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Research paper

Comparative Evaluation of Solubilization Strategies for an ABCG2 Transporter Inhibitor

Pálma Fehér[1], Kata Kárándi[1], Gergő Kis[1], Christelle Marminon[2], Marc Le Borgne[2] and Liza Józsa[1,*]

[1] Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Debrecen, 4002 Debrecen, Hungary
[2] Gastroenterology and Technologies for Health Team, Centre de Recherche en Cancérologie de Lyon (CRCL), Centre Léon Bérard, CNRS UMR 5286, INSERM U1052, Université Claude Bernard Lyon 1, Université de Lyon, 69008 Lyon, France
*Correspondence: jozsa.liza@pharm.unideb.hu

Abstract

Poor aqueous solubility remains a major challenge in the development of orally administered drugs, particularly for highly lipophilic molecules such as ABCG2 transporter inhibitors. These compounds typically exhibit high molecular weight, pronounced hydrophobicity, and limited water solubility, which restricts their dissolution and consequently their oral bioavailability. The present study aimed to enhance the solubility and dissolution behavior of a model ABCG2 inhibitor using different formulation strategies, including co-grinding with hydroxypropyl-β-cyclodextrin (HP-β-CD) or polyvinylpyrrolidone (PVP), and micellar solubilization with nonionic surfactants. The prepared systems were characterized in terms of drug content, equilibrium solubility, and dissolution performance under intestinal pH conditions (phosphate buffer, pH 6.8). Drug loading was determined by UV/VIS spectrophotometric analysis to verify formulation accuracy. Among the tested approaches, micellar solubilization provided the highest enhancement in apparent solubility and the most rapid and complete dissolution. HP-β-CD inclusion complexation resulted in a substantial improvement compared to the pure drug, whereas PVP-based co-grinding produced only a moderate effect. The results demonstrate that while simple solid-state modifications may offer limited benefit for highly lipophilic ABCG2 inhibitors, micellar systems represent a particularly effective strategy to overcome solubility limitations. These findings support the rational selection of formulation approaches to improve the oral delivery potential of poorly water-soluble transporter inhibitors.

1. Introduction

The ATP-binding cassette subfamily G member 2 (ABCG2), also referred to as the breast cancer resistance protein (BCRP), is an efflux transporter that plays a pivotal role in drug absorption, distribution, and elimination[1]. ABCG2 is highly expressed in barrier tissues such as the intestinal epithelium, liver, kidney, and blood–brain barrier, where it limits intracellular drug accumulation and contributes to multidrug resistance in cancer therapy[2]. Consequently, selective inhibition of ABCG2 has attracted increasing attention as a strategy to enhance the oral bioavailability of co-administered drugs and to overcome transporter-mediated drug resistance[3].

Despite their promising pharmacological potential, many ABCG2 inhibitors are characterized by high molecular weight and pronounced lipophilicity, resulting in poor aqueous solubility[4,5]. Low solubility often translates into insufficient dissolution in intestinal fluids, leading to erratic absorption and limited oral bioavailability[6–8]. These physicochemical limitations represent a major obstacle to the pharmaceutical development of ABCG2 inhibitors and necessitate the application of effective solubilization strategies.

Various formulation approaches have been developed to improve the solubility and dissolution behavior of poorly water-soluble drugs. Cyclodextrin-based inclusion complexation is a widely applied technique, as cyclodextrins can encapsulate hydrophobic drug molecules within their lipophilic cavity, thereby increasing apparent solubility and improving dissolution rates[9]. Hydroxypropyl-β-cyclodextrin (HP-β-CD) is particularly attractive due to its high aqueous solubility and favorable safety profile[10]. In addition, co-grinding with hydrophilic polymers such as polyvinylpyrrolidone (PVP) represents a simple and solvent-free method to enhance drug wettability and reduce crystallinity, often resulting in improved dissolution performance[11,12].

In parallel with solid-state approaches, colloidal delivery systems such as micellar formulations have gained importance for the solubilization of lipophilic compounds[13]. Nonionic surfactants, including Cremophor® EL and Tween® 80, are capable to form stable micelles in aqueous media, providing a hydrophobic core that can accommodate poorly soluble drugs. Micellar solubilization offers a straightforward and scalable strategy to increase apparent solubility without altering the chemical structure of the active compound[14,15].

