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ACCELERATING THE DEVELOPMENT OF SOLUBILITY-ENHANCED SOLID DISPERSIONS: USE OF MILLISCALE AND MATHEMATICAL PREDICTION OF DRUG-POLYMER MISCIBILITY

Abigail Garcia-Radilla[1], Mariana Ortiz-Reynoso[2]*, Edna T. Alcantara-Fierro[3] and Jonnathan G. Santillán-Benítez[4] and Fernando Hernández-Martínez[5]

[1,2,3,5]Laboratorio de Farmacia, Facultad de Química, Universidad Autónoma del Estado de México.
[4]Laboratorio de Biología Molecular, Facultad de Química, Universidad Autónoma del Estado de México.

***Corresponding Author: Mariana Ortiz-Reynoso**

Laboratorio de Farmacia, Facultad de Química, Universidad Autónoma del Estado de México.

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ABSTRACT

Introduction: Most solid oral drugs currently in a developmental phase, have low solubility in aqueous systems. This reduces their pharmacological efficacy because drug absorption is slowed down. Solid dispersions are an option to improve both dissolution rate and apparent solubility of poorly soluble drugs. **Aim:** This work shows the effect of different drug-polymer proportions and a plasticizer in ternary solid dispersions at a milligram scale, on the drug dissolution rate, and evaluates its correlation to the calculated Flory-Huggins theoretical model. **Methods:** We evaluated the drug-polymer miscibility using the melting point depression method by the Flory-Huggins theory and the dissolution rate of ketoconazole in ternary solid dispersions manufactured by melting granulation. **Results:** All ternary solid dispersions decreased the enthalpy of fusion of the drug, however, only those made with PVP/VA 64 and HPMCAS HF improved the solubility kinetics at pH: 1.2 and 6.8 respectively. The proportions with the best results were 1:2 for HPMCAS HF (p = 0.0023) and 2:1 for PVP/VA (p = 0.0053) (drug:polymer). The Flory-Huggins parameter yielded a correlation with PVP/VA 64 and HPMCAS HF, but not with *Soluplus*®, indicating that the theoretical model needs to be improved to reflect this last case. **Conclusion:** The studies carried out in the present work are useful, practical and simple to improving the dissolution of poorly soluble drugs (KTZ), reducing costs and mitigating risks associated with the development of solid dispersions manufactured by fusion techniques.

KEYWORDS: Solid dispersion, Drug-polymer miscibility, Melting process, Dissolution.

INTRODUCTION

Both solubility and dissolution rate of drugs are *sine qua non* conditions in the pharmacokinetic process. When active pharmaceutical ingredients (API) do not dissolve in the gastrointestinal tract, it is impossible to achieve effective absorption, and the result is a low plasma concentration of the active molecule and a failure in the therapeutic goal. The exact amount of drug must enter into the bloodstream to seek target cells and achieve a pharmacological effect.[1] Most solid oral dosages (SOD) facing a developmental stage have low solubility in aqueous systems, which reduces their pharmacological efficacy because of slow drug absorption rates.

Solid dispersions

Solid dispersions (SD) are defined as systems in which hydrophobic API are molecularly dispersed in at least one solid polymeric carrier (either in crystalline or amorphous state), which can be hydrophobic or hydrophilic. The fact that the tiny drug particles are uniformly distributed in a polymeric carrier makes SD an effective technology for promoting both dissolution and apparent solubility of poorly soluble API in aqueous media. Firstly, reducing the particle size of the drug generates a greater surface area exposed to the surrounding medium. Furthermore, the resulting particles have high porosity (translated into greater uptake of medium) and improved wettability[2], allowing the aqueous medium to penetrate the system, thus increase the drug release rate. In DS systems, being the dispersion of drug particles close to a molecular level the crystalline lattice of the drug depletes. Fine separation of the drug particles promotes intermolecular interactions – such as Van der Waals forces and hydrogen bonds – with the polymeric carrier, transforming API's crystalline structure into an amorphous state in which the energy needed to solubilize the drug is reduced.[3,4]

The general classification of the manufacturing methods of SD groups them into three categories: "solvent evaporation", "melting" and a combination of these.[3,5] In all three cases, the mixture of the drug and the

polymeric carrier interacts at a molecular level through physical processes, without significant chemical changes being verified. The development of SD aims to obtain materials with improved physicochemical, pharmacotechnical and biopharmaceutical propierties as compared to a simple mixture of components. Other goal is to reduce manufacturing steps for SOD products leading to leaner processes and reducing failure modes that impact the quality of the final product: the medicine[5] and more importantly, improving the patients' health. A limitation of SD is the physical instability of the drug within the polymeric carrier, which can lead to the recrystallization of the API or the polymer during the storage stage, or even to precipitation of the ingredients in the gastrointestinal tract.[6]

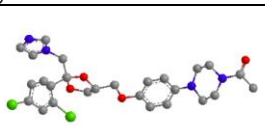
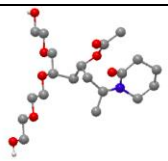
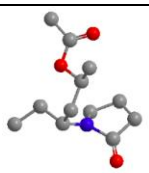
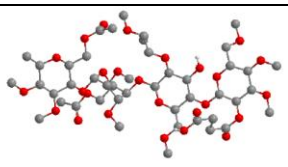
The choice of a polymeric *carrier* has a great influence on the dissolution rate and the physical stability of the SD. Amorphous polymers are preferred for the preparation of SD, because this loosened solid state requires less energy to dissolve. However, materials in the amorphous state are less stable. Hydrophilic polymeric carriers such as polyvinylpyrrolidone /vinyl acetate (PVP/VA) or *Kollidon* ® VA 64 have shown to improve solubility and dissolution rate in aqueous media. Drug molecules are released from the solid dispersed system as the dissolution of the hydrophilic carrier takes place, creating a supersaturated solution of the active ingredient. Hydroxy propyl methyl cellulose acetate succinate (HPMCAS) is available in three grades (L, M and H) that differ in the content of acetyl and succinate functional groups. Solubility of HPMCAS depends on the pH of the aqueous medium, since the functional groups of the salts ionize at different pH.

