 1 M NaOH, D) after exposure to 3% H_2O_2, (E) control for thermal and photolytic degradation, F) after exposure to 80 °C and G) after exposure to daylight and UV light

radation of paracetamol did not exceed 20% after exposing the formulations and standards to any of the applied stress conditions, confirming the adequacy of the selected conditions.

Figure 1 present the percentage loss of paracetamol in the tested samples (formulations and standard) relative to their initial content in the control samples, following exposure to individual stress factors. Figure 2 shows chromatograms of control samples and samples exposed to stress conditions for the selected formulation K. Overall, it was observed that the retention time of paracetamol (1.97 ± 0.01 min) remained unchanged under the influence of stress conditions.

The highest percentage of paracetamol loss under the influence of 1 M HCl was observed in sample K, which consists of tablets produced by direct powder compression, amounting to 5.3%. Additionally, in the chromatogram of sample K after exposure to acidic conditions, an additional peak appeared compared to the control, with a retention time of 3.112 minutes (Figure 2B). Tablets formulated with PVP K30 (GP formulation) exhibited the lowest percentage of paracetamol degradation among the tested formulations. In contrast, no degradation was observed in the standard paracetamol substance following exposure to acidic conditions (Figure 1A). In a study conducted by Payghan et al., the highest degradation of the active ingredient was observed during acid hydrolysis (0.1 M HCl for 30 minutes) of paracetamol tablets.[18] Similarly, Kamble et al., who investigated the stability of commercial paracetamol and tramadol tablets, reported a 32.82% loss of paracetamol under acidic conditions (0.1 N HCl for 12 hours).[19] According to the literature, in both acidic and alkaline media, paracetamol undergoes hydrolysis, forming para-aminophenol as the primary product of chemical degradation.[20]

Overall, the highest degree of paracetamol degradation in all tested formulations, as well as in the standard substance, was observed under basic hydrolysis conditions. Following exposure to 1 M NaOH, paracetamol loss in the tablet formulations ranged from 13.63% to 16.06%. The highest degradation was observed in the GS formulation, consisting of tablets prepared by wet granulation and contained lactose (filler) and sucrose (binder) (Figure 1B). The standard paracetamol substance exhibited a lower percentage of degradation under basic conditions compared to the tablet formulations, amounting to 10.41%. In all tested samples (formulations and standard), an additional peak was observed on the chromatograms at a retention time of 3.12 ± 0.06 minutes, compared to the corresponding control samples. Figure 2C shows the chromatogram of sample K after exposure to basic conditions. Similar results have been reported in previous studies. Aminu et al. investigated commercial paracetamol and caffeine tablets and found that the highest degree of paracetamol degradation occurred in a basic environment (2 M NaOH) after 24 hours, with approximately 18% degradation.[2] A significant effect of the alkaline conditions on paracetamol degradation was also observed in the study by Jahan et al., where under the same conditions as in the present study, a paracetamol loss of 32.5% was recorded.[21]

As shown in Figure 1C, exposure to 3% H_2O_2 resulted in a paracetamol loss exceeding 10% in the GP and K formulations, whereas no degradation was observed in the GS formulation or the standard substance. Additional peaks were detected in the chromatograms of all formulations and the standard at retention times of 1.47 ± 0.001 min, 5.26 ± 0.02 min, and 5.99 ± 0.02 min. Figure 2D presents the chromatogram of sample K after exposure to the oxidizing agent. In previously published studies, a significant degradation of paracetamol (29.54%) was observed in all samples following exposure to 3% H_2O_2 for 1 hour.[22] Jahan et al. reported a substantial degradation of the paracetamol standard (53.4%) after exposure to 10% H_2O_2 for 24 hours.[21] Ahmad et al. noted a complete loss of paracetamol after exposing a solution of the paracetamol and caffeine standards to 30% H_2O_2 for 30 minutes.[3] In contrast, the results of our study indicate significant paracetamol loss during oxidation (3% H_2O_2 for 24 hours) only in formulation K (12.17%) and formulation GP (11.48%). These findings suggest that the use of a lower concentration of oxidizing agent is sufficient to achieve the desired degree of degradation of the active substance.

After exposure of the investigated formulations and the standard substance to elevated temperature (80 °C for 2 hours), the highest percentage of paracetamol loss was observed in the standard substance (2.63%). Among the prepared formulations, only the GS formulation, produced by wet granulation using sucrose as a binder, showed slight degradation of the active substance (0.29%), while no changes in paracetamol content were recorded in the other formulations (Figure 1D). Chromatograms of the formulations and the standard recorded at a wavelength of 235 nm revealed no additional peaks corresponding to degradation products following exposure to elevated temperature (Figure 2F).

After exposure of the prepared formulations and the standard substance to daylight and UV light for 24 hours, no degradation exceeding 5% was observed in any of the samples. In formulation K, no loss of the active substance was detected. The highest percentage of paracetamol degradation was recorded in the standard substance, amounting to 2.49% (Figure 1E). Chromatograms of both the formulations and the standard, recorded at a wavelength of 235 nm, showed no additional peaks after exposure to daylight and UV light (Figure 2G).

