OUTPUT 1	Prototype of the technique for offline preformulation screening and inline process optimisation analysis
Project specific objective	1) Innovative pharmaceutical formulations and technologies
Output description	Prototypes of techniques for off line preformulation screening and processing optimisation analysis. The novel thermal imaging technique with rapid formulation screening and process (HME and 3D printing) optimisation will significantly speed up the product delopment process with extremely low quantity of APIs (TRL5)
Project Output Target	1
Expected project specific result (s)	1 new technique that allows: i) significant time saving for multicomponent formulation screening (expected gain 75% in processing time) and ii) reducing costs since it requires very low quantities of drug (expected gain 75% in products quantities). The developed technology will be ready-to-use and increase the competitiveness of SMEs. The technology will be developed in collaboration with SMEs with the aim to be implemented as a part of their future advanced product/service to increase the competitiveness of SMEs'. 1 Patent is targeted.
Partner responsible	PP5 (University of East-Anglia)
Other Partners involved	PP7 (University of Greenwich), OP5(Cyversa), OP6(Linkam Scientific Instruments Ltd)

Summary of the objectives, activities and achievements obtained during the project

There are 4 Deliverables composes the Output 1 as follow. These reflect the key **objectives** of output 1.

- D 1.1.1. Technique development for polymorphic and co-crystal/amorphous screening (report submitted)
- D 1.1.2. Validation of new applications in rapid preformulation screening and process optimisation (report submitted)
- D 1.1.3. Filed patent application
- D 1.1.4. Granted patent

Activities:

- ***Research***: research work has been conducted in collaboration with PP7, OP5 and OP6. A full-time PDRA has been employed to work alongside of the PP5 research team led by Dr Qi. Two streams of research focuses have been developed/under development, novel preformulation screening technology (D 1.1.1 and D 1.1.2; both deliverable reports were completed and submitted) and patentable drug printing technology for medical devices (D 1.1.3 and D 1.1.4).
- ***Industrial and stakeholder engagement***: the IMODE team has been actively reach out to the industrial users of the technologies developed in O1 through conferences, exhibitions, company face-to-face visits. As a result of such interaction and outreach effort, PP5 has now obtained a 2-year research collaboration project fully funded by a world-leading medical device companies starting Sep 2019. PP5 has also jointly put in a 2 PhD studentship funding application with a world leading pharmaceutical company in Dec 2019 (the outcome will be expected in March 2020). Due to confidentiality reasons, we are not allowed to reveal the identities of these companies.
- ***Training***: PP5 has been visiting a wide range of companies and universities to communicate our technologies and provide training to their staff/students. The PDRA employed on this output has received a wide range of scientific and soft translational skill training to enhancement their future employability.

The **achievements** can be categorised into:

1. Knowledge: Created/Increased skill and capacities

1 new technique that allows: i) significant time saving for multicomponent formulation screening (expected gain 75% in processing time) and ii) reducing costs since it requires very low quantities of drug (expected gain 75% in products quantities).

2. Socio-Economic: Increased business activities/capacities (new products, processes, services, techniques)

The developed technology is ready-to-use. The technology has been developed in collaboration with the SMEs (Linkham, Cyversa) with the aim to be implemented as a part of their future advanced products/services to increase theur competitiveness.

3. Socio-Economic: Patent application

1 Patent in preparation of filling

1) Description of the scientific and technological achievements

Introduction

Polymers have been widely used in pharmaceutical solid dosage forms as the functional excipients to create matrices that the drug can be molecularly dispersed in (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 facilitate the enhanced dissolution of the drugs that are 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). The similar material selection principle can be also applied to the screening of co-amorphous and co-crystal drug combinations.

