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Automation Potential of a New, Rapid, Microscopy-Based Method for Screening Drug–Polymer Solubility

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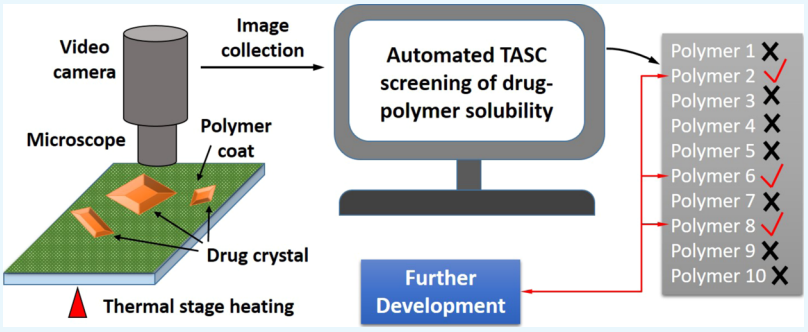

ABSTRACT: For the pharmaceutical industry, the preformulation screening of the compatibility of drug and polymeric excipients can often be time-consuming because of the use of trial-and-error approaches. This is also the case for selecting highly effective polymeric excipients for forming molecular dispersions in order to improve the dissolution and subsequent bio-availability of a poorly soluble drug. Previously, we developed a new thermal imaging-based rapid screening method, thermal analysis by structure characterization (TASC), which can rapidly detect the melting point depression of a crystalline drug in the presence of a polymeric material. In this study, we used melting point depression as an indicator of drug solubility in a polymer and further explored the potential of using the TASC method to rapidly screen and identify polymers in which a drug is likely to have high solubility. Here, we used a data bank of 5 model drugs and 10 different pharmaceutical grade polymers to validate the screening potential of TASC. The data indicated that TASC could provide significant improvement in the screening speed and reduce the materials used without compromising the sensitivity of detection. It should be highlighted that the current method is a screening method rather than a method that provides absolute measurement of the degree of solubility of a drug in a polymer. The results of this study confirmed that the TASC results of each drug–polymer pair could be used in data matrices to indicate the presence of significant interaction and solubility of the drug in the polymer. This forms the foundation for automating the screening process using artificial intelligence.

1. INTRODUCTION

Polymers have been widely used in pharmaceutical solid dosage forms as functional excipients to create matrices in which the drug can be molecularly dispersed.[1−3] Such solid dispersions have been widely studied for oral dosage forms and can significantly alter the release rate of the drug in comparison to the crystal form of the drug.[4−6] When a molecular dispersion is formed, if the polymer is highly soluble in the gut fluid, the formation of the drug–polymer dispersion will enhance the dissolution of the drug that is molecularly dispersed in the polymer.[7] If the polymer is poorly soluble, the drug release will be retarded and can be used to control the release rate of the drug.[8] In order to allow the drug to form a molecular dispersion with the polymer, the drug needs to be soluble in the polymer and form a kinetically stable supersaturated solution in the polymer, or to form a thermodynamically stable solution in which the drug is available at therapeutically useful levels.[9] In much of the pharmaceutical literature, these conditions have been loosely termed "drug–polymer miscibility" and often used interchangeably with "drug–polymer solubility".[10,11] Therefore, it is highly useful in the pharmaceutical industry when developing such drug–polymer-based products to first know whether the drug is soluble in the polymer and can form stable miscible products.

In the true thermodynamic terms, formation of true solutions requires a negative change in the free energy of mixing, ΔG_{mix}. Most of the pharmaceutical polymers and low molecular weight drug combinations have limited solubility ranges. A range of theoretical and experimental methods has been reported for measuring this.[10,12,13] Examples of such

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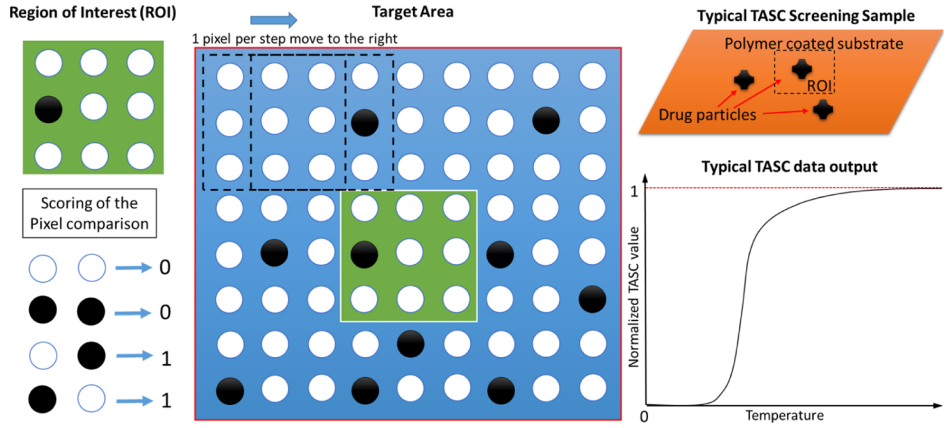

Figure 1. Illustration of the working principle of TASC, the typical sample configuration used for TASC screening, and the typical TASC data output.