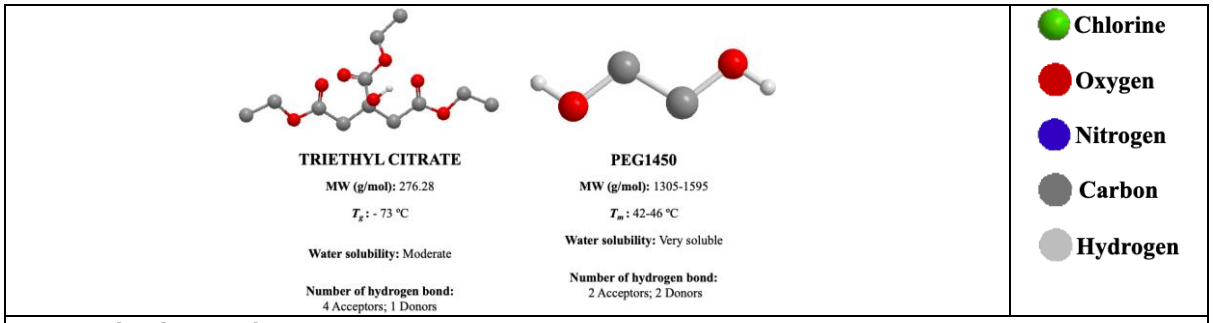
Another mechanism for solubility enhancement of SD is micelle forming. There are amphiphilic polymers that enhance the solubility of a given API dispersed in these carriers, by forming micelles that can modify solubility even to a greater extent than that obtained in their amorphous state. This formation of micelles can be achieved by adding surfactants to the formulation, as is the case of the carrier/surfactant system commercially known as *Soluplus*®. These polymeric carriers are suitable for manufacturing SD by melting methods, due to the wide interval between the glass transition temperature (T_g) and degradation temperature (T_d).[3] The use of plasticizers in carrier systems is essential to reduce the T_g of the polymers because itallows to carry out a manufacturing process at low temperatures while still promoting drug dissolution in the final system. Some of the plasticizers commonly used with the polymers mentioned above are polyethylene glycol (PEG) and triethyl citrate (TEC).[7,8]

The development of enhanced-solubility SD includes the selection of the manufacturing method (melting, solvent evaporation or combinations of them) and a suitable polymeric carrier system (with or without surfactants) for a given API. Previous works have used model drugs to evaluate the impact of solubility on several solid dispersed systems.[5] In the present work, ketoconazole (KTZ) was chosen because of its low aqueous solubility (17 µg/ml) and high intestinal permeability. This molecule is classified as Class II according to the Biopharmaceutical Classification System (BCS)[9] and is one of the few broad-spectrum oral drugs used to treat superficial (topical) and severe systemic fungal infections. There are other antifungals available such as: itraconazole, terbinafine, amphotericin B, griseofulvin and fluconazole; however, there have been reported species of microorganisms resistant to these drugs when administered orally, especially in patients with diseases that cause immunosuppression.[10]

Table 1 shows the main physicochemical properties of three of the most recent carrier polymers to formulate SD: *Soluplus*®, PVP/VA and HPMCAS, as well as those of the active ingredient KTZ, which was selected as a low solubility model drug for this study.

Table 1: Main physicochemical properties of raw materials.

Drug Polymers			
			
KETOCONAZOLE **MW (g/mol):** 531.44 T_m**:** 148 – 152 °C T_g**:** 42.1 °C **Water solubility (25 °C):** 17 µg/ml **Number of hydrogen bond:** 7 Acceptors; 0 Donors	**SOLUPLUS®** **MW (g/mol):** 118,000 T_g**:** 70 °C T_d**:** 250 °C **Solubility:** Amphiphilic **Number of hydrogen bond:** 7 Acceptors; 2 Donors	**PVP/VA** **MW (g/mol):** 45,000-70,000 T_g**:** 100–105 °C T_d**:** 230 °C **Solubility:** Amphiphilic **Number of hydrogen bond:** 2 Acceptors; 0 Donors	**HPMCAS** **MW (g/mol):** 50,000 T_g**:** 119 °C (L); 120 °C (M); 122 °C (H) T_d**:** 190 - 204 °C **Solubility (pH):** 5.8 (L); 6 (M); 6.8 (H) **Number of hydrogen bond** 22 Acceptors; 2 Donors
Plasticizers			



MW: Molecular Weight
T_m: Melting temperature
T_g: Glass transition temperature
T_d: Degradation temperature.

Source: Own elaboration with information from[3,8,9,11,13] and Chem3D *Software*.

Previous studies to predict drug-polymer interaction

In order to design SD, it is important to have prior knowledge of the physicochemical properties of the selected raw materials and their intermolecular interactions, so previous search in databases such as PubChem and DrugBank. Review of molecular docking results to simulate coupling is also crucial. Differential Scanning Calorimetry (DSC) is one of the most used analytical method to characterize SD, mainly those manufactured by melting, because of its worth to infer whether the drug and the polymer are compatible. This test involves melting the sample, so miscibility can be determined mainly by recording the melting temperature (T_m) and the T_g of the mixture. Predictive mathematical models have also been used to deepen into theoretical knowledge of component miscibility, one of which being F-H theory.

F-H theory is a mathematical model described by Paul J. Flory and Maurice L. Huggins in 1942 to predict polymer-solvent miscibility with a Gibbs free energy-based approach.[14] This prediction is based on the fact that the greater the interaction between the drug and the polymer is, the greater is the dispersion of the drug in the polymer, since the interactions between drug molecules are replaced by drug-polymer interactions, thus increasing the possibility of the medium solvating the drug molecules, which can be reflected in the decrease in the enthalpy of fusion of the drug. Currently, research works that apply this theory to predict drug-polymer miscibility in SD have focused on the determination of the F-H interaction parameter, χ.[15] Marsac *et al*., for example, obtained the value of χ by the melting point depression method, which occurs in drug-polymer mixtures, considering that in a binary system solid dispersion (BSD), the polymeric carrier is the solvent of the drug.[16,17] This model is applied mostly to binary physical mixtures, but it can be extended to ternary systems considering the contribution of water as a third component. Although when manufacturing SD by melting methods there is usually no water in the process, this component can be replaced by the values of another compound present in the mixture, considering that the data for this third component must be obtained through DSC. However, it must be taken into account whether the contribution of this third compound is relevant or if the binary model is enough, since complicated calculations may be faced when using a third material.[14] Another way to obtain the parameter χ is to use the solubility value focused on what was said by Hildebrand and Scott.[17] As mentioned above, the F-H value is a predictive parameter that allows to know if two components (drug and polymer) are compatible with each other, without the need to perform an SD. As far as the melting point depression method goes, it is only necessary to prepare a physical mixture and obtain thermo-gravimetric values through a DSC, thus saving costs in material and manufacturing times. The solubility value method requires performing experimental solubility tests to obtain the same parameter. Upon equipment availability, one method or the other may be preferred.

