

Article

Design and Characterization of Ceritinib Eutectic Solvent Systems for Pharmaceutical Formulation

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Abstract

One of the main challenges facing the pharmaceutical industry today is the low solubility of active pharmaceutical ingredients (APIs), which leads to low bioavailability, reduced therapeutic efficacy, and the need for higher drug doses. Eutectic solvents (ES) offer a promising solution by effectively dissolving APIs, creating API-ES systems that can significantly improve drug solubility and delivery. In this study, three distinct ESs were prepared by combining various components, with their successful formation confirmed through Fourier Transform Infrared Spectroscopy. Key physicochemical properties, including the density, viscosity, and pH of the prepared solvents, were subsequently determined. Ceritinib (CRT), an API utilized in the treatment of non-small cell lung cancer, was then incorporated into the prepared ESs to yield the API-ES systems. A comparative analysis was conducted to assess the release profiles of pure CRT versus CRT within the API-ES systems. Furthermore, the permeability and diffusion coefficient of the drug within these systems were also determined. The results conclusively demonstrated that the formation of the API-ES system increased the solubility of CRT in water. This achievement represents a vital initial step toward optimizing the delivery of this drug and highlights the significant potential for developing a novel, improved pharmaceutical formulation.

Keywords: API-ES; ceritinib; drug delivery; permeability

1. Introduction

The modern pharmaceutical industry faces many challenges. In addition to problems related to production, availability of raw materials and environmental regulations, one of the leading problems is the development of new drugs. The development process is expensive and complex and can last from 10 to 15 years, with no guarantee that the drug will pass all the clinical testing phases and enter production [1]. Namely, due to various problems, many drugs do not pass the clinical testing phases, which causes significant financial losses to the pharmaceutical industry. Therefore, instead of developing new drugs, the pharmaceutical industry strives to improve existing ones. One of the biggest problems in drug formulation is the solubility of the active pharmaceutical ingredient (API) in water, because it affects the body's ability to absorb the drug. A large number of approved drugs and drugs under development have poor solubility in water [1–3]. Due to their ability to dissolve the API without changing its chemical properties, deep eutectic solvents (DES) and eutectic solvents (ES) have attracted significant attention as a potential



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solution for improving drug delivery [4]. They are a relatively new class of solvents and represent a viable alternative to traditional organic solvents used in the synthesis of APIs in the pharmaceutical industry. DESs and ES can be defined as mixtures of components that have a melting point lower than the melting point of the individual components of which they are composed [5,6]. Although classical DES refers to a fixed molar ratio that yields the lowest melting point, drug dissolution systems often use a broader range of ratios in which the system remains liquid at room temperature. Even if the ratio is not at the eutectic point, interactions between the components are still present [4,5]. These solvents are generally considered to be environmentally friendly, among other things, because they are biodegradable, non-toxic, cheap and easy to prepare [7]. They can be prepared from raw materials from natural sources, and no secondary products are formed during their preparation. However, for such solvents to be safe for use, their toxicity and biodegradability need to be tested. In some cases, a synergistic effect may occur, which could result in DESs being more toxic than their individual components [7,8]. Besides their non-toxicity, these solvents are non-flammable, stable liquids over a wide temperature range, and are chemically tailorable, allowing them to be used in the production of new, stable formulations in the pharmaceutical industry [6,9]. The preparation of DES with an API as a hydrogen bond donor (HBD) or hydrogen bond acceptor (HBA) creates a therapeutic deep eutectic solvent (THEDES). The possibility of preparing such solvents has been tested on a number of APIs, including ibuprofen [10–13], ketoprofen [13], diclofenac diethylamine [14], celecoxib [15], lidocaine [13,16,17], acetylsalicylic acid [18,19], benzoic acid [19], phenylacetic acid [19], pifrenidone [20], methotrexate [21], metronidazole [22], ranitidine [23] and fosamprenavir calcium [24]. DESs that contain an API as a dissolved component in a previously prepared solvent are called API-DES systems [25], and these types of formulations have been used for improving drug delivery of several APIs such as piroxicam [26,27], aprepitant [26], indomethacin [26], clavulanic acid [28], naproxen [27], doxorubicin [29], acetylsalicylic acid [30], celecoxib [27], ibuprofen [31], and ketoprofen [30].

Unlike conventional solvents, DES and ES systems form an intricate hydrogen-bonding network that creates a synergistic effect, significantly enhancing the solubility of poorly water-soluble APIs. These types of structures provide superior thermodynamic stability, preventing rapid drug precipitation upon dilution in physiological fluids, which is a common limitation of organic solvents. This not only optimizes the chemical environment for the API but also facilitates improved membrane permeability, as the DES and ES components can act as functional permeation enhancers, ultimately leading to higher bioavailability compared to pure acidic or organic media [3,32,33]. Furthermore, the tunability of ESs through adjustment of molar ratios enables precise control of viscosity and polarity. Because ES systems allow for greater variation in molar composition compared to strictly defined DESs, they offer possibilities for tailoring API properties. Although terminology in this field is still evolving, the growing body of research underscores the significance of these systems in pharmaceutical development [34–36].

This study investigated the possibility of improving the solubility and permeability of ceritinib (CRT) by using different ESs as a medium for dissolving CRT. CRT is a BCS class IV drug, an anaplastic lymphoma kinase (ALK) inhibitor used in the treatment of ALK-positive metastatic non-small cell lung cancer, and offers the possibility of treatment for patients who have shown resistance to crizotinib [37]. Class IV drugs are the least suitable for oral administration because they are difficult to dissolve in digestive juices, and even the portion that does dissolve has difficulty passing through the intestinal wall into the bloodstream. By changing the formulation, the goal is to increase the drug concentration at the absorption site, which directly increases its effectiveness. Additionally, to achieve a therapeutic effect, class IV drugs often must be given in very high doses, which places

an unnecessary burden on the liver and digestive system [38,39]. Three different ESs were prepared, which were obtained by mixing lactic acid with various non-toxic components in certain molar ratios. Their physicochemical characteristics and toxicity to the bacterium *Vibrio fischeri* were determined. By adding CRT to the prepared ESs, API-ES systems were obtained. Improved solubility and permeability were established for the selected API-ES system compared to pure powdered CRT.

2. Materials and Methods

All chemicals used for the preparation of ESs (Table 1) were vacuum-dried at 60 °C for 8 h. CRT dihydrochloride was purchased from Hui Chem Co., Ltd. (Shanghai, China). CRT form A used for the preparation of API-ES was produced through a combination of cooling crystallization and pH adjustment [40].

Table 1. List of chemicals.