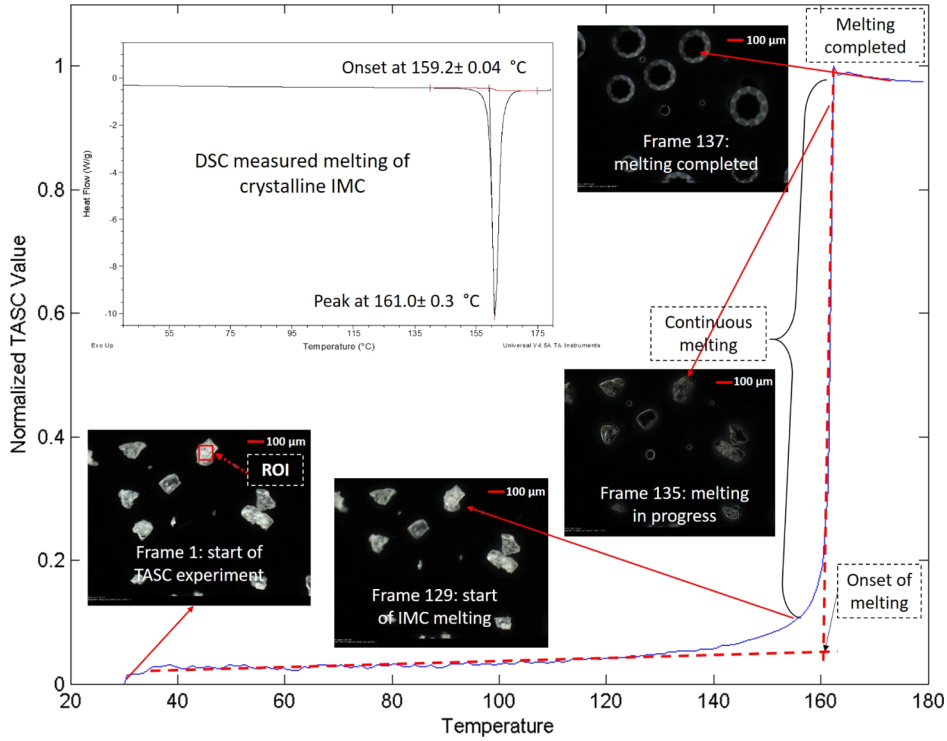

Figure 2. Typical TASC plot of the melting of a crystalline drug particle (IMC) with the microscopic images at different stages of heating, and the comparison with the melting onset temperature with the DSC (insert). The heating rate was 20 °C/min in both cases.

measurement include using the solubility parameter to estimate the favorable interaction of drugs and polymers,[14,15] using melting point depression and the subsequent calculation based on the extended Flory–Huggins theory to determine drug solubility in the polymer,[12,16,17] using thermal analysis such as differential scanning calorimetry (DSC) to measure the recrystallization and dissolution end point of a preprepared supersaturated solid dispersion.[18,19] However, the experimental procedures are highly time-consuming and all rely on theoretical models of uncertain accuracy to predict miscibility and solubility.[20] Here, we report on the use of thermal analysis by structure characterization (TASC) to rapidly obtain data that are indicative of drug–polymer solubility. TASC is a microscopy-based method and is performed by analyzing the feature changes of the crystalline drug particle as it is heated in a linear fashion and melted on a thin layer of the polymer of interest.[21] The speed of the detection of the key measure of the drug–polymer interaction (melting point depression) using TASC is 20–40 times faster than the conventional DSC method without loss of the sensitivity of detection.[22] Each TASC run only required 1/1000th of the quantity of the material that is needed for a conventional DSC test.[22]

The working principle of the screening method has been described in detail previously.[21] It is a conventional light microscope-based method which detects changes in images automatically. It does this by comparing a sequence of images pixel by pixel. In brief, a series of images of the samples during the thermal treatment (either being heating, cooling or isothermal) is taken, and the TASC algorithm quantifies the changes of features in successive micrographs of samples. Such quantification is performed by subtracting the numerical value of each pixel of the selected region of interest (ROI) from its

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precursor, and the sum of the moduli of differences is calculated (as illustrated in Figure 1). The normalization of the TASC value within one thermal scan is performed by taking the ratio of each image to the final set of images in which there is no sequential change. In practice, for samples melted on a polymer film surface, the flow of liquid may take some time to cease, in which case, the stable state is reached at a temperature higher than that shown in the graphs. Hence, the normalized TASC values as plotted may not reach unity.

Our previous data demonstrated the ability to screen a single drug against a range of pharmaceutical grades of polymers.[22] Using this as the conceptual foundation, the potential for automating the screening method is being explored in this study. In order to validate the automation potential, it is vitally important to demonstrate that the behavior observed in a single drug case can be generalized to a wide range of different drugs with a wide range of physicochemical properties. For this purpose, five drugs were tested against ten polymers. Using conventional methods, screening fifty drug/polymer combinations would have required an impractical amount of time, but the speed of the TASC method allows such large-scale measurements. Such a rapid throughput indicates the potential for automation as the next stage of the development of the TASC screening method.