In the present study the melting point depression method was performed, since it is a direct, practical process that does not require the preparation of the media for the solubility method. Despite having a manufactured TSD in this work, the calculation was carried out for a binary physical mixture stand point since it was in our interest to focus on measuring drug-polymer interactions. The use of a plasticizer as a third component pursuit processability purposes only.

The F-H interaction parameter by the melting point depression criterion is described by the following equation

$$\left(\frac{1}{Tm^{mix}} - \frac{1}{Tm^{pure}}\right) = -\frac{R}{\Delta H_{fus}}\left[ln\,\emptyset_{drug} + \left(1-\frac{1}{m}\right)\emptyset_{polymer} + \chi\emptyset^2_{polymer}\right]$$

(Equation 1)

To calculate χ, solve the previous equation **(*Equation 1*)**.

$$\chi = \frac{\left(\frac{1}{Tm^{mix}} - \frac{1}{Tm^{pure}}\right)\frac{\Delta H_{fus}}{-R} - \ln\emptyset_{drug} - \left(1-\frac{1}{m}\right)\emptyset_{polymer}}{\emptyset^2_{polymer}}$$

(*Equation 2*)

Where T_m ^{mix} is the melting temperature of the physical mixture, T_m ^{pure} is the melting temperature of the pure drug, R is the ideal gas constant, ΔH_{fus} is the enthalpy of fusion of the pure drug, $\emptyset_{drug}$ is the volume fraction of the pure drug, $\emptyset_{polymer}$ is the volume fraction of the polymeric carrier, m is the value of the lattice (ratio from the volume of the polymer and the drug) and χ is the F-H interaction parameter. The values of T_m ^{mix}, T_m ^{pure} and ΔH_{fus} are obtained directly from the DSC. $\emptyset_{drug}$ and $\emptyset_{polymer}$ are calculated by using the formula $\emptyset_x = \frac{V_x}{V_{mix}}$ and m is obtained with the following equation: $m = \frac{Vmol_{drug}}{Vmol_{Polymer}}$. The value of the parameter χ indicates the miscibility of the drug in the polymer: if χ is greater than or close to 0, the miscibility of the system is low, and if it is less than 0, it means that the miscibility is strong.[15] or significant, which would make that system a candidate to evaluate its performance (solubility) when applied to SD.

Given the fact that the results of theoretical predictions with mathematical models must be verified experimentally, conducting small-scale preliminary testing helps in identify problems, optimize experimental designs, maximize the probability of valid and significant results, and contribute to the acquirement of new scientific knowledge. SD prepared by melting at millimetric scales allow for simple, rapid, and inexpensive processes, making them an acceptable option for preliminary research. This is as simple as physically mixing the pharmaceutical components and heating the mixture through readily available devices such as water or sand baths or a hot plate, although these experiments may lack robustness and reproducibility if the process conditions are not thoroughly controlled.[18]

The aim of the present work is to determine the effect of different proportions of drug:polymer in plasticized TSD systems at a milligram scale, on the dissolution rate of KTZ and to correlate this data with the theoretical calculated χ, in order to provide a quick, low-cost strategy to be implemented prior to facing complete experimental tests when developing SD by melting methods either on pilot or industrial scales. **Figure 1** shows this strategy.

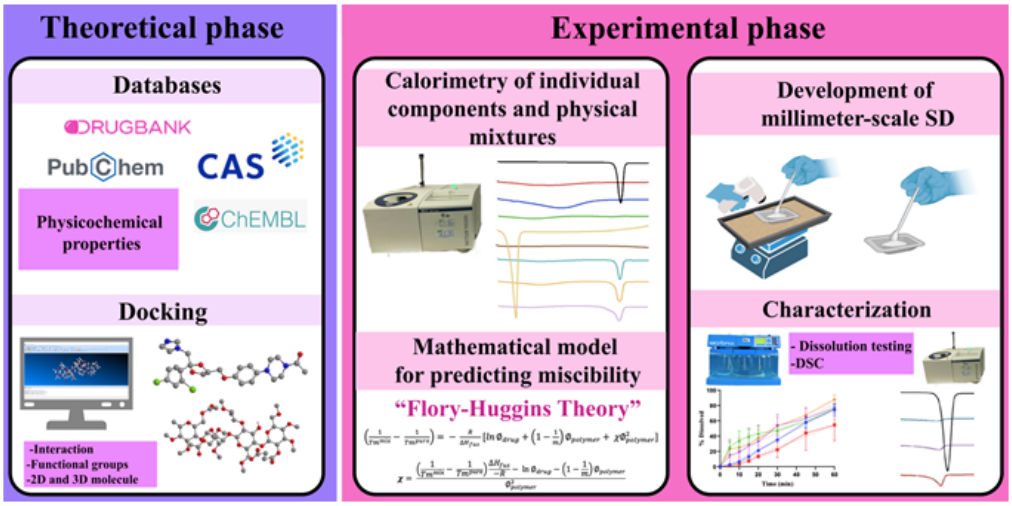


Figure 1: Strategy for preliminary SD development.

Source: Own elaboration

MATERIALS AND METHODS

Materials

Active ingredient: Ketoconazole (Piramal Enterprises Ltd., batch: KET/M-10217, donated by Moléculas Finas, S.A. de C.V.). Excipients: *Soluplus*® (BASF, batch: 30724424U0), PVP/VA 64 (BASF, *Kollidon VA® 64*, batch: 56741056P0) and PEG 1450 (BASF, *Kollisolv* ®, batch: GNF00421B); fine particle HPMCAS HF (Ashland, batch: 65G-810002) and TEC (Sigma-Aldrich, batch: W308302-1KG-K), all donated by their manufacturers.

Methods

Binary physical mixtures (BPM), ternary physical mixtures (TPM) and ternary solid dispersions (TSD) were manufactured at a milligram (millimeter) scale, using KTZ and three polymers: *Soluplus*®, PVP/VA 64 and HPMCAS HF, along with the plasticizers polyethylene glycol (PEG) and triethyl citrate (TEC) added to reduce the polymers' T_g. The selection of plasticizers was made based on the available literature, choosing PEG 1450 for the polymers: *Soluplus*® and PVP/VA 64, and TEC for HPMCAS HF.