In a study by Kamble et al., the loss of paracetamol in commercial paracetamol and tramadol tablets due to thermal and photodegradation was found to be below 5% for all samples.[19] Similarly, in our study, exposure of formulations and standard samples to elevated temperature, daylight, and UV light did not result in the desired degradation levels (between 5 and 20%). The highest loss of

paracetamol under these stress conditions was observed in the standard, with a 2.63% degradation due to thermal exposure and a 2.49% loss due to photodegradation. The greater degradation of the standard compared to formulations containing excipients suggests that the excipients influence the chemical stability of paracetamol when exposed to elevated temperature and light. Kanthal et al. reported that elevated temperature has the minimalt effect on the degradation of paracetamol.[22] These findings align with the results of the present study, where exposure to a temperature of 80 °C for 2 hours led to the lowest average degradation of paracetamol. Additionally, no change in paracetamol content was observed in the GP and K formulations compared to the control sample.

When evaluating the stability of different tablet formulations, sample GS was identified as the most stable, i.e., paracetamol exhibited the lowest average degradation in tablets produced by compressing granules obtained through wet granulation with lactose as a filler and sucrose as a binder. The difference in degradation observed between the GS and GP formulations, both prepared by wet granulation, suggests that the choice of binding agent influences paracetamol stability. Specifically, the GS sample showed a higher percentage of paracetamol degradation (2.71%) compared to the GP sample (0.54%) following exposure to HCl. Compared to PVP K30, which was used as the binder in the GP formulation, sucrose is a more hygroscopic substance and is susceptible to hydrolysis under acidic conditions, which may adversely affect the stability of the active ingredient.[22] Formulation K, prepared by direct compression of powder with microcrystalline cellulose as a filler, demonstrated the lowest stability due to a high percentage of degradation observed during oxidation, as well as acid and base hydrolysis. According to literature data, microcrystalline cellulose, present in formulation K, is a highly hygroscopic substance and is incompatible with oxidizing agents.[23,24] In a study by Patel et al., the effect of different excipients on the stability of sodium levothyroxine pentahydrate tablets was investigated under storage conditions of 40 °C and 75% relative humidity for 3 and 6 months. In both time intervals, the highest loss of active ingredient was observed in the formulation containing microcrystalline cellulose.[25] Based on the obtained results, it can be concluded that both the choice of excipients and the tablet producinging method significantly influence the stability of the active pharmaceutical ingredient (API).

The novelty of this study lies in the systematic comparison of different tablet formulations under standardized stress conditions, varying in both excipient composition and production method. These findings contribute to a better understanding of excipient-API interactions and support more rational selection of formulation strategies to enhance the stability of immediate-release solid dosage forms. In general, the tested pharmaceutical formulations of paracetamol contributed to increased stability of the API under conditions of thermal and photolytic degradation compared to the pure substance. However, under acidic and basic hydrolysis, as well as oxidative stress, stability varied among formulations and was generally reduced in comparison to the pure paracetamol. Generally, tablets produced by wet granulation exhibited better stability compared to those prepared by direct compression, possibly due to improved distribution and binding of excipients, leading to reduced porosity and limited exposure of the API to external stressors, Furthermore, the higher degradation observed in formulation K under acidic, basic, and oxidative conditions can be attributed to the use of MCC, a hygroscopic excipient that could interact unfavorably with oxidizing agents and promote moisture uptake, potentially accelerating hydrolytic and oxidative degradation. The increased degradation of the formulation GP containing PVP K30 under basic and oxidative conditions may be attributed to the hygroscopic nature and solubilizing properties of PVP, which can enhance the exposure of the API to degrading agents. It has been shown that PVP forms the keto tautomer under acidic conditions, whereas under basic conditions, it exists predominantly in the enol tautomeric form. The presence of hydroxyl groups in the enol tautomer increases its reactivity and enables PVP to act dually as both a capping agent and a reducing agent.[26] Additionally, under oxidative stress, PVP may facilitate degradation by interacting with reactive species. In contrast, under acidic conditions, PVP exhibits better chemical stability and may even contribute to the protection of paracetamol by limiting its direct exposure to the acidic medium. The differences in sucrose hydrolysis under acidic and basic conditions are likely the reason for the greater instability of paracetamol under basic conditions in the GS formulation.

The choice of binder did not significantly influence the release of paracetamol from the GS and GP formulations. Based on the calculated difference f_1 (2.80) and similarity f_2 (77.24) factors, the dissolution profiles of the GS and GP formulations can be considered the same. However, the formulation K prepared by direct compression usingMCC as a diluent exhibited a statistically significantly slower release profile compared to the formulations GS

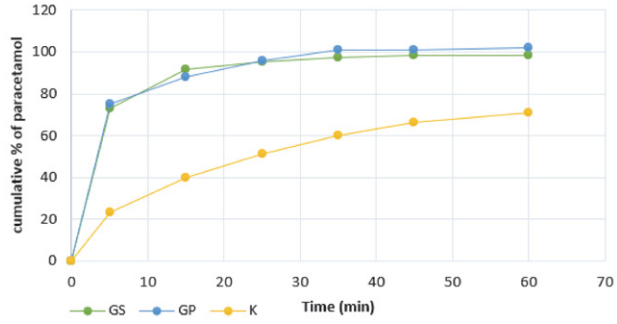

Figure 3: Dissolution profiles of paracetamol from tested tablet formulations

and GP prepared by wet granulation with lactose as a diluent. Values of f_1 were 43.73 and 44.57, and values of f_2 were 20.83 and 20.29. Dissolution profiles of tested formulations are presented in Figure 3. As shown in Table 2, all three formulations demonstrated the best fit to the Korsmeyer-Peppas model based on R^2 values. Korsmeyer-Peppas model parameters are shown in Table 3.