It is important to be clear what TASC does and does not measure. TASC is a screening method rather than a method that provides absolute measurement of the degree of solubility of a drug in a polymer. If the drug crystal is able to dissolve in the polymer, a reduced melting point of the drug crystal will be detected by TASC. However, this observation does not necessarily carry any information about the concentration range over which the system is soluble or the temperature range of solubility. If no depression of the melting point is detected, this is a clear indication of the lack of solubility. The TASC method, when it is limited to simple melting point determination, must therefore be regarded as a screening method which can eliminate combinations of the drug and polymer where thermodynamically stable solutions cannot be formed. This in itself can be valuable as the method requires very small amounts of material and is very rapid. Melting point depression is a single point determination; in this paper, we extend this to the use of the whole TASC curve by employing principal component analysis (PCA). This approach allows the construction of a database which will enable the behavior of new drug/polymer combinations to be compared directly with the behavior of a wide range of other combinations. Such a database will be a requirement if the method is to be developed as a high throughput automated system.

2. RESULTS AND DISCUSSION

Figure 2 shows an example of the sequence of feature changes observed in the melting of a crystalline drug particle, indomethacin (IMC), and their corresponding normalized TASC value on a TASC plot. The point where the curve for the pure drug deviates from the baseline is well defined and may be used to measure the onset of the melting point of the drug.[21,22] As seen in Figure 2, the extrapolated melting onset measured by TASC is 160.5 ± 1.4 °C, which is very close to that measured by DSC (DSC melting onset = 159.2 ± 0.04 °C and DSC melting peak = 161.0 ± 0.3 °C). The 2 °C deviation between the onset measured by TASC and DSC could be attributed to the difference on the method used to measure the melting of the drug particles. In a DSC pan, the melting signal is an average of the bulk powder in the pan through a highly thermal-conductive metal pan surface, whereas in TASC, the signal is the feature change of individual drug particles.

When the glass substrate is coated with a thin film of the polymer of interest, the same principle of measurement applies. An example TASC plot for a crystalline drug particle heated on a variety of polymer surfaces is shown in Figure 3 (the complete set of plots for all five drugs is shown in the Supporting Information). In comparison to the IMC drug particle melting on the un-coated glass substrate, the behavior of the crystals on polymer surfaces is somewhat different: the curves are more complex and deviate from the baseline at a temperature below the pure drug melting point. This behavior is typical of a melting point depression effect because of the interaction of the drug and the polymer. As shown in Figure 3, the degree of depression of the melting of the crystalline drug particle changes depending on the type of the polymer underneath. In this case, the data show that Eudragit EPO (EU) induced the highest level of depression of the IMC melting and polyvinyl alcohol (PVA) (with a high degree of hydrolysis of 88%) caused least depression. This indicates that EU is most soluble with IMC and PVA being the least soluble when comparing the set of polymers' capability of mixing with IMC. These results agree extremely well with the data reported in the literature and measured using other methods.[23−25] Therefore, such a difference can be used as the underlying principle for using TASC to rank the usefulness of the polymeric excipients for solid dispersion formulation development.

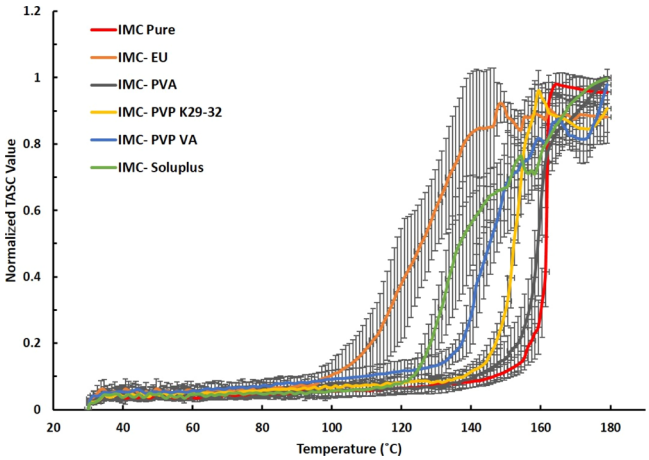

Figure 3. TASC plots for IMC as a pure drug and on PVA, PVP K29/32, PVPVA, Soluplus, and EU (n = 5).

For studying individual cases, the depressed onset of melting temperature measured by TASC may be measured using a number of methods.[22] However, as shown in Figure 4, the TASC curves can become less easy to be analyzed using any of the methods used previously, and a certain amount of subjectivity can be introduced. In addition, using a single onset data point, as demonstrated in Figure 2, does not make use of the whole data set and, for the purposes of a high throughput method, does not lend itself readily to automation.

Classification of the TASC curves by PCA is rapid. It allows the use of the whole TASC data set of each run which builds the potential foundation for automation. In addition, each data set may be added to an existing set so that new measurements may be classified by comparison with existing data on drug−

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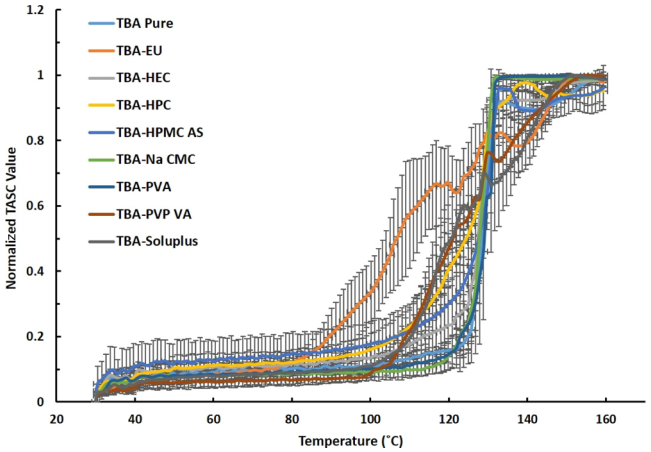