Chemical	Abbreviation	Manufacturer	CAS Number
DL-Lactic Acid, 90%	LA	VWR Chemicals (Radnor, PA, USA)	50-21-5
D-Fructose, p.a.	Fru	Lach-Ner (Neratovice, Czechia)	57-48-7
Glycerol anhydrous, p.a.	Gly	Lach-Ner (Neratovice, Czechia)	56-81-5
Glycine, p.a.	Gne	Carlo Erba Reagents (Milan, Italy)	56-40-6

2.1. ES Preparation and Characterization

Three ESs were prepared by weighing previously dried components in specified molar ratios, mixing them on a magnetic mixer at 300 rpm, and heating to 70 °C until a homogeneous liquid formed. The prepared solvents and their corresponding molar ratios are shown in Table 2. Due to its high viscosity and density, deionized water was added to Gly-Fru-LA 2:1:2 to facilitate further work. After preparation, the ESs were stored at room temperature and have remained stable liquids over time.

Table 2. Prepared ESs.

ES	Molar Ratio
Gly-Fru-LA-W	2:1:2:3.4
Gly-LA	1:3
Gne-LA	1:9

Fru—fructose, Gly—glycerol, Gne—Glycine, LA—lactic acid, W—water.

The prepared ESs were characterized by measuring their density, viscosity and pH value at a temperature of 37 °C. Density was measured using a digital Mettler Toledo 30PX densitometer (Greifensee, Switzerland). Measurements were repeated three times for each solvent and the mean density value was calculated. The viscosity of the solvents was determined on a Brookfield DV-111 ULTRA viscometer (Toronto, ON, Canada), using a concentric SC4-21 spindle. pH values of 0.5 M solutions of each ES were determined using a WTW InoLab pH/Cond 740 device (Xylem Analytics, Weilheim, Germany) and a Sentix 91 pH electrode (Xylem Analytics, Weilheim, Germany).

2.2. Ecotoxicity Testing

The ecotoxicity of the prepared ESs was evaluated using the Gram-negative, rod-shaped bacterium *Vibrio fischeri*. The aerobic ecotoxicity assessment was carried out in

accordance with the standard HRN/EN ISO 11348-3:2007, Water quality—Determination of the inhibitory effect of water samples on the light emission of *Vibrio fischeri* [41]. The method is based on the evaluating the reduction in the physiological activity of a pure culture of the bacterium *Vibrio fischeri* in the presence of toxic substances, i.e., the ES sample. Luminescence intensity was measured at the start of the test and after 30 min for both the control and each prepared dilution. The test was performed using a Lumistox 300 luminometer (Hach Lange, Loveland, CO, USA) in combination with a Lumistherm (Hach Lange, Loveland, CO, USA) thermostated incubation block. The instrument provides two results: EC₂₀ and EC₅₀, which represent the volume fraction (%) of the sample causing a 20% and 50% reduction in luminescence, respectively. After the test, the inhibition was calculated according to the equation:

$$INH = \frac{Lu_{\text{control}} - Lu_{\text{sample}}}{Lu_{\text{control}}} \quad (1)$$

where *INH* is the inhibition (%), *Lu*_{control} is the bioluminescence intensity of the control sample after 30 min, and *Lu*_{sample} is the bioluminescence intensity of the sample after 30 min.

2.3. API-ES and Capsule Preparation

Certain amounts of CRT were added to the previously prepared ESs and mixed on a magnetic mixer at 300 rpm and 25 °C until the CRT dissolved. To conduct the dissolution test of pure CRT and prepared API-ES systems, capsules were filled with 150 mg of CRT and equivalent weights of API-ES systems containing 150 mg of CRT, which corresponds to one commercial dose.

2.4. FTIR Analysis of ES and API-ES

The formation of hydrogen bonds between the components (formation of ES), as well as the solubilization of API in ES, was confirmed by FTIR analysis using a Bruker Vertex 70 ATR-FTIR device (Billerica, MA, USA) at a resolution of 4 cm^{−1} and a spectral range of 400 to 4000 cm^{−1} with 32 scans. Data were collected using OPUS (version 7.2.139.1294), and MestReNova (version 6.0.2-5475) was used for processing and plotting the spectra.

2.5. Nuclear Magnetic Resonance Spectroscopy

Nuclear magnetic resonance (¹H NMR) spectroscopy analyses of CRT, ES and API-ES systems were performed on a Bruker Avance 600 device (Billerica, MA, USA). The analyses were performed at room temperature using deuterated chloroform, with tetramethylsilane as the internal standard. For the ¹H NMR experiments, data were collected with 128 scans and a recycle delay of 10 s, maintaining a spectral width of 12 019 Hz and an FID resolution of 0.55 Hz.

2.6. Dissolution Test

The release profile of CRT over time was monitored from capsules containing the Gne-LA 1:9-CRT, Gly-Fru-LA-W 2:1:2:3:4-CRT and Gly-LA 1:3-CRT API-ES systems and pure powdered CRT. The in vitro experiments were conducted under controlled laboratory conditions, following FDA guidelines [42] using the USP Apparatus II. The medium used was 900 mL of 0.01 M HCl solution, pH 2, and the temperature was maintained at 37 ± 0.5 °C. In order to ensure thorough mixing, a paddle impeller (Zhengzhou Nanbei Instruments, Zhengzhou, China) with a speed of 60 rpm was used. The samples were taken at predetermined time intervals and analyzed using a UV-1280 UV/VIS spectrophotometer (Shimadzu, Kyoto, Japan) at a wavelength of 265.8 nm to determine the amount of CRT

in all samples. For the preparation of the calibration curve, a $100 \text{ mg} \cdot \text{L}^{-1}$ CRT solution in 0.01 M hydrochloric acid was prepared, diluted, and the absorbance of these dilutions was measured at the same wavelength. The concentration of released CRT was calculated using the calibration curve equation:

$$\text{absorbance} = 0.0356 \cdot c [\text{mg} \cdot \text{L}^{-1}] (R^2 = 0.9996) \quad (2)$$

The percentage of released CRT and the release profile from the prepared capsules was determined using the without volume correction tab in the Excel add-in DDSolver.

2.7. Determination of API-ES Solubility, Permeability and Diffusion Coefficients

The solubility of the prepared API-ES systems in water at 37°C was determined by dissolving a mass of API-ES that met the high solubility criterion in 100 mL of water. The permeability test through a semipermeable membrane was carried out with Franz glass diffusion cells on the RYJ 68 device (Xiangtan Xiangyi Instrument Ltd., Xiangtan, China). The measurements were carried out in a setup consisting of three Franz diffusion cells with two chambers, at a temperature of 37°C and a mixing rate of 300 rpm . In each cell, a 0.01 M HCl solution filled both the donor and acceptor compartments, which were separated by a membrane containing a weighed amount of the sample. Pure CRT is added to one cell, API-ES to the second cell and 0.01 M HCl solution to the third cell, which is used to replenish the first two cells after sampling. For sampling, $200 \mu\text{L}$ is taken from the acceptor cell over 8 h and $200 \mu\text{L}$ of the HCl solution is returned to the cell to keep the total volume in the cell constant. The samples were diluted to 5 mL in flasks and analyzed using a UV/VIS spectrophotometer (Shimadzu, Kyoto, Japan) at a wavelength of 265.8 nm .