The aim of the present study was to perform a comparative evaluation of different solubilization strategies for a model ABCG2 transporter inhibitor. Inclusion

complexation with HP-β-CD, co-grinding with HP-β-CD and PVP, and micellar solubilization using nonionic surfactants were systematically investigated. The formulations were assessed in terms of equilibrium solubility and dissolution behavior under intestinal pH conditions to identify the most effective and practically applicable approach for improving the aqueous solubility of this lipophilic ABCG2 inhibitor.

2. Materials and methods

2.1. Materials

The ABCG2 inhibitor used as a model compound (purity > 98%) was synthesized and provided by the CRCL research laboratory (Lyon, France)[5]. Hydroxypropyl-β-cyclodextrin (HP-β-CD; average degree of substitution 0.6) and polyvinylpyrrolidone (PVP) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Cremophor® EL (polyoxyl 35 castor oil) and Tween® 80 (polysorbate 80) were obtained from BASF (Ludwigshafen, Germany). All other chemicals and solvents were of analytical or pharmaceutical grade and used as received. Phosphate buffer (pH 6.8) was prepared according to the European Pharmacopoeia.

2.2. Preparation of Formulations

2.2.1 HP-β-CD Inclusion Complex

The inclusion complex of the ABCG2 inhibitor with HP-β-CD was prepared by the co-grinding method. The drug and HP-β-CD were accurately weighed in a 1:2 molar ratio and mixed in a porcelain mortar[9]. The mixture was ground manually with a pestle for 30 min to obtain a homogeneous powder. The resulting solid was passed through a 250 µm sieve and stored in a desiccator at room temperature until further analysis.

2.2.2 PVP Co-grinding Dispersion

Solid dispersions with PVP were prepared by co-grinding. The ABCG2 inhibitor and PVP were mixed in a 1:2 weight ratio and ground in a mortar for 30 min until a uniform powder was obtained. The samples were sieved (250 µm) and stored in airtight containers under dry conditions to prevent moisture uptake[16].

2.2.3 Micellar Formulation

Micellar formulations were prepared using nonionic surfactants. Cremophor® EL (5% w/v) and Tween® 80 (2% w/v) were dissolved in phosphate buffer (pH 6.8) under gentle magnetic stirring at room temperature. The ABCG2 inhibitor was added to the surfactant solution at a concentration of 10 mg per 5 mL, and the mixture was stirred at 37 °C for 30 min. The dispersion was then equilibrated for 24 h to allow complete solubilization. Before further experiments, the formulation was centrifuged at 10,000 rpm for 10 min to remove undissolved drug, and the supernatant was collected[17].

2.3. Solubility Studies

The apparent solubility of the ABCG2 inhibitor in the different formulations was determined in phosphate buffer (pH 6.8) at 37 ± 0.5 °C. An excess amount of each formulation, corresponding to approximately 10 mg of drug, was added to 5 mL of buffer in sealed centrifuge tubes. The samples were vortexed briefly and incubated in a shaking water bath at 100 rpm for 24 h to reach equilibrium. After incubation, the suspensions were centrifuged at 10,000 rpm for 10 min, and the supernatants were filtered through 0.45 µm PTFE syringe filters. The drug concentration in the filtrate was quantified by a spectrophotometer at 415 nm. All measurements were performed in triplicate.

The solubility enhancement factor (SEF) was calculated according to the following equation:

$$SEF = \frac{C_{\text{formulation}}}{C_{\text{pure drug}}}$$

where $C_{\text{formulation}}$ and $C_{\text{pure drug}}$ represent the equilibrium solubility of the drug in the formulated system and in its unprocessed form, respectively[18].*2.4. Dissolution Studies*

Dissolution testing was carried out using a USP type II (paddle) dissolution apparatus at 37 ± 0.5 °C and a paddle speed of 100 rpm. The dissolution medium consisted of 900 mL phosphate buffer (pH 6.8)[19]. Solid formulations (HP-β-CD inclusion complex and PVP co-grinding dispersion) equivalent to 10 mg of drug were directly added to the dissolution vessel. For micellar formulations, an appropriate volume containing 10 mg of dissolved drug was dispersed into the medium[20].