In order to allow the drug to form a molecular dispersion with the polymer, the drug needs to be 'soluble' in the polymer matrix to a certain degree (9). This has been loosely used in the most pharmaceutical literature as drug-polymer miscibility (10, 11). Therefore it is highly useful to pharmaceutical industry when developing such drug-polymer based products to firstly know whether the drug and polymer can form stable miscible productsIn the true thermodynamic terms, miscibility requires the negative change in the free energy of mixing, ΔG_{mix}, Most of the pharmaceutical polymer and low molecular weight drug combinations have limited miscibility ranges. A range of theoretical and experimental methods have been reported for measuring miscibility (10, 12, 13). Examples of such measurement include using the solubility parameter to estimate the likelihood of mixing (14, 15), using melting point depression and the subsequent calculation based on the extended Flory-Huggins theory to determine drug solubility in polymer (12, 16, 17), using thermal analysis such as DSC to measure the recrystallization and dissolution end point of a pre-prepared supersaturated solid dispersion (18, 19). However they highly time-consuming and rely on models of uncertain accuracy to predict miscibilities (20). Here we report on the use of thermal analysis by structure characterization (TASC) to address the problem of predicting drug polymer miscibility. TASC is a microscopy based method and is performed by analyzing the feature changes of the crystalline drug particle that is heated in a linear fashion and melted on a thin layer of the polymer of interest (21) (as seen in **Figure 1**). The speed of the detection of the key measure of drug-polymer miscibility (melting point depression) using TASC is 20-40 times faster than the conventional differential scanning calorimetry (DSC) method without loss of the sensitivity of detection. Each TASC run only required 1/1000th of the quantity of the material that is needed for a conventional DSC test (22).

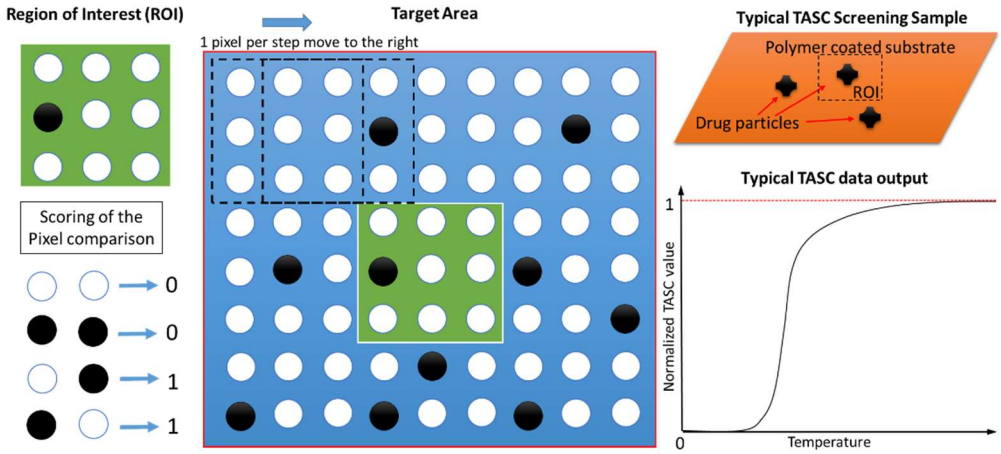


Figure 1. Illustration of the working principle of TASC, the typical sample configuration used for TASC screening and the typical TASC data output.

The working principle of the screening method has been described in detail previously (21). It is a conventional light microscope based method which detect changes in images automatically. It does this by comparing a sequence of images pixel by pixel, as illustrated in Figure 1. In brief, the video of the samples during 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 precursor and the sum of the moduli of differences is calculated. The normalisation 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.

Here in the Section I of the Results and Discussion part of the report we present the data that demonstrates the pharmaceutical applications TASC in formulations screening for drug-polymer and co-crystal/amorphous. These are delivered **Deliverable 1.1.1**. In the Section II of the Results and Discussion we present the data on validation of the screening method we developed. These are delivered **Deliverable 1.1.2**. In the As TASC is a microscopic method, instead of using a bulk physical mixture of drug and polymer, the analysis only requires the observation of a single drug particle's melting behaviour in the presence of polymer/drug. We developed polymer/drug coated microscopic slides as the solid substrate to sprinkle the drug particles on. **Figure 2** illustrates the procedure of a single test on a pair of drug and polymer which can be easily scaled up to screening multiple combinations of drug and polymer.