The permeability coefficient, P for both API and API-ES was determined using the following equation:

$$-\ln\left(1 - \frac{2C_t}{C_0}\right) = \frac{2A}{V} \cdot P \cdot t \quad (3)$$

where C_t represents the concentration in the receptor compartment at time t , C_0 is the initial concentration in the donor compartment, V denotes the total volume of both compartments, and A is the effective permeation area. The permeability coefficient, P was derived from the slope of the curve plotted as $-\frac{V}{2A} \cdot \ln\left(1 - \frac{2C_t}{C_0}\right)$ versus time.

Furthermore, the diffusion coefficient, D of API and API-ES across the membrane was calculated based on Fick's Law of diffusion, utilizing the following equation:

$$D = \frac{V_1 \cdot V_2}{V_1 + V_2} \cdot \frac{h}{A} \cdot \frac{1}{t} \ln\left(\frac{C_f - C_i}{C_f - C_t}\right) \quad (4)$$

In Equation (4), D is the diffusion coefficient. C_i and C_f represent the initial and final (equilibrium) concentrations, respectively, while C_t is the concentration at time t in the receptor compartment. V_1 and V_2 are the liquid volumes of the donor and receptor compartments, respectively. The membrane's thickness is denoted by h , and A is the effective diffusion area of the membrane [43,44].

3. Results and Discussion

3.1. ES Preparation and Characterization

Since the application of ESs largely depends on their physicochemical properties, the prepared solvents were characterized by determining the density, acidity and viscosity at 37°C (Table 3). The measurements were performed at 37°C due to the potential application of the resulting API-ES in the pharmaceutical industry, and release and permeability tests that are also performed at that temperature. Lactic acid was used as HBD in the prepared

ESs. It functions not only as a solvent but also as an active participant that, through hydrogen bonding and polarity tuning, extracts API molecules from their solid lattice and maintains their stability in the solution. The molar ratios in ES were selected by the stability of the liquid phase (Gne-LA) and the physical properties of the eutectic mixtures. For the Gly-Fru-LA and Gly-LA systems, particular emphasis was placed on viscosity, as excessive values represent a technical barrier to the successful incorporation of the API into the system.

Table 3. Measured pH values, density, ρ , and viscosity, η , at a temperature of 37 °C.

ES	ρ , g·cm ^{−3}	η , Pa·s	pH
Gly-Fru-LA-W 2:1:2:3.4	1.285	0.1586	2.61
Gly-LA 1:3	1.214	0.0508	2.09
Gne-LA 1:9	1.226	0.0719	2.45

The densities of the prepared ESs are higher than the density of water, ranging from 1.214 to 1.285 g·cm^{−3}. The lowest density is that of the Gly-LA 1:3 solvent, while the highest density is found in the system Gly-Fru-LA-W 2:1:2:3.4, due to the presence of fructose. Fructose, with its large number of hydroxyl groups, facilitates the formation of a greater number of hydrogen bonds within the liquid. This reduces the available free space in the ES structure, increasing its density and leading to stronger intermolecular forces, resulting in the highest viscosity among all prepared ESs, regardless of the addition of water. Water was added to this ES, without which it would not be possible to dissolve CRT due to its high density and viscosity. The addition of a small amount of water (around 10 wt.%) did not cause the hydrogen bonds to break, as previous research [45,46] has determined that hydrogen bonds in ES are stable up to the addition of 50 wt.% water.

The viscosities of the prepared solvents vary significantly depending on the components used for preparation, their ratio, and the portion of added water. The viscosities of ES range from 0.0508 Pa·s to 0.1586 Pa·s, with the least viscous solvent being Gly-LA 1:3. Table 3 shows that the pH values of all 0.5 M aqueous ES solutions are very acidic, in the range from 2.09 to 2.61. The highest acidity is found in Gly-LA 1:3 due to the high portion of lactic acid containing -COOH functional groups, which increases the acidity of ES. The least acidic solvent is Gly-Fru-LA-W 2:1:2:3.4, which contains glycerol and fructose. The higher pH value of this solvent resulted from its HBD components being polyols, which have lower acidity compared to organic acids [47].

3.2. Ecotoxicity Test and Selection of ES for Further Work

The ecotoxicity testing of prepared ESs was conducted to assess their potential environmental impact using the bioluminescent bacterium *Vibrio fischeri*. ES Gly-LA 1:3 was the most acidic formulation, while the remaining two ESs, Gly-Fru-LA-W 2:1:2:3.4 and Gne-LA 1:9 represent the least acidic systems, with the latter containing an amino acid, which may influence biological interactions. The aim of this testing was to preliminarily evaluate the ecological safety of the prepared ESs by measuring their inhibitory effects on bacterial luminescence, a widely used indicator of acute aquatic toxicity. The test results include the percentage of luminescence inhibition, as well as EC₂₀ and EC₅₀ values, which are presented in Table 4.

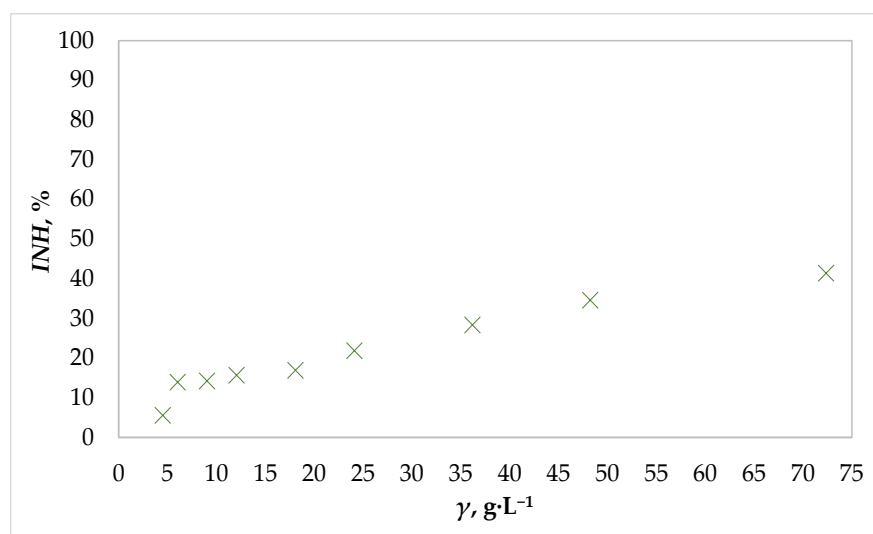
Table 4. Inhibitions of the tested ESs and obtained EC₂₀ and EC₅₀ values.