Samples (2 mL) were withdrawn at predetermined time points (5, 10, 20, 30, 60, 120, and 180 min) and immediately replaced with fresh dissolution medium to maintain sink conditions. The withdrawn samples were filtered through 0.45 µm syringe filters and analyzed by a UV/VIS spectrophotometer at 415nm to determine the cumulative amount of drug released[21].

2.5. Determination of Drug Loading and Entrapment Efficiency

Drug loading and entrapment efficiency were determined for all prepared formulations to verify formulation accuracy and consistency with the theoretical composition. The theoretical drug concentration of the micellar system was 2.0 mg/mL. For the solid co-ground systems, the theoretical drug concentration was calculated based on the drug-to-carrier ratio used during preparation.

In the case of the HP-β-CD inclusion complex (1:2 molar ratio), the calculated drug content in the final powder corresponded to approximately 28% (w/w), resulting in a theoretical drug concentration of 2.8 mg/mL when 10 mg of the co-ground powder was dispersed in 1 mL medium.

For the PVP co-ground system (1:2 w/w ratio), the drug represented 33.3% (w/w) of the final mixture, corresponding to a theoretical drug concentration of 3.3 mg/mL when 10 mg of powder was dispersed in 1 mL medium.

For the co-ground systems (HP-β-CD and PVP), an accurately weighed amount of the prepared powder corresponding to approximately 10 mg of the theoretical drug content was dissolved in an ethanol–water mixture under sonication to ensure complete drug extraction. The resulting solution was filtered through a 0.45 µm membrane filter and analyzed by a validated UV/VIS spectrophotometric method. Drug loading (%) was calculated as the ratio of the experimentally determined drug content to the theoretical drug content × 100.

For the micellar formulations, samples were centrifuged at 10,000 rpm for 5 min to separate any non-solubilized drug. The supernatant was carefully collected and analyzed by a spectrophotometer. Drug loading (%) was calculated relative to the initially added drug amount. Entrapment efficiency (%) was calculated as the amount

of drug detected in the supernatant divided by the total amount of drug used during preparation × 100. All measurements were performed in triplicate.

Drug loading (%) was calculated as:

$$\text{Drug loading (\%)} = \frac{\text{Measured drug amount}}{\text{Theoretical drug amount}} \times 100$$

Entrapment efficiency (%) was calculated as:

$$\text{Entrapment efficiency (\%)} = \frac{\text{Amount of drug in supernatant}}{\text{Total drug added}} \times 100$$

2.6. Analytical Method

Drug quantification was performed using UV/VIS spectrophotometry at 415nm. Calibration was carried out using an external standard method. A series of standard solutions of the ABCG2 inhibitor was prepared in the concentration range of 2–20 µg/mL, and a calibration curve was constructed by plotting absorbance versus concentration. The method showed good linearity within the investigated range, with a correlation coefficient (R^2) greater than 0.999.

To minimize potential interference from excipients (PVP, HP-β-CD, Cremophor® EL, and Tween® 80), blank samples containing the respective formulation components without the drug were analyzed under identical conditions. No significant absorbance was detected at 415nm for any excipient at the tested concentrations. All measurements were performed in triplicate, and appropriate dilution was applied to ensure that sample concentrations fell within the validated linear range of the method.

The analytical procedure was therefore considered suitable for accurate and reproducible quantification of the drug in the studied formulations.

2.7. Data Analysis

Data are expressed as mean ± standard deviation (SD) of three independent experiments (n=3). Statistical analysis was performed using one-way analysis of variance (ANOVA) to compare differences among the investigated formulations. When statistically significant differences were detected, Dunnett's post-hoc test was applied for multiple comparisons against the control group (pure drug). A p-value of < 0.05 was

considered statistically significant. Statistical calculations were performed using GraphPad Prism (version 10.6.1., GraphPad Software, USA)[7].

3. Results

3.1. Equilibrium Solubility

The equilibrium solubility of the ABCG2 inhibitor in phosphate buffer (pH 6.8) is summarized in **Table 1**. The pure drug exhibited very low aqueous solubility, confirming its poor dissolution characteristics under intestinal pH conditions.

The PVP co-grinding dispersion resulted in a limited solubility enhancement, increasing the apparent solubility from 0.018 ± 0.003 mg/mL for the pure drug to 0.042 ± 0.005 mg/mL, corresponding to a solubility enhancement factor (SEF) of 2.3.