Figure 4. TASC plots for TBA as the pure drug and on HEC, HPC, HPMCAS, NaCMC, PVA, PVPVA, Soluplus, and EU (n = 5).

polymer interactions. The first two components (P1 and P2) separate the data well, and P2 correlates well with the estimated reduced melting point. P1 accounts for 91.9% of the variance and P2 accounts for 5.8% (the loading plot of the P1 and P2 can be found in the Supporting Information). As is often the case in PCA, component 1 responds to the whole shape of the curve. Component 2 has contributions that are evenly balanced around the zero of the reduced temperature, which corresponds to the melting point of the pure drug. Thus, transition points or flatter regions near the pure melting point of a TASC curve tend to cancel out and reduce the value of P2. At lower temperatures, the higher intensities results in more positive values of P2, tending to make lower melting point curves contribute to the positive intensity of P2. However, it is important to point out that all sections of the curve contributes significantly to P2 and that as data bases are further developed, the contributions from all of the curves to P2 may become useful in the classification of drug−polymer interactions.

Using the combined data, it is possible to put any drug−polymer combination on a universal scale. Thus, for any particular combination, it is possible to compare with a range of drug−polymer interactions. A plot of the first two principal components (P1, P2) of the five model drug and 10 model polymer combinations is shown in Figure 5. Usually, in such an analysis, it would be expected that PCA would separate the data into clusters rather than the spread of values observed here. However, this spread merely reflects the range of drug−polymer solubility/interactions that exist.

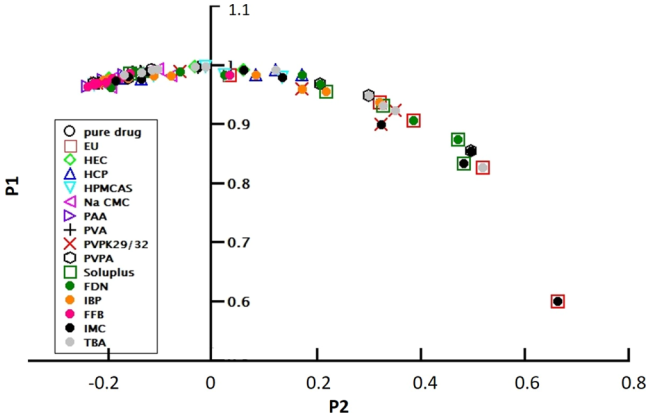

Figure 5. Plot of the first and second principal components, P1 vs P2, of the PCA analysis of the TASC full curve data of five drugs with ten polymers.

Using IMC as the example, the P2 component separates clearly the highly soluble pair of IMC−EU from the poorly soluble pair of IMC−PVA, which agrees well with the existing literature data obtained using other solubility measurement methods.[23−25] The TASC data of the IMC melted on the other polymer are scattered in between the P2 scale of EU and PVA, possibly indicating different degrees of solubility. The TASC data of the pure drug crystals on uncoated glass slides (with no melting point depression) are all clustered at the left-hand side of the PCA plot. Therefore, it is valid to suggest that the drug−polymer pairs clustered in the left-hand side of the PCA plot are poorly soluble, and the higher P2 values on the scale the pairs have the higher likelihood of being soluble. However, as discussed below, some degree of caution is necessary.

In order to compare P2 with the onset of melting, a parameter, ΔT, has been defined as the difference between the onset temperature of the depressed melting (measured by TASC when the drug crystals were placed on top of the polymer-coated glass substrate) and the melting of the pure drug (measured without the presence of polymer). A plot of ΔT versus P2 is shown in Figure 6. P2 is negative for all systems having a value of ΔT between 0 and −6 °C. Melting point depressions (the absolute value of ΔT) greater than 6 °C lead to a positive value of P2.

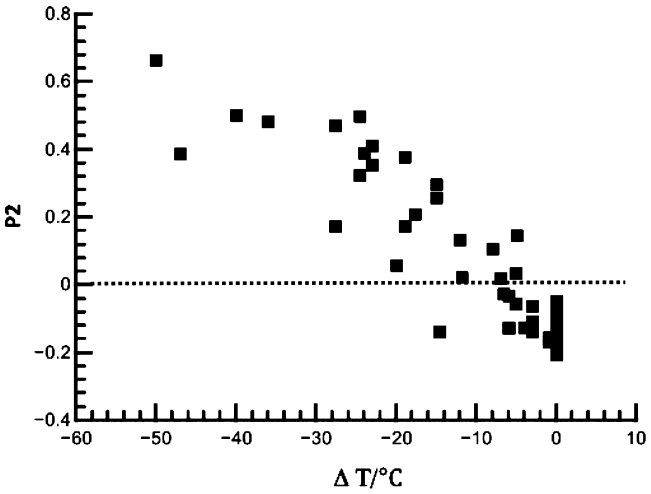

Figure 6. Plot of the values of the second principal component (P2) vs the depression of onset of the melting temperature (ΔT).