ES	INH, %	EC ₂₀ , g·L ⁻¹	EC ₅₀ , g·L ⁻¹
Gly-Fru-LA-W 2:1:2:3.4	31.06	12.65	/ *
Gly-LA 1:3	29.05	23.98	/ *
Gne-LA 1:9	0	/ *	/ *

* the value cannot be estimated because the inhibition of the initial solution is lower than 20 or 50%.

The values obtained for Gly-LA 1:3 and Gly-Fru-LA-W 2:1:2:3.4 indicate a low level of luminescence inhibition in *Vibrio fischeri*, with estimated EC₂₀ values of 23.98 g·L⁻¹ and 12.65 g·L⁻¹, respectively. The test results further revealed that Gne-LA 1:9 exhibited a negative inhibition, suggesting that it acts as a potential nutrient source, providing carbon and energy to *Vibrio fischeri*, and can therefore be considered non-toxic. Since none of the tested ES samples caused inhibition greater than 50% under the tested conditions, EC₅₀ values could not be determined. According to standard classification criteria, a substance is considered toxic if its EC₅₀ is below a defined threshold, typically <10 mg·L⁻¹ (0.01 g·L⁻¹) for acute aquatic toxicity [48]. Given that EC₅₀ values were not reached and the measured EC₂₀ values were significantly higher than this threshold, all tested ESs can be classified as non-toxic to *Vibrio fischeri* under the applied test conditions.

Figure 1 illustrates the concentration-dependent inhibitory effect for the ES Gly-Fru-LA-W 2:1:2:3.4, showing a gradual increase in inhibition with rising concentration of the test substance, consistent with dose–response behavior. These findings align with previous studies indicating that many natural component-based ESs exhibit low or negligible ecotoxicity, particularly those formulated with amino acids, sugars, organic acids, and polyols [49,50]. According to the literature [50,51] choline chloride-based ESs with glycerol or urea showed minimal inhibition towards aquatic microorganisms. Furthermore, Halder et al. [52] emphasized that the toxicity of ESs is highly dependent on the nature of the HBD, with organic acids generally being more toxic than polyols or amino acids. Complementary to this finding, it has also been observed that an increased number of HBDs tends to reduce the overall toxic potential of ESs. In this context, the low inhibition observed for Gne-LA 1:9 containing an amino acid as the HBD aligns with literature reports that associate amino acid-based ESs with improved biocompatibility and reduced ecotoxicity.

**Figure 1.** The concentration-dependent inhibitory effect for the ES Gly-Fru-LA-W 2:1:2:3.4.

Taken together, the results of this study support the conclusion that the prepared ESs, particularly those containing amino acids or sugar-based components, exhibit low environmental impact and represent promising candidates for further application in green and sustainable technologies, provided their toxicity remains low across broader biological test systems and environmental matrices.

3.3. Preparation of API-ES

After conducting the ecotoxicity tests, CRT was gradually added to a weighed amount of prepared ES to obtain API-ES systems. These API-ES systems, containing 15 wt.%, remained stable for over six months, as evidenced by micrographs recorded 3 months after preparation (Figure 2). Adding a higher percentage of CRT to ES led to precipitation of CRT. Figure 2 shows micrographs of the prepared Gne-LA 1:9-CRT API-ES system with (a) 15 wt.% CRT, and (b) with 18 wt.% CRT. With the addition of 18 wt.% CRT, crystallization occurred after a certain time at room temperature, forming a paste, as visible in the micrograph (Figure 2b). As the system with 15 wt.% remained stable for a longer period, it was decided that, for further preparation of the API-ES systems, a maximum CRT content of 15 wt.% would be used. This concentration was also sufficient to load a single capsule with an API-ES system quantity that delivers 150 mg of CRT, matching one dose of the commercial dosage form.

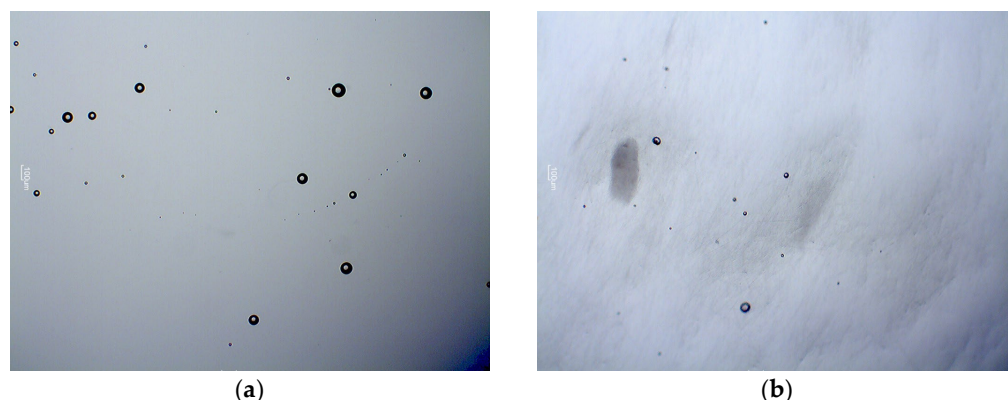


Figure 2. Micrographs of prepared Gne-LA API-ES systems containing (a) 15 or (b) 18 wt.% of CRT at a 40× magnification (recorded 3 months after preparation).

3.4. FTIR and ^1H NMR Characterization of ES and API-ES

The preparation of three ESs by combining lactic acid with fructose, glycerol and/or glycine was confirmed using FTIR analysis (Figures 3–5). Characteristic changes were observed in the FTIR spectra of the ESs, indicating the formation of hydrogen bonds and a stable ES structure. In ESs containing both glycerol and lactic acid (Figures 3 and 4), a shift in the band corresponding to O-H stretching and a visible broadening and lowering of the peak at $3600\text{--}3000\text{ cm}^{-1}$ were observed (marked with blue rectangular). The carbonyl group signal of lactic acid at 1722 cm^{-1} remains present in all prepared ESs, but the intensity and width of the bands in the -OH stretching region change. This indicates the formation of a strong hydrogen-bond network between glycerol, fructose, and lactic acid. [53]. In the C-O stretching and O-H bending region (below 1500 cm^{-1}), almost all peaks of the individual components were slightly shifted, broadened and/or changed in intensity in ESs. This confirms that a stable structure has formed [54,55].