Ueda *et al.*, found that in SD, both recrystallization and dissolution rate of the drug depend on the selected

HPMCAS grade, which means that the proportion of the acetyl and succinate functional groups affect these parameters.[19] The HPMCAS used in the present study was grade H with a fine particle size, following through on experimental evidence suggesting greater drug stability.[20]

Preparation of physical mixtures (PM)

Binary physical mixtures (BPM): 500 mg batches were manufactured by mixing KTZ:Polymer in 1:1, 2:1 and 9:1 (w/w) proportions, for 10 minutes in a porcelain mortar.

Ternary physical mixtures (TPM): 500 mg batches were manufactured by mixing KTZ:Polymer+plasticizer in a 1:1 (w/w) proportion for 10 minutes in a porcelain mortar. The proportions of the physical mixtures used to calculate F-H (χ) were established in order to obtain the corresponding values for different amounts of KTZ, by means of mathematical calculations. These proportions for TPM were chosen independently of those selected for TSD.

SD manufacturing: Ternary solid dispersions

Ternary solid dispersions (TSD): 500 mg batches were manufactured by adding KTZ:Polymer+plasticizer in 1:2, 1:1 and 2:1 (w/w) proportions. 10% (w/w) of plasticizer was used with respect to the carrier polymer; TEC was used for TSD manufactured with HPMCAS HF, while PEG1450 (w/w) was selected for *Soluplus*® and PVP/VA 64.

Materials were mixed in a mortar for 10 minutes, transferred to a stainless-steel container and heated in a sand bath. Mixtures were heated 20 °C above the T_g of each polymer. The choice of temperatures was made according to the literature, since the T_g must be exceeded to achieve a liquid state in which the viscosity of the polymer allows the correct mixing of the components.[21] The choice of these temperatures was based on bibliographical background.[6]

Evaluation PM and SD

Calorimetric evaluation

Calorimetric studies were performed to all raw materials, BPM, TPM and TSD (n=1). Samples of 12-15 mg were accurately weighed in an OHAUS analytical balance (Pioneer PA21) using aluminum crucibles of 40 µl, perforated and hermetically sealed. The evaluation was performed under a nitrogen atmosphere (10 ml/min) and a heating rate of 3 °C/min in a temperature range from 25 to 200 °C using a DSC-3 calorimeter (Mettler Toledo) previously verified with an Indium standard (Batch ME-119442). The melting point, enthalpy and glass transition temperature were obtained using a *Stare® software*. With the recorded data, the F-H interaction parameter (χ) was obtained from Equation 2 for BPM.

Evaluation of dissolution rate "*in vitro*"

30 mg samples (n=2) of KTZ, BPM, TPM and TSD were evaluated in 900 ml of dissolution medium at 37 ± 0.5 °C, using the "basket" apparatus (USP I) in a Sotax dissolution bath (AT7, Switzerland). As dissolution medium, 0.1 N hydrochloric acid having a pH=1.2 (gastric fluid without enzymes) was used to evaluate the SD based on *Soluplus® and* PVP/VA 64. The dissolution of HPMCAS HF-based SD was evaluated in phosphate buffer pH: 6.8 (to simulate the intestinal environment), because this polymer is not soluble at pH< 5 (3,19,22). In all cases, 5 ml aliquots were taken at time intervals of 5, 10, 15, 20, 30, 45 and 60 minutes, replacing the dissolution medium.

Samples were analyzed in a UV-Vis spectrophotometer (Thermo Scientific, Genesys 10S) at wavelengths of 223 nm (for HCl medium) and 208 nm (for phosphate buffer medium). drugfree KTZ concentration was obtained from a standard curve prepared for each of the dissolution media. The percentage dissolved was plotted against time and, through a linear regression analysis, the dissolution rate (slope of the line) was calculated, as well as the total % dissolved at 60 min.

Statistical analysis

A one-way analysis of variance (ANOVA) was performed to determine if there is a significant difference ($p < 0.05$) between percent dissolved (t = 60 min) and the dissolution rate, following Tukey's multiple comparison test, and using a Prism 8.0.1 *software* (Graphpad Software, Inc.).

RESULTS AND DISCUSSION

Evaluation of PM and SD

The calorimetric evaluation of the raw materials rendered thermal events that correspond to what is described in the literature, namely T_m and T_g of each one[3,8,9,11,13] **(Fig. 2)**.

Calorimetric evaluation of PM

As observed in the thermogram **(Fig. 3)**, the BPM in different proportions preserved the endothermic peak of KTZ, indicating that the drug's crystallinity persists; on the other hand, a partial miscibility shows, evidenced by the reduction of both temperature and enthalpy of fusion.

Decreasing melting energy values were observed with each of the polymers evaluated **(Fig. 3a, b and c)**, as the polymer proportion increases. The enthalpy of fusion data show that higher ratios of polymeric carrier correspond to lesser energy requirements for the system to melt down. This data point to a higher drug dispersion within the molecular lattice of the polymer.

TPM exhibited a considerable decrease in enthalpy and melting point of KTZ when prepared with *Soluplus*® or HPMCAS HF, showing higher miscibility **(Fig. 3a and c)**. Being the ternary component a plasticizer which naturally decreases the polymer's T_g, the DSC curve depicts notorious increases in drug-polymer interaction.

Calorimetric evaluation of TSD: Figure 4 shows the thermograms of the TSD manufactured with the three polymers. In every one of the three proportions evaluated (2:1, 1:1 and 1:2), TSD show a gradual reduction in the temperature and energy required to reach the melting point of KTZ as the amount of polymeric carrier increases (1:2). This is consistent with the decrease in the enthalpy of fusion of KTZ. The KTZ:polymer ratios that decreased the enthalpy of fusion the most were 1:2 in all cases, and the greatest decrease in this value was the TSD made with the polymer PVP/VA 64 (ΔH= 6.26 J/g) (Fig. **4b)**, followed by *Soluplus*® (ΔH= 15.09 J/g) **(Fig. 4a)**, and thirdly by HPMCAS HF (ΔH= 24.72 J/g) **(Fig. 4c)**. These data are consistent with that reported by Medarevi ´ *et al.*, who explained that the decrease in the melting point of the drug depends on the amount of the polymeric carrier; the higher is the polymer ratio in the formula, the bigger the decrease in melting point[23], since having more polymer molecules available increases the number of possible interactions drug-polymer, allowing for a greater dispersion capacity in the molecular lattice. These results suggest that a strong interaction takes place in SD, reducing the enthalpy of fusion way beyond than the physical mixture. The, greater the amount of polymer, the higher the miscibility of the API in the polymer.