A markedly higher solubility was achieved with the HP-β-CD inclusion complex. The apparent solubility increased to 0.128 ± 0.012 mg/mL, representing a 7.1-fold enhancement compared to the pure drug. This result indicates effective drug–cyclodextrin interaction and improved aqueous compatibility.

The micellar formulation showed the highest solubilization capacity among all tested systems. The equilibrium solubility reached 0.462 ± 0.031 mg/mL, corresponding to an SEF of 25.7. Statistical analysis confirmed significant differences between all formulations (one-way ANOVA, $p < 0.05$).

Formulation	Solubility (mg/mL)	SEF
Pure drug	0.018 ± 0.003	1.0
PVP co-grinding	0.042 ± 0.005 ***	2.3
HP-β-CD inclusion complex	0.128 ± 0.012 ****	7.1
Micellar formulation	0.462 ± 0.031 ****	25.7

Table 1. Equilibrium solubility and SEF of the ABCG2 inhibitor in phosphate buffer (pH 6.8, 37 °C).Values are expressed as mean ± SD (n=3). One-way ANOVA followed by Dunnett's test vs. pure drug was performed to evaluate the effects of the excipients. Statistically significant differences are indicated by *** ($p < 0.001$) and **** ($p < 0.0001$).

3.2. Dissolution Studies

The dissolution profiles of the ABCG2 inhibitor from the different formulations are presented in **Figure 1**. The pure drug showed minimal dissolution, reaching only 8.5 ± 1.2% cumulative release after 180 min. The PVP co-grinding dispersion exhibited a slightly improved dissolution rate, achieving 21.4 ± 2.8% drug release at 180 min. Although the initial dissolution was faster than that of the pure drug, the overall release remained limited. The HP-β-CD inclusion complex significantly improved dissolution behavior. Approximately 62.7 ± 4.1% of the drug was released within 60 min, reaching 78.9 ± 3.6% at 180 min. The enhanced dissolution rate reflects improved wettability and inclusion complex formation. The micellar formulation demonstrated the most rapid and extensive drug release. More than 85% of the drug was dissolved within the first 30 min, and near-complete release (96.3 ± 2.4%) was achieved by 60 min. The dissolution profile remained stable throughout the test period, with no evidence of drug precipitation.

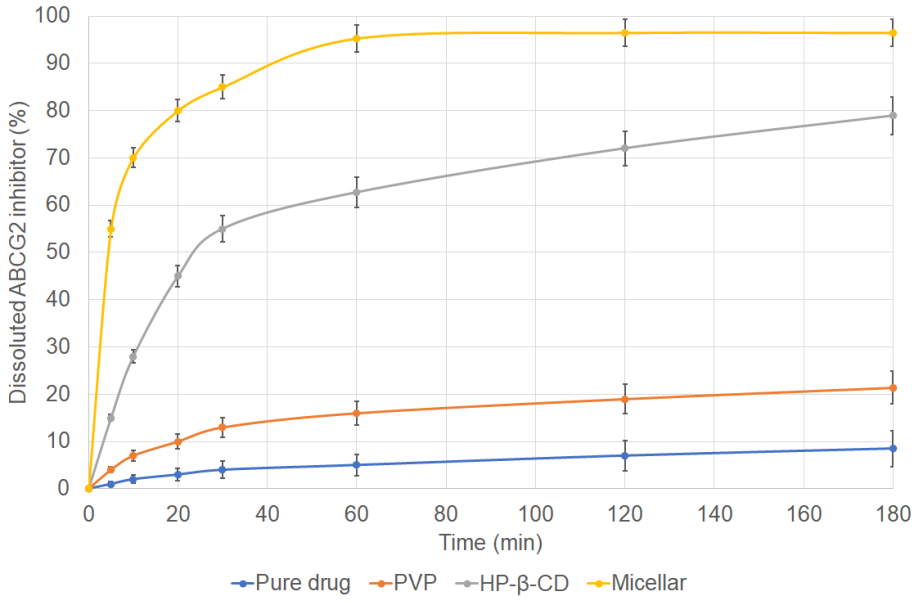

Figure 1. Dissolution profiles of the ABCG2 inhibitor from different formulations in phosphate buffer (pH 6.8, 37 °C, USP type II apparatus, 100 rpm). Data are presented as mean ± SD; n=3. One-way ANOVA followed by Dunnett's test vs. pure drug was performed to evaluate the effects of the excipients. Significant differences ($p < 0.001$) were found for all formulations.