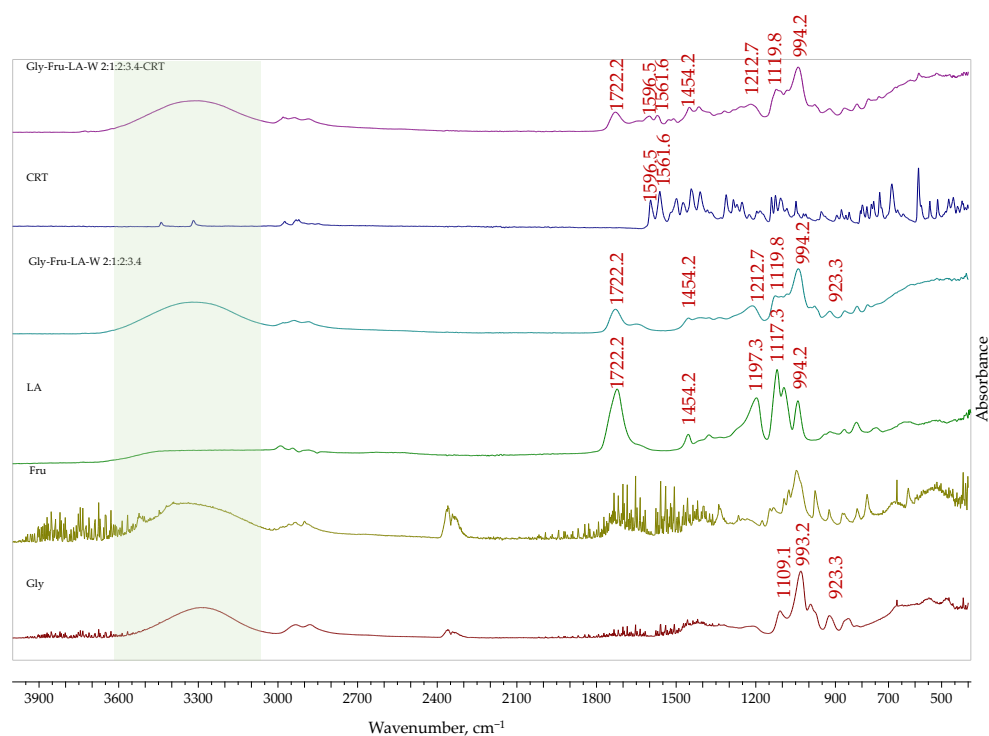


Figure 3. FTIR spectra of Gly, Fru, LA, Gly-Fru-LA-W 2:1:2:3:4, CRT and Gly-Fru-LA-W 2:1:2:3:4-CRT.

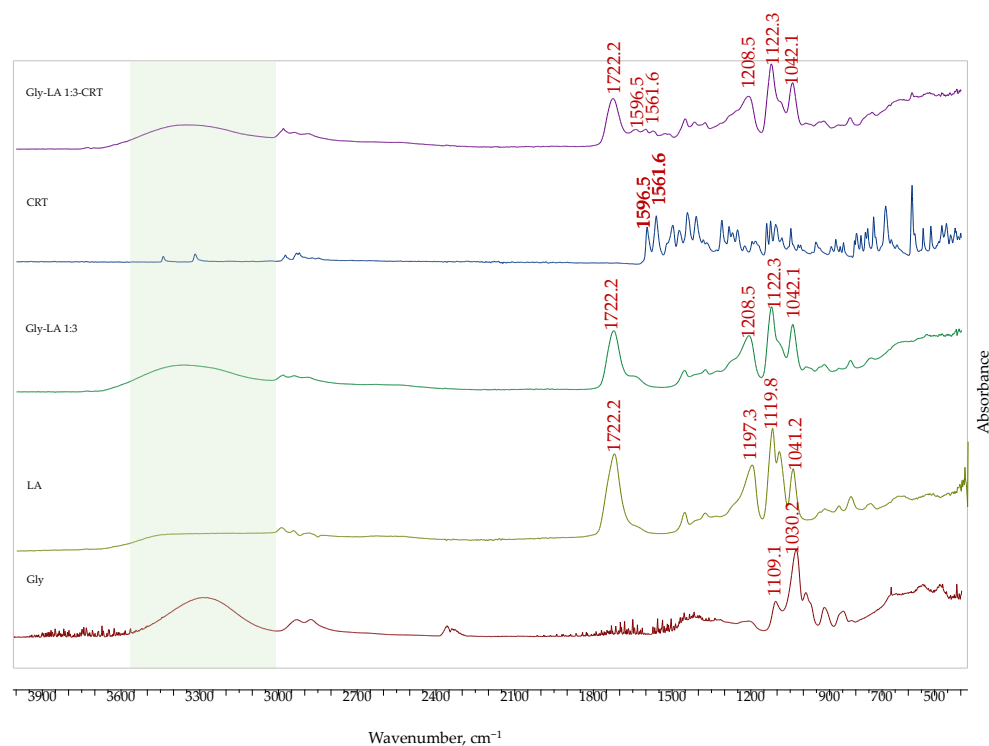


Figure 4. FTIR spectra of Gly, LA, Gly-LA 1:3, CRT and Gly-LA 1:3-CRT.

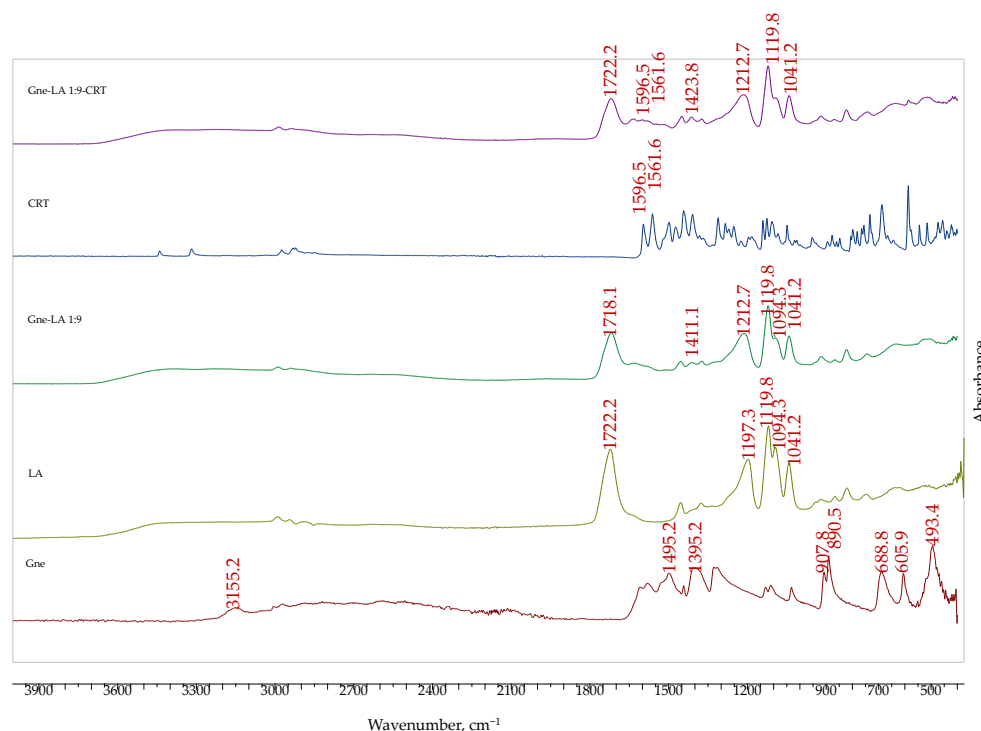


Figure 5. FTIR spectra of Gne, LA, Gne-LA 1:9, CRT and Gne-LA 1:9-CRT.