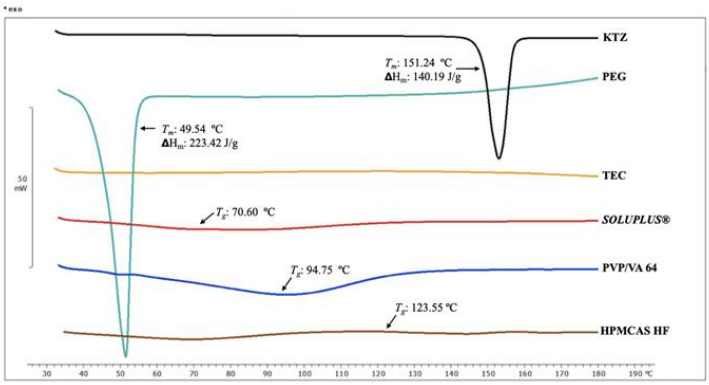
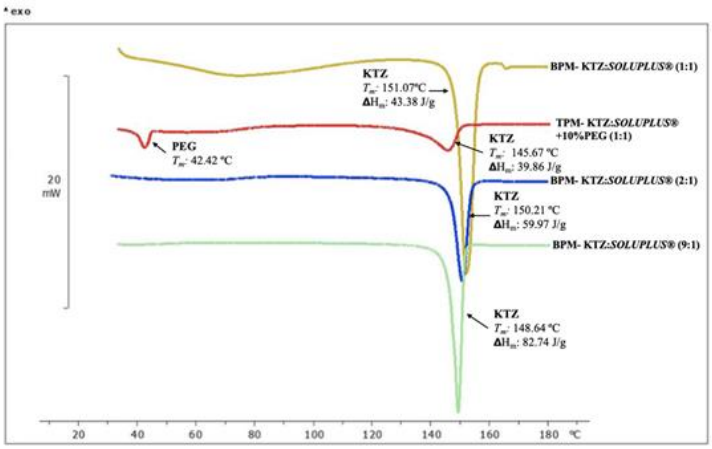


Figure 2: Thermogram of pure raw materials.

Source: Own elaboration.



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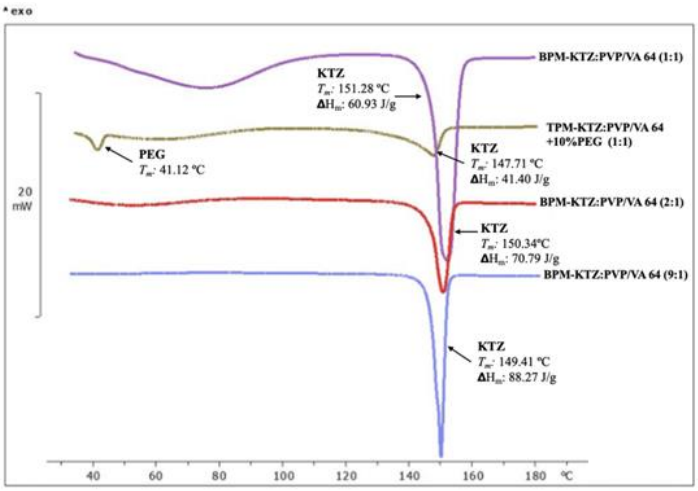
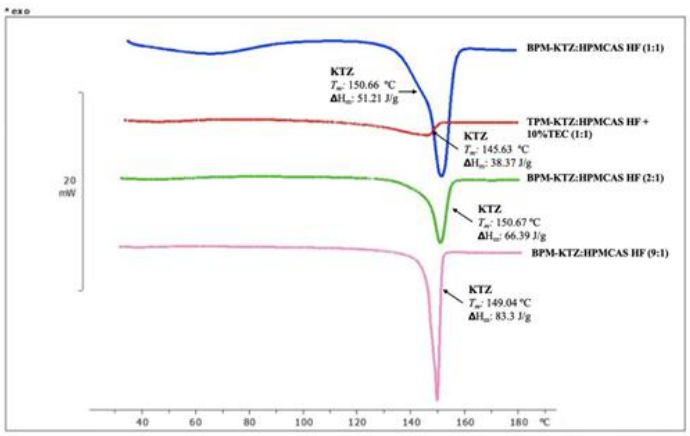


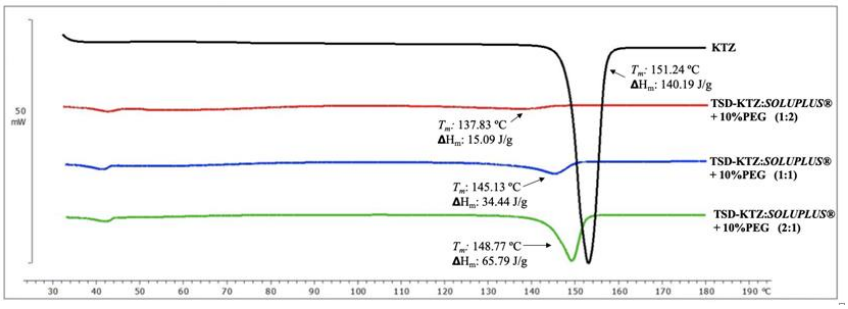
b.



c.

Figure 3: Thermograms of BPM and TPM in different proportions. a) BPM KTZ:*Soluplus*® (1:1, 2:1 and 9:1) and TPM (1:1), b) BPM KTZ:PVP/VA 64 (1:1, 2:1 and 9:1) and TPM (1:1), c) BPM KTZ:HPMCAS HF (1:1, 2:1 and 9:1) and TPM (1:1).

Source: Own elaboration.