Table 2: Correlation coefficient (R^2) values for selected mathematical models

Model	GS	GP	K
First-order	0.9912	0.9844	0.9340
Higuchi	0.5852	0.6310	0.9902
Korsmeyer-Peppas	**0.9921**	**0.9971**	**0.9960**
Hixson-Crowell	0.7359	0.7499	0.8869
Hopfenberg	0.9912	0.9844	0.9339

Table 3: Korsmeyer-Peppas model parameters

Parameter	GS	GP	K
k_{KP}	64.2947	62.4808	12.3832
n	0.1132	0.1267	0.4355

Previously published studies have shown that the use the MCC as a diluent can slow down release rate of the API from tablets. Akin-Ajani et al. investigated the tabletability properties and the release rate of paracetamol from tablets prepared with binary mixtures of MCC and lactose. The release rate was strongly influenced by the mechanical characteristics, and it was demonstrated that the addition of MCC to lactose can result in a slower release.[27] Furthermore, Zhao et al. determined that disintegration, a property closely related to dissolution, in MCC containing tablets is influenced by several factors such as mechanical strength, microstructure, liquid absorption rate, and particle swelling.[28] In our study, all three formulations were prepared under the same working conditions, resulting in tablets with varying characteristics based on their composition. This further highlights the need to optimize the process parameters for tablet preparation with MCC in order to accelerate the release rate of paracetamol.

The release rate from all three tested formulations followed the Korsmeyer-Peppas model, considering R^2 value[29] similar to previously published study.[27] The diffusional exponents (n) were below 0.45, indicating Fickian diffusion as the drug release mechanism. Higher values of parameter n observed in formulation K compared to formulations GS and GP indicate a more complex paracetamol release process. The exponent n is used to differentiate the mechanisms of API release from the formulation. Generally, values below 0.45 indicate Fickian diffusion and are characteristic of non-swelling systems. Although all three formulations exhibited n values below 0.45, in formulation K the value was notably higher and close to the threshold associated with anomalous transport, which represents a mechanism intermediate between Fickian diffusion and case II transport (erosion-controlled release).[30]

4. Conclusion

The conducted forced degradation study revealed varying degrees of paracetamol degradation in the tested immediate-release tablets and the standard active substance under different stress factors, including acidic and basic hydrolysis, oxidation, thermal degradation, and photodegradation. The highest percentage of paracetamol loss was observed under basic conditions, while the effect of elevated temperature was generally the lowest. It was also demonstrated that the formulation, specifically the different tablet producing processes (direct compression of powder and compression of granules obtained by wet granulation), as well as the presence of different excipients (microcrystalline cellulose, lactose, sucrose, polyvinylpyrrolidone), significantly impact the stability of the active substance. The dissolution profile was influenced by the choice of diluent, i.e., the manufacturing process. Tablets containing lactose, prepared by granulation, showed faster release compared to tablets with MCC prepared by direct compression. The type of binder had no effect on the dissolution kinetics. In future studies, the evaluation of properties such as tablet hardness, friability, and disintegration will be included to further assess the performance and robustness of the developed formulations, particularly at higher paracetamol doses.

Acknowledgements

This research was supported by the Ministry of Science, Technological Development and Innovation of the Republic of Serbia (project 451-03-136/2025-03/200114).

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Povzetek

Kemijska stabilnost zdravilnih učinkovin vpliva na varnost in učinkovitost zdravila. Cilj tega dela je bil raziskati stabilnost in raztapljanje paracetamolskih tablet, proizvedenih z mokro granulacijo (GS, GP) in direktno kompresijo (K). Največji delež razpada je bil opažen med alkalno hidrolizo (med 10,41 % in 16,06 %). Kisli pogoji so povzročili največjo razgradnjo pri vzorcu K (5,3 %). Oksidativni pogoji so povzročili največjo razgradnjo pri dveh formulacijah (K, GP). Razpad je bil pod 5 % po toplotni in fotolitični razgradnji pri vseh vzorcih, pri čemer je bila največja izguba opažena pri čistem paracetamolu po toplotni razgradnji (2,63 %). Profili raztapljanja so najbolje ustrezali Korsmeyer-Peppasovemu modelu, pri čemer je bilo najpočasnejše sproščanje opaženo pri formulaciji K. Študija različnih formulacij je pokazala pomemben vpliv formulacijskih dejavnikov (način izdelave, prisotnost pomožnih snovi) na stabilnost in raztapljanje paracetamola.