In the Gne-LA ES (Figure 5), a reorganization of the glycine and lactic acid molecules was observed, as evidenced by changes in the vibrational peaks. Proton transfer from the lactic acid to the amino group of glycine was confirmed, as evidenced by the disappearance/weakening of the glycine peaks at 3155.2 and 1495.2 cm^{-1} . In addition, the reduction in the intensity of the peaks of glycine at 907.8, 890.5, 688.8, 605.9 and 493.4 cm^{-1} in the ES confirms that glycine is no longer in its pure, crystalline state, but is actively involved in the coordination and interactive network of the ES.

FTIR analysis was performed on all prepared API-ES systems to confirm that adding CRT resulted in dissolution and the formation of new hydrogen bonds, rather than a chemical reaction. The resulting spectra are presented in Figures 3–5. The figures compare the spectra of pure components, ES, CRT and the spectrum of the resulting API-ES. In all the attached FTIR spectra of API-ES, changes are minor compared to pure ES. Due to the low concentration of CRT, the peaks are faint and overlap with the ES peaks in the range from 1600 to 1200. Low-intensity peaks are visible at 1596.5 cm^{-1} and 1561.6 cm^{-1} [56]. To confirm the dissolution of API in all prepared ESs, the ^1H NMR spectra of pure CRT, the prepared solvents, and API-ES were obtained (Figures S1–S3). In the spectrum of pure CRT, sharp signals from aromatic protons characteristic of the CRT structure appear in the 7.0 to 8.5 ppm range, while the aliphatic region (1.0 to 4.5 ppm) shows multiplets corresponding to protons of isopropyl groups and other saturated segments of the molecule. The spectra of the solvents are much simpler and are dominated by signals characteristic of the individual solvent components. Figures S1–S3, which compare the spectra in the API-ES system, show that 15 wt.% of CRT was successfully incorporated into the ES liquid. The CRT signals in the range of 7.0–8.5 ppm remain present, confirming that the API is chemically stable and dissolved in the ES. Small shifts in the CRT signal are noticeable compared to the pure substance. These shifts indicate the formation of intermolecular hydrogen bonds between CRT and the ES components.

3.5. Dissolution Test

After FTIR and ^1H NMR analyses confirmed that no chemical reaction occurred upon the addition of CRT to the prepared ESs, dissolution tests were performed on both pure CRT and the obtained API-ES systems to determine if there would be an improvement in CRT release from these formulations. The resulting release profiles (Figure 6a–d) indicate that while the overall shape of the release curves remained consistent, the CRT release from API-ES systems is higher than that of pure powdered API. The Gne-LA 1:9-CRT system achieved the highest release of CRT compared to the powdered drug with an increase of approximately 8%. Specifically, the CRT powder reached about 85–86% dissolution within 15–20 min (Figure 6a), whereas the Gne-LA 1:9 formulation demonstrated faster dissolution, releasing around 94–95% of the drug within the first 5 min (Figure 6c). This enhancement in the release rate may be the result of the difference in physicochemical properties of the liquid API-ES system versus the powdered API, including the acidity of the API-ES. Despite the desirable increase, the extremely rapid release profile observed with this cytostatic drug formulation is not optimal due to concerns about potential peak toxicity [57]. A suitable formulation (incorporation in biopolymers) for API-ES would probably change the release profile and improve its application [1,58].