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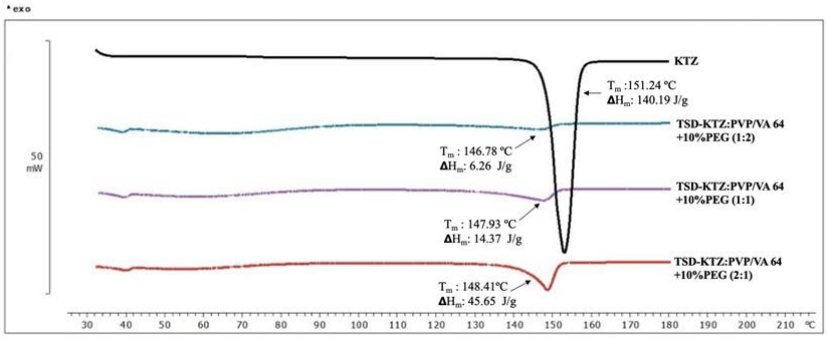

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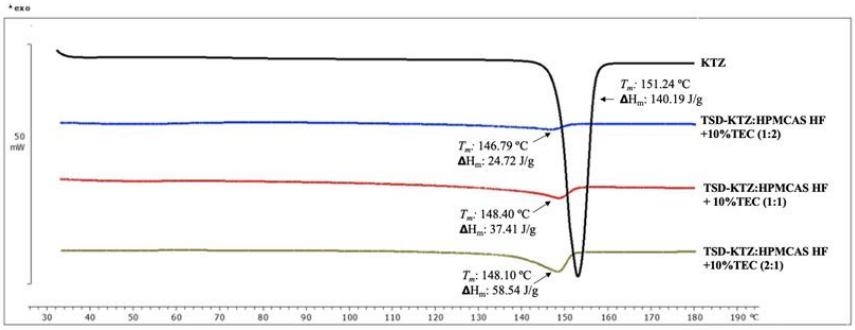


c.

Figure 4. Thermograms of TSD in different proportions. a) TSD KTZ: *Soluplus*® +10% PEG (1:2, 1:1 and 2:1), b) TSD KTZ:PVP/VA 64+10% PEG (1:2, 1:1 and 2:1), c) TSD KTZ:HPMCAS HF+10%TEC (1:2, 1:1 and 2:1).
Source: Own elaboration.

Theoretical prediction of drug-polymer miscibility

Using the values rendered by the calorimetric thermograms showed in **Figure 3**, the theoretical values χ for KTZ in each of the polymers were calculated for all BPM. **Figure 5** shows that the greater the amount of the active ingredient, the greater the miscibility. The data show that KTZ:HPMCAS HF 9:1 proportion is the most miscible BPM, yielding the most negative χ value (χ= -5.4528), followed by *Soluplus*® (χ= -4.7969) and PVP/VA 64 (χ= - 4.2320). The three carriers show theoretical miscibility values with KTZ at high polymer concentrations. The interaction parameters χ obtained for HPMCAS HF and PVP/VA 64 in BPM correspond to those obtained by Chen *et al.*, who found that KTZ has greater miscibility in HPMCAS HF as compared to PVP/VA 64.[24] However, for the polymer-surfactant system known as *Soluplus*® , Lu *et al.*, reported that the KTZ: *Soluplus*® value χ is a positive value, indicating the immiscibility between the components.[17] This is divergent to the results we obtained. The χ values rely directly on the chemical structure of the polymers and the drug. The molecular structure of KTZ has the ability to form hydrogen bonds as it contains seven hydrogen acceptors. HPMCAS contains twenty-two acceptors and two hydrogen donors that can form hydrogen bonds with KTZ[25], as seen in the Chem 3D *software*. This explains the lowest F-H interaction value with the HPMCAS HF.[24] The exact number of these HPMCAS hydrogen donors and acceptors varies according to the degree of substitution of the acetyl and succinate groups. In the case of PVP/VA 64, its chemical structure has two hydrogen bond acceptors and no donors, so the interaction with KTZ is only possibly via Van der Waals forces, dipole-dipole and hydrophobic interactions.[24] Lastly, *Soluplus*® has seven acceptors and two hydrogen donors at the tails of its chains, possibly maintaining strong interactions with KTZ at these sites.

	BPM-KTZ:HPMCAS HF			BPM-KTZ:PVP/VA 64			BPM-KTZ:*SOLUPLUS*®		
	1:1	2:1	9:1	1:1	2:1	9:1	1:1	2:1	9:1
χ=	0.7380	0.5727	-5.4528	0.8301	0.4690	-4.2320	0.8269	0.5137	-4.7969

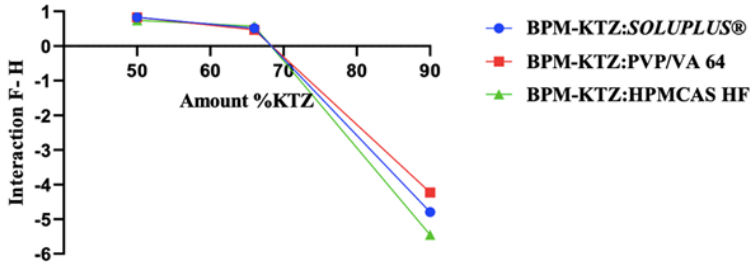


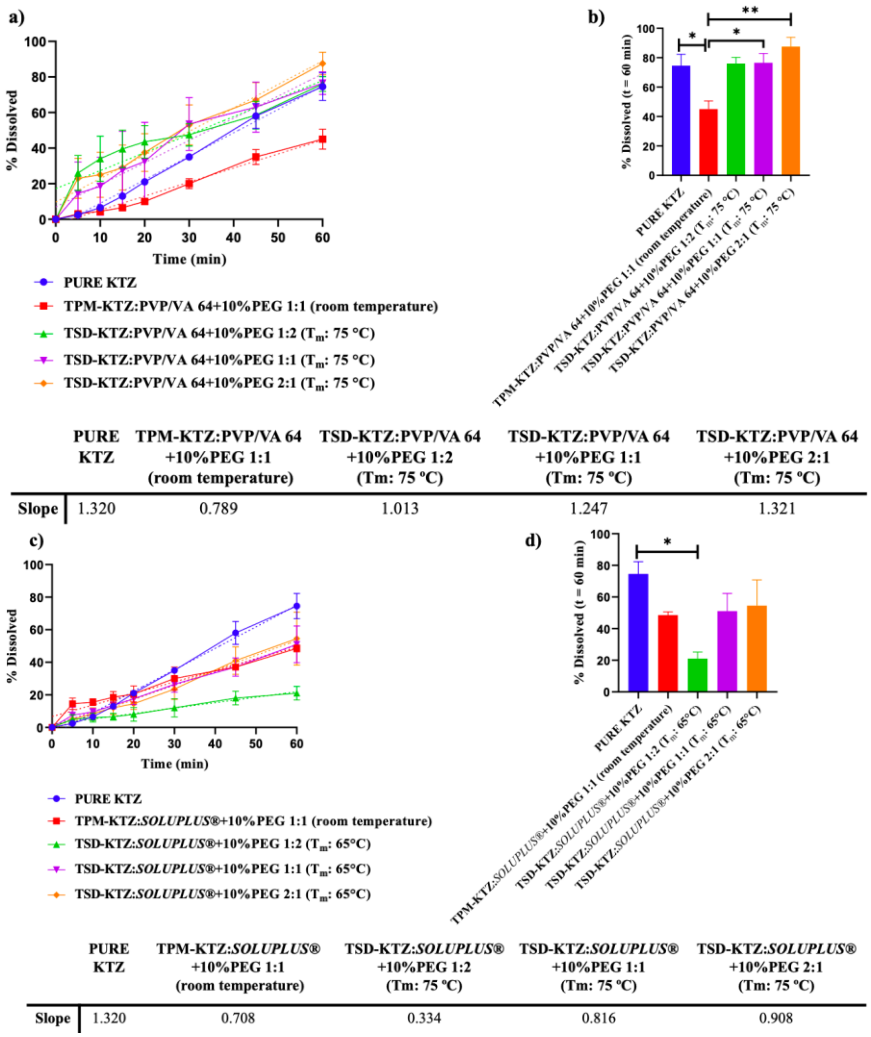
Fig. 5: F-H interaction parameters (χ value) of KTZ in BPM of HPMCAS, PVP/VA 64 and *Soluplus*® at different proportions.
Source: Own elaboration