In the TASC experiments described here, the amount of drug available at the point of contact with the polymer film underneath is very limited. Therefore, the ratio of the drug to polymer detected in each TASC measurement is very low. If the drug was soluble in the polymer at room temperature, from the thermodynamic point of view, merely placing a crystal of the drug on the polymer would result in the spontaneous formation of a solution. This happens with sodium chloride and water, for example. In our case, the dynamics of the situation are such that the spontaneous behavior is not possible. Therefore, as the system is heated, two things happen, the polymer becomes more mobile (increased molecular mobility with increasing the temperature by heating to the temperature below the T_g of the polymer, and the trans-

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formation to its rubbery state when it is heated to above the T_g of the polymer) and more able to form solutions and, in general, increasing temperature results in increasing solubility. The drug crystal is absorbing heat energy, and therefore, intermolecular interactions are being weakened. At some point during heating, the increasing solvent properties of the polymer and increasing weakening of the intermolecular bonds are sufficient that the energy derived from solution formation is enough to cause the drug to dissolve with the consequent observation of crystal melting. The lower the melting point of the drug is, the less will be the energy required to overcome the internal bonding of the crystal.

The depressed melting (ΔT) observed in our experiments is not easily compared to the depressed melting observed in calorimetric experiments because of the difference in the working principle of these two analytical methods. In the calorimetric method for measuring melting point depression in the presence of the polymer, an intimate mixture of the drug and polymer is made, and conditions as near possible to thermodynamic equilibrium are sought.[20] This necessarily involves a very slow heating regime of typically 0.5 or 1 °C/min.[10,13] The experiment measures the solubility of the drug in the polymer by reaching the temperature where the drug–polymer ratio is such that a saturated solution of the drug may be formed. At this temperature, the drug melts, and a solution is formed. This is observed calorimetrically as the uptake of the heat of fusion of the drug and the temperature of melting is used to calculate the reduction of the melting point. Therefore, the variations of ΔT measured by TASC may not carry an implication about the magnitude of the drug solubility, except in the case where ΔT is close to zero, as in this case, no solution takes place. Generally, ΔT will depend on the intrinsic intermolecular bonding in the drug crystal and both the dynamics and solvating power of the polymer. For this reason, the ΔT value may not be a very good indicator of actual solubility, and the use of PCA to classify curves as a whole may be a better way to build a database in which comparisons are made between curves of test materials and the known behavior of existing combinations that are already stored in the database.

Therefore, our methodology for each drug sorts the polymers into a comparative spectrum of being soluble, partially soluble, and insoluble with the drug but does not measure the absolute degree of solubility of the drug in the polymer. In order to explore the predictive capacity of the TASC method, the literature search on the physical stability of this study's model drug–polymer combinations reported by other studies was carried out (the systems and references can be found in the Supporting Information). It became clear that in the literature, the methods of preparation of drug–polymer dispersions and storage conditions were highly variable. In this study, experiments were carried out with the sample of drug–polymer dispersions being prepared by spin-coating and being stored under a unified storage condition, ambient temperature/75% RH. The conditions are commonly used for accelerated testing of storage stability. Therefore, it is useful to examine the predictive capacity and correlation of the TASC measurement to real storage stability. The analysis was performed based on the assumption that drug–polymer combinations with good solubility would have good storage stability. The system was classified as stable if there was no drug crystallization after one month of storage. Two drug loadings, 30 and 60% (w/w), were used. Table 1 compares the stabilities with the second principal component (P2) of the PCA analysis.

Table 1. Summary of the TASC-Predicted Storage Stability and 1 Month Real-Time Storage Stability Data of 14 Pairs of Drug–Polymer Dispersions with 30 and 60% (w/w) Drug Loading

drug–polymer dispersions	P2 value from PCA	TASC-predicted stability	1 month real-time stability (30% drug loading)	1-month real-time stability (60% drug loading)
FFB–PVPVA	−0.22	No	no	no
IBP–PAA	−0.21	No	no	no
IMC–PAA	−0.18	No	**yes**	no
TBA–PAA	−0.17	No	no	no
FFB–HPC	−0.17	No	no	no
IMC–HPC	−0.13	No	**yes**	**yes**
FDN–PAA	−0.12	No	no	no
TBA–HPMCAS	−0.01	No	no	no
FFB–EU	0.03	Yes	yes	**no**
IBP–PVP K29/32	0.17	Yes	**no**	**no**
FDN–Soluplus	0.21	Yes	yes	yes
IBP–EU	0.32	Yes	yes	**no**
TBA–EU	0.51	Yes	yes	yes
IMC–EU	0.66	Yes	yes	yes

It is clear from the data in Table 1 and Figure 7 that ΔT and P2 (generated from TASC data) correlate well in prediction of storage stability, but it is notable that the two IMC samples show anomalous behavior, being stable when the TASC results suggest instability. This may be the formation of stable supersaturated solutions.[26] In some cases, the 60% system is not stable but the 30% system is. This agrees well with the general trend described in the literature that a lower drug-loaded system containing less amorphous drug and significantly more polymer is characterized by having a greater physical stability than the sysytems with higher drug loading. For some drug–polymer combinations, this could be also caused by the drug loading being over the solubility limit for the system which is not predicted using the TASC method. This highlights the fact that TASC is an indicator of solubility but does not make quantitative predictions of solubility limits not the effects of varying humidity.