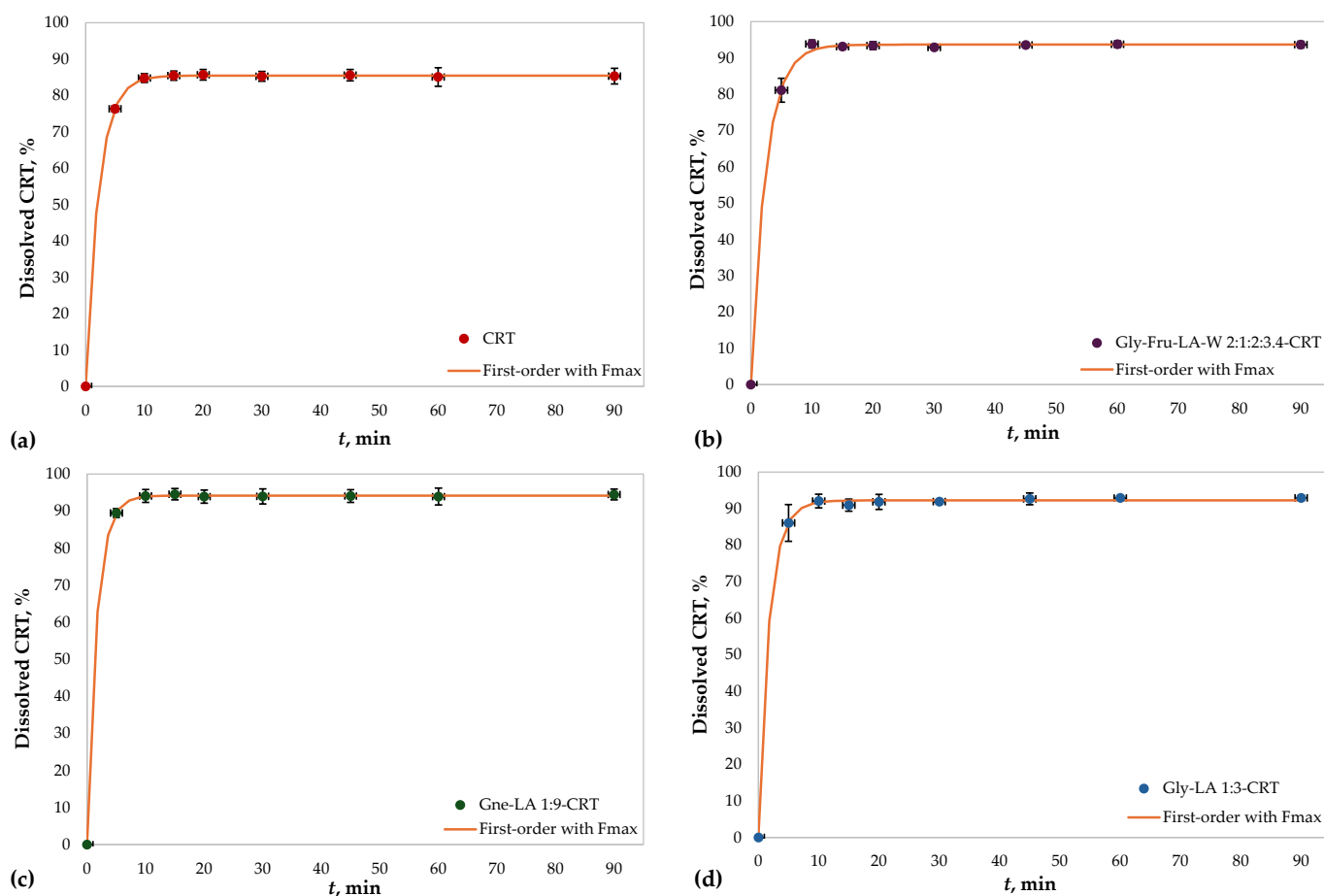


Figure 6. The dissolution profiles of (a) pure CRT, (b) Gly-Fru-LA-W 2:1:2:3.4-CRT, (c) Gne-LA 1:9-CRT and (d) Gly-LA 1:3-CRT with the selected mathematical model.

The obtained release profiles were mathematically described using DDSolver by the First-order with $F_{\max}$ (Equation (5)) model, whose parameters, SD, RSD and adjusted determination coefficient, R^2_{adj} values are shown in Table 5.

$$F = F_{\max} \cdot \left[1 - e^{(-k_1 \cdot t)} \right] \quad (5)$$

Table 5. Parameters, SD, RSD and R^2_{adj} values for the First-order with F_{max} model, Equation (5).

CRT ($R^2_{adj} = 0.9996$)				Gly-Fru-LA-CRT ($R^2_{adj} = 0.9992$)			
	Mean	SD	RSD, %		Mean	SD	RSD, %
k_1	0.452	0.039	8.540	k_1	0.413	0.048	11.584
F_{max}	85.444	1.672	1.957	F_{max}	93.647	0.475	0.507
Gne-LA-CRT ($R^2_{adj} = 0.9997$)				Gly-LA-CRT ($R^2_{adj} = 0.9982$)			
	Mean	SD	RSD, %		Mean	SD	RSD, %
k_1	0.620	0.114	18.391	k_1	0.587	0.161	27.340
F_{max}	94.191	1.742	1.849	F_{max}	92.246	0.687	0.745

The First-order with F_{max} model was designed to describe drug release kinetics where the release follows first-order kinetics and does not result in total release, but rather in a maximum release value (F_{max}). It is especially useful when experimental data demonstrate that some of the API is not released, such as due to low solubility [59]. The First-order with F_{max} model provided a particularly good fit for all tested samples, with the R^2_{adj} values above 0.99 (Table 5). In addition, the presence of a plateau in the dissolution profiles indicates that the F_{max} value has been reached (Figure 6a–d), which further supports the suitability of this model. Based on its favorable ecotoxicity results, good stability, and highest recorded CRT release, the Gne-LA 1:9-CRT system was chosen for further investigation.

3.6. Determination of Permeability and Diffusion Coefficients

Permeability testing was performed for pure powdered CRT and the selected API-ES system Gne-LA 1:9-CRT containing an equivalent amount of CRT. The concentrations used in these tests ($1950 \text{ mg} \cdot \text{L}^{-1}$ in both cells) were higher than those in the dissolution test, as they were determined by the amount of the API-ES system needed to uniformly cover the entire surface of the semipermeable membrane. Figure 7 shows the dissolution profiles in the Franz diffusion cell, expressed as the fraction of dissolved CRT over time. The profiles exhibit an initial linear dependence, followed by a decrease in the dissolution rate in both cases. When comparing the dissolution rates of pure powder and API-ES, it is visible that CRT from the API-ES system dissolves significantly faster and to a greater extent, while the powdered form shows clear solubility limitations. A significant increase in CRT solubility from the API-ES system is observed, with a maximum of approximately 60%, compared to less than 20% for the powdered CRT.

The permeability coefficient was calculated from the slope of the linear part of the release profiles (Figure 8), in which the concentration changes significantly and the process takes place at steady state. The API-ES system showed a significantly higher concentration of released substance than pure CRT, indicating that ES greatly enhances API permeation. This is supported by the permeability coefficient (Table 6) values of $5.59 \times 10^{-7} \text{ cm} \cdot \text{s}^{-1}$ for powdered CRT and $29.10 \times 10^{-7} \text{ cm} \cdot \text{s}^{-1}$ for the Gne-LA 1:9-CRT system. This multi-fold increase is likely due to the acidity of the ES and the formulation's effect on mass transfer. Notably, while permeability increased sharply, the diffusion coefficients remained similar for both systems (Table 6). This suggests that the structural interactions within the API-ES complex do not significantly affect the mobility of the API within the membrane; instead, the improvement results from the much higher equilibrium concentration in the donor chamber compared to the nearly insoluble pure CRT.

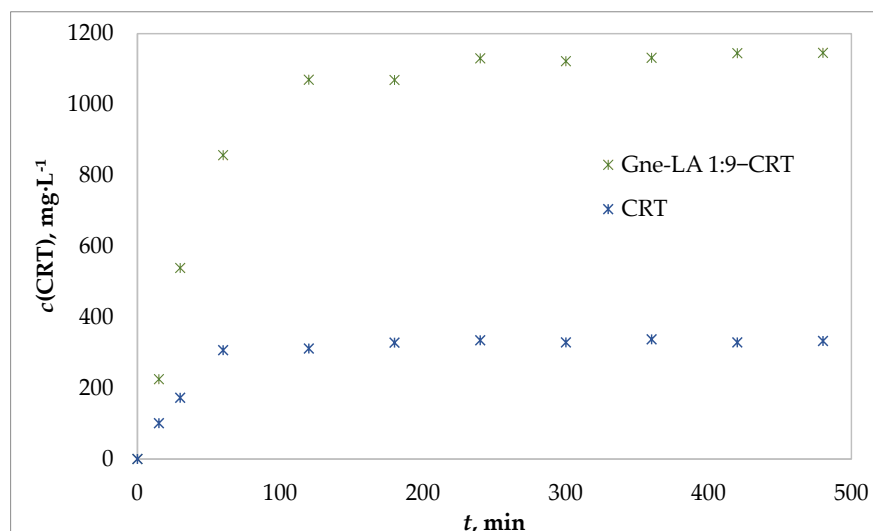


Figure 7. Change in concentration of CRT in the acceptor part of the Franz cell.