***In vitro* dissolution rate study**

Tests in pH 1.2 medium (PVP/VA 64 and *Soluplus*®)

All drug:polymer+plasticizer proportions (1:2, 1:1 and 2:1) of the TSD formulated with PV/PVA 64 improved the dissolution rate as compared to the pure KTZ, although showing differentiated behaviors among them, and compared to the physical mixtures. **Figure 6a** shows the effect of the amount of polymer on the dissolution rate of TSD with KTZ. These data correlate with the negative value χ calculated for KTZ:Polymer 9:1, indicating that there is miscibility between KTZ:PVP/VA 64. For this polymer, TSD 1:2 and 2:1 showed a higher initial dissolution rate (first 30 minutes), but the 2:1 proportion upheld the highest slope and a higher tendency of the amount dissolved (t = 60 min), compared to pure KTZ and to all other TSDs, as seen in **Figure 6b**.

Figures 6c and **d** show that TSD did not improve the dissolution rate of pure KTZ, in any of the formulas comprising *Soluplus*®, as depicted on **Figure 6c.** As it can be seen in **Figure 6d**, even the TSD with the highest content of polymeric carrier decreases the API's dissolution rate, having a statistically significant difference as compared to the pure active (p = 0.0189)**.** It is notable that the thermograms and the BPM value χ suggested the existence of miscibility between the components, according to our data, none of the conditions tested improves the dissolution rate for *Soluplus*®-based formulas. It should be taken into account that the F-H model by obtained by the melting point depression method in BPM has some limitations, associated to the type of system being evaluated. It should be considered that DSC is a method carried out in the absence of water, so it does not accurately reflect the KTZ-*Soluplus*® interaction in an aqueous media; *Soluplus*®'s mechanism of action via micelle formation would most likely change the real-time interactions between polymer-drug molecules, completely changing the outcome during the dissolution process. To solve this, the calculation of the F-H model with three components should be carried out, adding the contribution of water to the system, also modifying the equations for a ternary mixture. Another possible explanation is that KTZ does not contain donor hydrogens[17], consequently it is unlikely that it upholds strong interactions with *Soluplus*®, because the polymer's donors are found only at the ends of the molecule and are not repeated in each monomer.



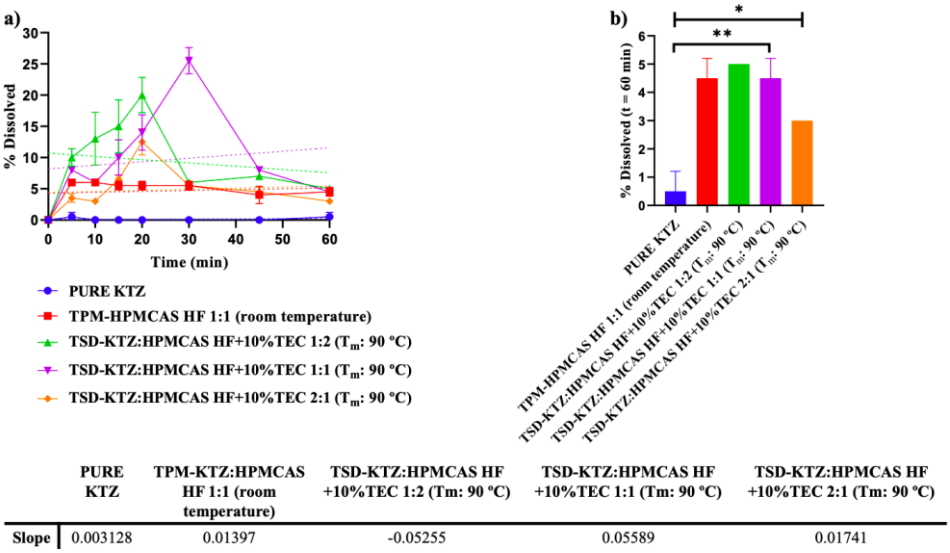
	PURE KTZ	TPM-KTZ:PVP/VA 64 +10%PEG 1:1 (room temperature)	TSD-KTZ:PVP/VA 64 +10%PEG 1:2 (Tm: 75 °C)	TSD-KTZ:PVP/VA 64 +10%PEG 1:1 (Tm: 75 °C)	TSD-KTZ:PVP/VA 64 +10%PEG 2:1 (Tm: 75 °C)
Slope	1.320	0.789	1.013	1.247	1.321

	PURE KTZ	TPM-KTZ:*SOLUPLUS*® +10%PEG 1:1 (room temperature)	TSD-KTZ:*SOLUPLUS*® +10%PEG 1:2 (Tm: 75 °C)	TSD-KTZ:*SOLUPLUS*® +10%PEG 1:1 (Tm: 75 °C)	TSD-KTZ:*SOLUPLUS*® +10%PEG 2:1 (Tm: 75 °C)
Slope	1.320	0.708	0.334	0.816	0.908