A glaring anomaly is the IBP-PVP K29/32 dispersion where no stability is observed, but the reduction in melting point is very clear. However, the polymer PVP K29/32 is highly hygroscopic and absorbs water very readily. Under these storage conditions, it can absorb a considerable amount of water (20% at 25 °C) which can disrupt drug polymer hydrogen bonding.[27] It should be born in mind that TASC measurements and predictions do not take account of the effects of moisture. Therefore, the instability of the model samples may be attributed to the effect of humidity instead lack of drug–polymer solubility in the dry state.

In the case of IMC–HPC, the melting of IMC is 44 °C below the T_g of HPC. This may help with kinetic stabilization. In addition, crystallization requires the presence of appropriate nuclei. If these are absent, crystallization will not take place unless supersaturation is so high that homonucleation occurs. Both of these might lead to kinetic stability as opposed to thermodynamic stability. These results indicate that using thermodynamic measurement for solubility detection is more

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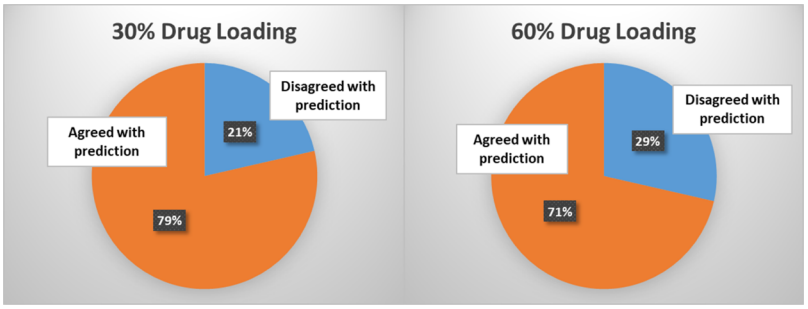

Figure 7. Distribution of the agreement between TASC prediction (using the P2 value of the PCA analysis of the TASC data) and the real-time storage stability data using ambient temperature/75% RH.

reliable than kinetic approaches. The kinetically stabilized systems are inherently unstable, and slight changes in storage conditions may result in crystallization.

A more extensive study on the physical stability of drug−polymer dispersions (prepared by film formation) is reported by Fridgeirsdottir and co-workers, in which 10 different drugs at 10% loading with 3 different polymers (HPMCAS, PVPVA, and Soluplus) were prepared and stored under 75% RH/40 °C.[28] In all cases, the storage resulted in drug recrystallization within a year, with one exception.[28] FFB−PVPVA and FDN−Soluplus at 30 and 60% loadings in our work (stored at ambient temperature/75% RH) can be compared with the same samples at 10% loadings (stored at 40 °C/75% RH) reported by Fridgeirsdottir and co-workers,[28] as shown in Table 2. We find that for FFB−PVPVA, drug crystals were formed after 1 month, but for FDN−Soluplus, we did not observe any drug crystal formation (which may be related to the higher storage temperature used in ref 28). It might be expected that with very high drug loading of the FDN−Soluplus dispersion, drug crystallization would have occurred in one month if it occurred for 10% drug loading in 24 weeks. This suggests that in a system that is intrinsically unstable, the effect of preparation history might be critical. It seems clear that the prediction of storage stability under extreme storage conditions is not easy and that sample preparation history may play an important role so that simple comparisons are not straightforward.[20]

Table 2. Comparison of the Predicted Storage Stability Using P2 Values of the PCA Analysis of TASC Results of This Study and the Experimental Storage Stability Reported in ref 28

drug	polymer	P2 value from PCA	stability*[a]
FDN	HPMCAS	0.02	1 week[b]
	PVPVA	0.22	16 weeks[b]
	Soluplus	0.47	24 weeks[b]
FFB	HPMCAS	−0.21	6 weeks[c]
	PVPVA	−0.22	less than 4 weeks[c]
	Soluplus	−0.16	6 months[c]

[a]Stability* here refers to the storage stability using drug recrystallization as the key indicator under the storage condition of 40 °C/75% RH. [b]Data given as numerical values in ref 28. [c]Data estimated from figures in ref 28.

An interesting sub-group of drug−polymer systems are listed in Table 3. For these drug−polymer combinations, the onset of the drug melting temperature is well below the T_g of the polymer. It would be expected that in a polymeric system below the glass transition temperature, polymer dynamics would be so slow that any interaction with the drug crystal would be precluded. However, the interaction is not with the bulk polymer, but at the polymer surface where the interface with air allows a greater free volume than in the bulk. Therefore, it must be concluded that the mobility at the interface is much greater than in the bulk, allowing crystal/polymer interactions to take place.

Table 3. Drug−Polymer Combinations in which the Onset of Drug Melting Temperature is below the T_g of the Polymer

system	T_m (°C)[a]	T_g (°C)[b]	depression (ΔT) (°C)[c]	$T_g - T_m$ (°C)
TBA−HEC	121	130	−7	9
IBP−Soluplus	61	72.2	−15	11.2
IMC−PVP K29/32	136.5	160.3	−24.5	23.8
TBA−PVP K29/32	105	160.3	−23	55.3
FDN−HPC	117.4	205	−27.6	87.6
TBA−HPC	109	205	−19	96
IBP−PVP K29/32	61	160.3	−15	99.3

[a]Onset of drug melting measured by DSC. [b]T_g of polymer measured by DSC. [c]Depression of the onset of drug melting in the presence of the polymer measured by TASC.