3.3. Drug Loading and Entrapment Efficiency

The drug content analysis confirmed successful incorporation of the ABCG2 inhibitor in all investigated systems. For the PVP co-ground system (1:2 w/w ratio), the measured drug content was 31.2 ± 1.8% (w/w) compared to the theoretical 33.3%. This corresponded to a drug loading of 93.6 ± 5.4%. The slight deviation from the theoretical value may be attributed to minor processing losses during grinding and sieving. In the case of the HP-β-CD inclusion complex (1:2 molar ratio), the experimentally determined drug content was 26.5 ± 1.2% (w/w) compared to the theoretical ~28%. The calculated drug loading was 94.6 ± 4.3%, indicating efficient complex formation and minimal drug loss during preparation. The micellar formulation demonstrated the highest incorporation efficiency. Following centrifugation, the measured drug concentration in the supernatant was 1.92 ± 0.05 mg/mL, corresponding to 9.60 ± 0.25 mg of solubilized drug out of the 10 mg initially added. The calculated drug loading and entrapment efficiency were 96.0 ± 2.5%.

Overall, all systems exhibited high drug incorporation (>90%). However, the micellar system showed the highest drug loading and entrapment efficiency, followed by the HP-β-CD complex, while the PVP co-ground dispersion exhibited the lowest incorporation efficiency among the tested formulations.

Formulation	Drug Loading (%)	Entrapment Efficiency (%)
PVP co-ground (1:2 w/w)	93.6 ± 5.4	93.6 ± 5.4
HP-β-CD inclusion complex (1:2 molar)	94.6 ± 4.3	94.6 ± 4.3
Micellar formulation	96.0 ± 2.5	96.0 ± 2.5

Table 2. Drug loading and entrapment efficiency of the ABCG2 inhibitor formulations.

4. Discussion

The present study demonstrates that the solubility and dissolution behavior of a lipophilic ABCG2 transporter inhibitor can be markedly improved by appropriate formulation strategies, with substantial differences observed among the evaluated approaches.

Among the tested systems, PVP-based co-grinding provided the least pronounced enhancement. Although a modest increase in solubility and dissolution rate was observed compared to the pure drug, the overall improvement remained limited. This outcome suggests that the hydrophilic polymer alone was unable to sufficiently disrupt

the strong hydrophobic interactions and crystalline lattice of the drug. Partial recrystallization or insufficient molecular dispersion may have restricted the effectiveness of the PVP co-grinding approach[22].

In contrast, HP-β-CD inclusion complexation resulted in a significant improvement in both equilibrium solubility and dissolution performance. The 7-fold increase in solubility and the rapid dissolution observed within the first hour indicate effective host–guest interactions between the ABCG2 inhibitor and the cyclodextrin cavity. Cyclodextrin complexation enhances drug wettability and reduces interfacial energy, facilitating faster dissolution[23]. Nevertheless, the solubilization capacity of HP-β-CD was still limited compared to micellar systems, likely due to saturation of complexation sites at higher drug concentrations[23,24].

The micellar formulation demonstrated superior performance, achieving the highest solubility enhancement and the fastest, most complete dissolution. The pronounced effect can be attributed to the formation of stable micelles with a hydrophobic core that efficiently accommodates the lipophilic drug molecules[25]. Cremophor® EL is recognized as a powerful solubilizer, while Tween® 80 improves micellar stability and reduces interfacial tension, resulting in a synergistic solubilization effect. Importantly, the micellar system maintained the drug in a solubilized state throughout the dissolution test, preventing precipitation and ensuring consistent release.