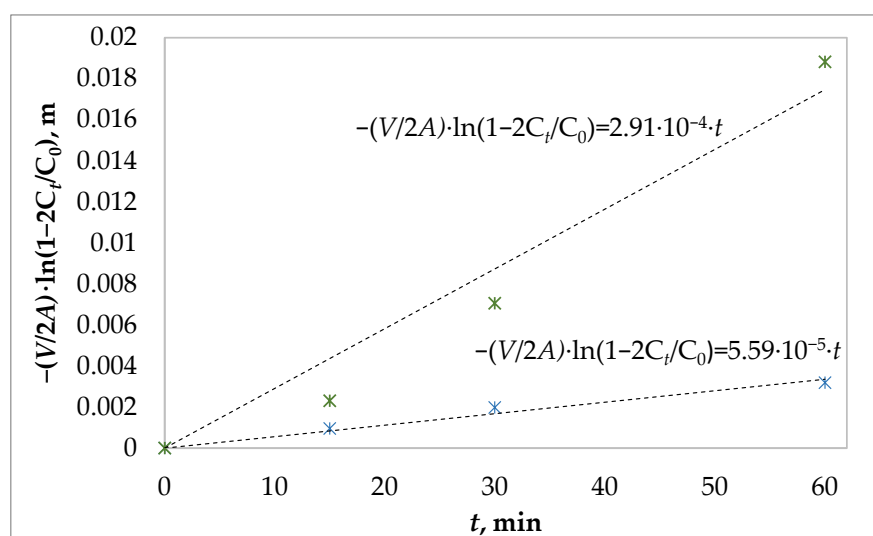


Figure 8. The linear parts of the release profiles with corresponding equations.

Table 6. Solubility, S , permeability, P , and diffusion coefficients, D , of CRT and Gne-LA 1:9-CRT.

	CRT	Gne-LA 1:9-CRT
$S, \text{mg}_{\text{CRT}} \cdot (100 \text{ mL})^{-1}$	<100	1538
$P, \text{cm} \cdot \text{s}^{-1}$	5.59×10^{-7}	29.1×10^{-7}
$D, \text{cm}^2 \cdot \text{s}^{-1}$	3.18×10^{-15}	3.24×10^{-15}

Table 6 also presents the solubility values of the drug dose in 100 mL of water for pure CRT and CRT dissolved in Gne-LA 1:9. A significant change in solubility is observed. For the Gne-LA system, the obtained value significantly exceeds the threshold that defines a highly soluble drug (a single dose dissolves in 250 mL or less of water across a pH range of 1 to 8) [60].

CRT is a BCS class IV compound, characterized by both low solubility in water and low permeability through the intestinal membrane. However, the API-ES formulation modified this profile, resulting in a shift to BCS class III, as clearly depicted by the X in the classification plot (Figure 9). Specifically, the formulation achieves high solubility, moving the drug below the 250 mL volume threshold. Despite its low permeability (Table 6), the

high solubility ensures that a sufficient concentration gradient is maintained for passive transport. As a result, the absorption of the drug is now primarily limited by its rate of permeation across the intestinal wall (a class III characteristic).

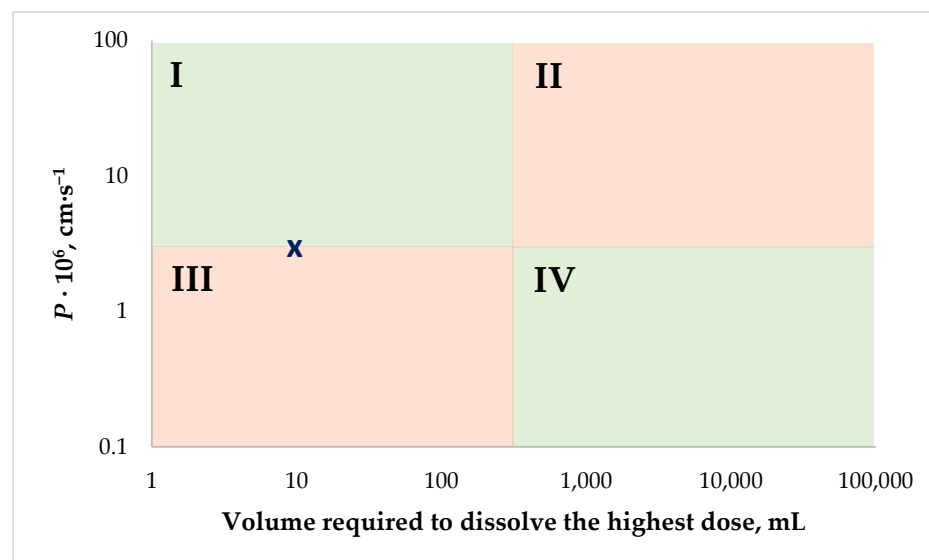


Figure 9. BCS classification (classes I–IV) of the Gne-LA 1:9-CRT API-ES formulation.

4. Conclusions

Three different ESs were prepared by combining lactic acid with various non-toxic components such as fructose, glycerol and/or glycine. Their stable formation was confirmed by FTIR analysis, which showed characteristic changes in the vibrational bands indicating the formation of hydrogen bonds and a stable ES structure. Ecotoxicity tests showed low toxicity to *Vibrio fischeri*, with Gne-LA 1:9 being the most promising solvent, as it showed no inhibition. Preparation of API-ES systems with 15 wt.% CRT was confirmed by FTIR and ^1H NMR analysis, indicating successful dissolution and molecular interactions without chemical reaction. The API-ES formulations showed a fast drug release, with a maximum 8% improvement in release compared to pure CRT powder. Permeability studies confirmed a significant increase in the permeability coefficient for CRT from the API-ES system, suggesting improved mass transfer. The efficient solubilization of CRT by ES results in a strong interaction, which is the key mechanism for achieving high solubility of CRT. The Gne-LA 1:9-CRT formulation successfully moved the BCS class IV compound (low solubility and permeability) to BCS class III by achieving high solubility, resulting in absorption now being primarily limited by low permeability.

Overall, these results emphasize that ESs, particularly amino acid-based systems, are promising solutions for the development of novel and more effective formulations for poorly soluble APIs. It is also important to stress that solutions for the formulation of API-ES should be established to adjust the release profile based on the unique drug's application. As the studied drug formulation is intended for oral administration in humans, further development and application require cytotoxicity studies.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/cryst16010077/s1>, Figure S1: ^1H NMR spectra of Gly, Fru, LA, Gly-Fru-LA-W 2:1:2:3.4, CRT and Gly-Fru-LA-W 2:1:2:3.4-CRT; Figure S2: ^1H NMR spectra of Gly, LA, Gly-LA 1:3, CRT and Gly-LA 1:3-CRT; Figure S3: ^1H NMR FTIR spectra of Gne, LA, Gne-LA 1:9, CRT and Gne-LA 1:9-CRT.

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