3. CONCLUSIONS

A large number of TASC data sets of the measurements of the crystalline drug particle melting on top of the thin films of a wide range of typically used polymers in solid dispersion formulations were generated. With the intension of exploring the automation potential of the TASC method for rapid formulation screening, the full TASC plots of all drug−polymer pairs were analyzed using PCA instead of comparing the depressed onset of melting as a single point measurement. This demonstrated the clear potential of TASC to be developed into an automatic rapid formulation screening tool for drug−polymer-based formulations to allow the formulators to rank the miscibility between the drug of interest and a list of potential polymeric excipients. It should be highlighted that the current method is a screening method rather than a method that provides absolute measurement of the degree of solubility of a drug in a polymer.

It is not simply the rapidity of the heating rate of the TASC measurement that facilitates high throughput; there is also the option of using arrays of microscopes or, more likely, borescopes. Off-the-shelf devices are readily available at low

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cost. Their tubelike shape is with a 6 mm diameter, which means an array of 10 × 10 could be easily achieved. Creating a hot stage of 60 × 60 mm is also straightforward. This would increase throughput by ×100. Within each field of view, 10 crystals could be automatically identified and located. This means carrying out 1000 experiments simultaneously is far from impossible. The instrument itself could be inexpensive with a small footprint on a laboratory bench. The data analysis could also be automated so the user could see averaged plots and PC graphs within minutes. The hot stage could be designed that each row of 10 borescopes could use a different heating rate, thus enabling the role of kinetics to be evaluated.

4. EXPERIMENTAL SECTION

4.1. Materials. The five model drugs used in this study are tolbutamide (TBA) (with >98% purity), IMC (with 98.5% purity), both of which were purchased from Sigma-Aldrich (St. Louis, US), felodipine (with ≥99% purity) (FDN) which was purchased from Molekula (Dorest, UK), and fenofibrate (FFB) (with ≥99% purity) and ibuprofen (IBP) (with ≥98% purity) were kindly donated by Merck Serono (Darmstadt, Germany) and BASF (Ludwigshafen, Germany), respectively. The 10 polymers used in this study are as follows: polyvinyl pyrrolidone vinyl acetate (PVPVA) Plasdone S630 (with an average molecular weight of 47,000 g/mol), hydroxyl propyl cellulose (HPC) Klucel EF PHARM (with an average molecular weight of 80,000 g/mol), hydroxypropyl methyl cellulose acetyl succinate (HPMCAS MG) AquaSolve (with an average molecular weight of 103,200 g/mol), sodium carboxy methyl cellulose (Na CMC) Aqualon CMC 7L2P (with an average molecular weight of 49,000 g/mol), polyvinyl pyrrolidone (PVP) Plasdone K29-32 (with an average molecular weight of 58,000 g/mol), hydroxyethyl cellulose (HEC) Natrosol 250 L PHARM (with an average molecular weight of 90,000 g/mol) were kindly donated from Ashland Industries Europe GmbH (Schaffhausen, Switzerland). Polyacrylic acid (PAA) (with an average molecular weight of 450,000 g/mol) was purchased from Sigma-Aldrich (St. Louis, US). Poly (butyl methacrylate-co-(2-dimethylaminoethyl) methacrylate-comethyl methacrylate) (EU) (with an average molecular weight of 47,000 g/mol) was kindly donated by Evonik Industries (Darmstadt, Germany). PVA (88%) (with an average molecular weight of 44.053 g/mol) hydrolyzed was purchased from Acros Organics (New Jersey, USA). Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus) (with an average molecular weight in the range of 90,000−140,000 g/mol) was kindly donated from BASF (Ludwigshafen, Germany). NaCl (with ≥99.0% purity) was purchased from Thermo Fisher Scientific (Geel, Belgium).

4.2. Preparation of the Polymer-Coated Substrates Using Spin Coating. Spin-coated thin films of different polymers on glass substrates were prepared using Spincoat G3P-8 (Specialty Coating Systems, Indianapolis, US). Solutions of the various polymers were prepared using different solvents and concentrations as shown in Table S1 in the Supporting Information. In all cases, 2−5 drops of the prepared solutions were transferred to the top of a glass coverslip (Academy cover slip 18 × 18 mm 01.6−0.19 mm thick, Smith Scientific Limited, Ken, UK) followed by continuous spinning using 2000 rpm for 120 s to evaporate the solvent and formation of the polymeric thin films. The complete solvent removal at the end of the spin-coating process was confirmed by no measurable weight loss when the samples were tested using thermal gravimetric analysis with heating to 105 °C and maintaining at isothermal conditions for 15 min. In our previous study, it was confirmed that the thickness of the polymer films does not significantly affect the TASC results.[22]

4.3. Preparation of Drug−Polymer Films and Stability Testing. In order to evaluate the stability of the five model drugs in the different polymers, spin-coated solid dispersions of each drug in three different polymers (which are predicted by TASC to have high, intermediate, and low drug−polymer solubility) were prepared. The solid dispersion films with the drug: polymer concentration ratios of 0:10 (w/w) to 10:0 (with 10% w/w increments) were prepared by spin-coating (using the same spin-coating conditions described in the section above). The films were stored under the conditions of 75% RH/ambient temperature (21.7 ± 1.8 °C). To rapidly screen the stability of the aged films, the recrystallization of drug in the aged films was used as an indicator of the instability of the dispersion. The spin-coated solid dispersion samples were examined using a Leica DM LS2 polarized light microscope (Leica Microsystems Wetzlar GmbH, Wetzlar, Germany) that was connected to JVC digital color video camera and a PC. The aged samples were examined thoroughly under the polarized light microscope after 1 week, 2 weeks, and 1 month of storage.