The drug loading and entrapment efficiency of all prepared formulations were high, exceeding 90% in each case, confirming the reliability of the preparation methods. Among the solid-state systems, the HP-β-CD inclusion complex exhibited slightly higher drug loading (94.6 ± 4.3%) compared to the PVP co-ground dispersion (93.6 ± 5.4%), indicating more efficient incorporation of the ABCG2 inhibitor into the cyclodextrin cavity. The micellar formulation demonstrated the highest incorporation, with a drug loading and entrapment efficiency of 96.0 ± 2.5%, reflecting the effective solubilization of the lipophilic compound within the micelles. These results indicate that, although all methods maintained most of the initially added drug, the micellar system not only enhances solubility but also ensures maximal drug retention in the formulation. The slightly lower incorporation in the PVP system may be attributed to incomplete dispersion or minor losses during co-grinding and sieving, while the HP-β-CD system benefits from specific host–guest interactions that stabilize the drug within the complex. Overall, the drug loading and entrapment efficiency data corroborate the dissolution

results and further support the superior performance of the micellar system in delivering the ABCG2 inhibitor.

From a formulation development perspective, these findings highlight that while simple solid-state approaches such as PVP co-grinding may offer limited benefits, more advanced solubilization techniques are required for highly lipophilic ABCG2 inhibitors. Cyclodextrin complexation provides a balanced improvement with good safety and regulatory acceptance[26], whereas micellar systems offer the most effective solution when maximal solubility and rapid dissolution are desired.

In addition to the quantitative solubility data, the structural characteristics of the investigated systems help to explain the observed differences in performance. In the PVP co-ground system, the improvement is likely related to partial amorphization and improved wettability of the drug.. However, the absence of strong specific interactions may allow partial recrystallization, limiting the overall enhancement[16]. In contrast, HP-β-CD forms host–guest inclusion complexes in which the hydrophobic moiety of the drug is partially accommodated within the cyclodextrin cavity, leading to improved apparent solubility and dissolution rate[26]. The micellar system operates via a different structural mechanism. The nonionic surfactants self-assemble into nanosized micelles with a hydrophobic core that efficiently solubilizes lipophilic drug molecules. This colloidal encapsulation not only enhances solubility but also maintains the drug in a solubilized state during dissolution, thereby preventing precipitation. These structural differences provide a mechanistic explanation for the superior performance of the micellar formulation compared to the solid-state approaches[15].

From a biopharmaceutical perspective, the observed increases in apparent solubility may have important implications for oral absorption. For highly lipophilic compounds such as ABCG2 inhibitors, dissolution is often the rate-limiting step in gastrointestinal uptake[5,21]. The substantially higher dissolved concentrations achieved with the micellar system suggest a potential improvement in the concentration gradient across the intestinal membrane, which may translate into enhanced bioavailability[15]. Furthermore, the ability of micelles to maintain the drug in a solubilized state reduces the risk of precipitation upon dilution in gastrointestinal fluids, a common challenge for supersaturated systems[25]. In contrast, the more moderate solubility enhancement observed with HP-β-CD and especially PVP systems may still provide benefit but could be more susceptible to precipitation under dynamic in vivo conditions. Although *in vivo*

studies are required to confirm these assumptions, the present findings indicate that micellar solubilization represents a particularly promising strategy for overcoming dissolution-limited absorption of lipophilic ABCG2 inhibitors.

Overall, the results clearly indicate that micellar solubilization is the most promising strategy for enhancing the aqueous solubility and dissolution of the investigated ABCG2 inhibitor, followed by HP-β-CD inclusion complexation, while PVP co-grinding was the least effective approach.

5. Conclusion

This study systematically compared different formulation strategies to overcome the poor aqueous solubility of a lipophilic ABCG2 transporter inhibitor. The results clearly demonstrate that the choice of solubilization approach has a decisive impact on both equilibrium solubility and dissolution performance. Among the investigated systems, PVP-based co-grinding provided only limited improvement, indicating that simple polymer-assisted solid dispersions are insufficient for highly lipophilic compounds. HP-β-CD inclusion complexation resulted in a substantial enhancement of solubility and dissolution, confirming the effectiveness of cyclodextrin-based host–guest interactions, although its capacity remained constrained at higher drug loadings. In contrast, micellar formulations based on nonionic surfactants exhibited the highest solubilization efficiency and the most rapid and complete dissolution, maintaining the drug in a solubilized state throughout the test conditions. Overall, these findings identify micellar solubilization as the most promising strategy for improving the oral delivery potential of ABCG2 inhibitors, while cyclodextrin complexation represents a viable alternative when balanced performance and regulatory familiarity are desired.

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Data Availability Statement:

The data that support the findings of this study are available from the corresponding author (jozsa.liza@pharm.unideb.hu) with the permission of the head of the department, upon reasonable request.

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