Figure 6: Dissolution profiles of pure KTZ, TPM and TDS in 0.1 N HCl. a) TSD (KTZ:PVP/VA 64+10%PEG) at different proportions 1:2, 1:1 and 2:1 at 75 ºC melting , b) Graph of the percentage dissolved in 60 min of TSD (KTZ:PVP/VA 64+10%PEG), c) TSD (KTZ: *Soluplus*® +10%PEG) at different proportions 1:2, 1:1 and 2:1 at 65 ºC melting and d) Graph of the percentage dissolved in 60 min of TSD (KTZ: *Soluplus*® +10%PEG). Pure KTZ and the physical mixture were used as controls. Results are presented as mean and SEM (n=2). A linear regression and one-way ANOVA test and Tukey's multiple comparison test were performed. *p = 0.0255, 0.0208, 0.0195, 0.0142, **p = 0.0053.
Source: Own elaboration

Tests in pH 6.8 medium (HPMCAS)

Figure 7 shows the effect of the proportion of the HPMCAS HF polymeric carrier in phosphate buffer at pH 6.8. All TSDs improved the dissolution rate compared to the pure drug in the first 5 minutes, even the physical mixtures maintained a constant amount dissolved for 30 minutes. However, proportions 1:1 and 1:2 gave the best results, exceeding the 1:2 dissolution rate in the first 20 min with 21% KTZ dissolved in the medium. The HPMCAS HF TSD 1:1 rendered 26% dissolved KTZ at t = 30 min. After 45 min, a decrease was observed in all proportions, although there is a significant difference (< 5% dissolved) at 60 minutes compared to pure KTZ (**p =0.0040 *and* 0.0023; *p =0.0304), as shown in **Figure 7b.** These results agree with those obtained theoretically by the calculation of the F-H interaction parameter χ, which would lead to think that drug-polymer molecular interactions are developing. It is noteworthy to mention that, although the dissolved amount of KTZ improves with the manufacture of TSD, the average rate taken from 0 to 60 minutes remains close to 0, shown by the slope value in **Figure 7**. Also, a decrease in the amount dissolved can be seen after 20 minutes for 1:2 and 2:1 proportions and after 30 minutes for 1:1 ratio. This depletion suggests a precipitation of KTZ, which can be explained upon the pH of the media being 6.8, considering that the drug is poorly soluble at pH greater than 3.



	PURE KTZ	TPM-KTZ:HPMCAS HF 1:1 (room temperature)	TSD-KTZ:HPMCAS HF +10%TEC 1:2 (Tm: 90 °C)	TSD-KTZ:HPMCAS HF +10%TEC 1:1 (Tm: 90 °C)	TSD-KTZ:HPMCAS HF +10%TEC 2:1 (Tm: 90 °C)
Slope	0.003128	0.01397	-0.05255	0.05589	0.01741

Figure 7: Dissolution profiles of pure KTZ, TPM and TSD in phosphate buffer pH: 6.8. a) TSD (KTZ:HPMCAS HF+plasticizer) at proportions 1:2, 1:1 and 2:1, d) Graph of the percentage dissolved in 60 min of TSD (KTZ:HPMCAS HF+plasticizer). Pure KTZ and the physical mixture were used as controls. Results are presented as mean and SEM (n=2). Linear regression and one-way ANOVA and Tukey post hoc test were performed. **p = 0.0040, 0.0023, *p = 0.0304.
Source: Own elaboration.

CONCLUSIONS

Part of the success of SD depends on an adequate prediction of the miscibility of materials starting from the study of the molecular structures and physicochemical properties of the individual components. Another predominant factor is the manufacturing process.

In the present study, we calculated the miscibility of BPM using the F-H theory via the melting point depression method. Experimentally, we evaluated the effect of the proportion of three different polymers, by means of DSC and dissolution tests methods. The thermograms show that the selected polymers are miscible with the low-solubility model drug KTZ, because of the considerable reduction in the enthalpy of fusion in the PM and TSD.

The TSD with the HPMCAS HF polymer enhance the dissolution of KTZ during the first 20 min (< 13% dissolved) when this carrier is added at the highest proportion. For this polymer, the dissolution rate is significantly higher at lower drug concentrations, indicating that uniform dispersion of the drug in the polymer lattice at the molecular level is achieved. TSD comprising PVP/VA 64 showed an increase in the dissolution rate in all proportions analyzed, specifically at the highest drug concentration (2:1). This high drug proportion maintained a higher percentage dissolved (88%) at 60 minutes and a slope of 1.321, but these systems do not have a statistically significant effect with respect to pure KTZ. TSD formulated with *Soluplus*® did not show an increase in the dissolution rate at pH 1.2 in any of the proportions tested (1:2, 1:1, 2:1).

Furthermore, we were able to observe the importance of correctly choosing the pH of the experimental model. Conditions in which the API will be analyzed must relay in the correlation with the absorption site in the digestive system. In this regard, milligram-scale studies can aid in quick assessment of this condition in a desired formulation.

The theoretical values of the F-H interaction are favorable for all three polymeric carriers, indicating miscibility with KTZ in BPM. However, in experimental conditions, this thesis was only verified for PVP/VA 64 and HPMCAS HF systems. In the case of *Soluplus*®, although the thermograms show a reduction in the enthalpy of fusion of KTZ, this depletion is not reflected in the dissolution rate, probably due to the interaction of this polymer-plasticizer carrier with water, which is not it is taken into account in the theoretical F-H calculations through melting point depression in the BPM.

These data demonstrate that dissolution rate depends on the correct choice of the polymeric carrier. Plasticizers are essential to reduce the T_g of the aforementioned polymers, allowing proper processing at low temperatures. Both theoretical and milligram-scale analysis can lead to reducing costs, and mitigating risks associated with SD's manufacturing methodologies, by carrying out a preliminary evaluation able to rule out systems that are not compatible with each other, using less amount of material and applying a methodology theory to make an educated guess. Theoretical and experimental calculations were useful to evaluate whether they can be applicable to scalable processes and perform an evaluation on the parameters that should be considered in SD manufacturing.

The studies carried out in the present work provide a practical and simple approach to guarantee the dissolution of low-solubility model drugs. However, further theoretical (docking) and characterization (FTIR, PXRD, etc.) studies are considered necessary to better understand the drug-polymer interactions at a molecular level and to extend our understanding of these systems, aiding in the decision making for polymeric carriers and their applications in SD manufacturing by melting technologies at a laboratory scale.

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