4.4. TASC Analysis. TASC analysis was performed using the TASC system composed of a Linkam MDSG600 heat−cool automated temperature-controlling stage attached to a Linkam imaging station equipped with a reflective LED light source and a x10 magnification lens (Linkam Scientific Instruments Ltd, Surry, UK). Liquid nitrogen was purged into the stage for controlled cooling of the stage during the cooling cycles. The drug particles used for TASC analysis were selected within a size range of (90−100 μm) using a sieving method. Particles passing through a 100 μm sieve and retained using a 90 μm sieve were collected and used for TASC analysis. TASC analysis was performed on the drug particles on different polymeric films with a heating rate of 20 °C/min.

For all TASC experiments, stacks of images of the sample were collected at a rate of 1 frame/°C (with a starting temperature of 30 °C) using a black background to restrict the analysis to the crystalline drug particles and reduce the noise to signal ratio. These acquired images were analyzed using TASC software, and the changes in the appearance of drug particles were converted into normalized TASC curves. For each drug−polymer combination, the TASC analysis was performed on at least five different drug particles for each set of data using relatively large ROIs. The optimization criteria of the selection of ROIs are the reproducibility of the data and the minimization of the variations in dimensionality between the particles. Such optimization is explained in detail in our previous work.[22] The TASC plots presented in all data figures are the average values taken from the TASC results of five different particles.

4.5. Differential Scanning Calorimetry. A Q-2000 MTDSC (TA Instruments, Newcastle, USA) equipped with a RC 90 cooling unit was used to characterize the melting and the glass transitions of all raw materials. The instrument was calibrated prior to the sample characterization. At least three repeats of 2−3 mg of each sample were analyzed using standard aluminum TA-crimped pans (TA Instruments, Newcastle, USA). Universal Analysis software was used to analyze the collected DSC results. A heating rate of 20 °C/min

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was used in all cases in order to be consistent with the TASC measurements. All DSC results were highly reproducible with standard deviations of all data point being less than 0.025% for the melting onset measurements and less than 0.18% for the melting peak temperature measurements.

4.6. Principle Component Analysis. PCA was carried out using the IBM SPSS 25 software package. The application of PCA to the whole data set of TASC profiles of drugs and polymers encountered the problem that the temperature range of each set of experiments was determined by the pure drug melting point. The range must run from the starting temperature (30 °C) to the drug melting point. In the experiments described here, the range of melting points is from 76 °C (IBP) to 161 °C (IMC). Because sampling is made at regular temperature intervals, this means that the number of data points for each set of drug measurements is different. Scaling the sampling interval to ensure the same number of data points on for each drug would change the density of points and, for low melting drugs, oversample the curves. The approach taken was to estimate the melting point of the pure drug by taking the maximum of the first derivative of the TASC curve, then subtracting this value from all the measured temperatures. Thus, the reduced temperature, termed as T_R, is defined as $T_R = T_S - T_M$, where T_S is the sampling temperature and T_M is the measured melting point of the pure drug by TASC. In this way, all the curves are set about a common temperature zero. In order to get the same number of points on each curve, only data in the range of T_R = +17 to −46 °C are used. PCA is applied using this normalized data.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c00429.

Polymeric solutions concentrations, solvent systems, and thickness for the prepared spin-coated films for TASC analysis; pure IMC on glass slides without polymer coating and the glass slides coated with 10 different polymers; all curves are taken as the average of 5 TASC measurements on 5 different drug particles; pure TBA on glass slides without polymer coating and the glass slides coated with 10 different polymers; pure felodipine (FDN) on glass slides without polymer coating and the glass slides coated with 10 different polymers; pure FFB on glass slides without polymer coating and the glass slides coated with 10 different polymers; pure IBP on glass slides without polymer coating and the glass slides coated with 10 different polymers; DSC thermograms showing the melting point depression of felodipine by Soluplus and PVPVA using 9:1 drug to polymer PM and 5 °C/min; loading plot of the PC1 and PC2 of the PCA analysis; literature search results of the relevant solubility and storage stability information of IMC−polymer pairs; literature search results of the relevant solubility and storage stability information of IBP−polymer pairs; literature search results of the relevant solubility and storage stability information of TBA−polymer pairs; literature search results of the relevant solubility and storage stability information of felodipine−polymer pairs; literature search results of the relevant solubility and storage stability information of FFB−polymer pairs (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

TASC	thermal analysis by structure characterization
ROI	region of interest
DSC	differential scanning calorimetry
TBA	tolbutamide
IMC	indomethacin
FDN	felodipine
FFB	fenofibrate
IBP	ibuprofen
PVPVA	polyvinylpyrrolidone/vinyl acetate
HPC	hydroxyl propyl cellulose
HPMCAS	hydroxypropyl methyl cellulose acetyl succinate
NaCMC	sodium carboxymethyl cellulose
EU	Eudragit EPO
PVP	polyvinylpyrrolidone
HEC	hydroxyethyl cellulose
PAA	polyacrylic acid
PVA	polyvinyl alcohol

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