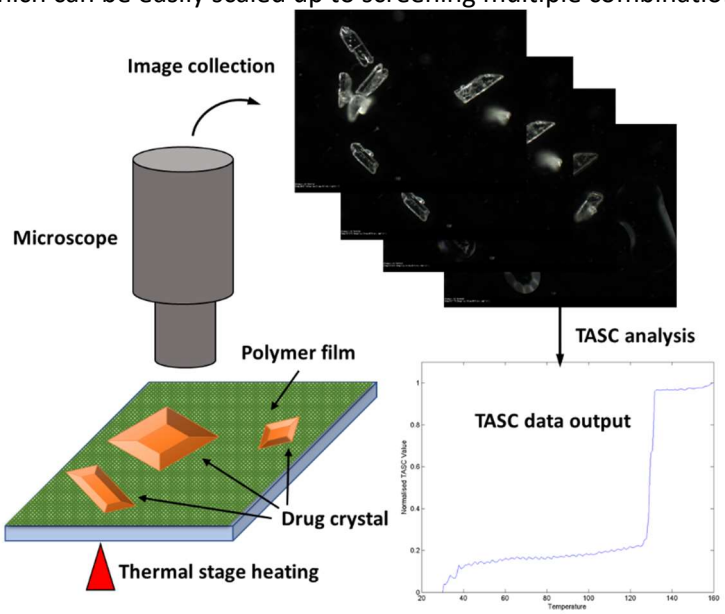


Figure 2. Illustration of the TASC based drug-polymer or drug-drug miscibility screening method

Experimental Section

Materials

The drugs used in this study, felodipine, paracetamol, ibuprofen and nicotinamide were purchased from Molekula (Dorest, UK). Polyvinyl pyrrolidone vinyl acetate with a commercial name known as Plasdone™ S630 (PVPVA), hydroxyl propyl cellulose, commercially known as Klucel™ EF PHARM (HPC), hydroxypropyl methyl cellulose acetyl succinate, commercially known as AquaSolve™ (HPMCAS-MG grade), sodium carboxy methyl cellulose, commercially know as Aqualon™ CMC 7L2P (Na CMC), polyvinyl pyrrolidone, commercially known as Plasdone™ K29-32 (PVP) and hydroxyethyl cellulose, commercially known as Natrosol™ 250 L PHARM (HEC) were kindly supplied by Ashland Industries Europe GmbH (Schaffhausen, Switzerland). Polyacrylic acid (PAA) was ordered from Sigma-Aldrich (St. Louis, US). Eudragit® E PO (poly(butyl methacrylate-co-(2-dimethylaminoethyl) methacrylate-comethyl methacrylate)) was kindly provided by Evonik Industries (Darmstadt, Germany). Polyvinyl alcohol (PVA) with 88% hydrolysation was purchased from Acros Organics (New Jersey, USA). Soluplus® (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer) was kindly supplied from BASF (Ludwigshafen, Germany). NaCl (≥ 99.0 %) was purchased from Thermo Fisher Scientific (Geel, Belgium).

Preparation of polymer/drug coated glass substrates by spin coating

Spin coated thin films of different polymers/drug were prepared using Spincoat G3P-8 (Specialty Coating Systems, Indianapolis, US). In all cases, 2-5 drops of the prepared solutions were transferred to the top of a glass coverslip

followed by continuous spinning using 2000 rpm for 120 seconds to evaporate the solvent and formation of the polymeric thin films.

Thermal Analysis by Structural Characterisation (TASC)

TASC characterisation was performed using TASC system composes of a Linkam MDSG600 heat-cool automated temperature controlling stage attached to a Linkam imaging station equipped with reflective LED light source and a x10 magnification lens (Linkam Scientific Instruments Ltd, Surry, UK). TASC characterisation was conducted using two experimental methodologies. Different TASC experimental settings were used to investigate drug-polymer miscibility. Heating only (30 - 180 ˚C) and heating-isothermal (heating to above the melting and keeping isothermal for 15 minutes) programs at 20 ˚C/min were used for the TASC screening. For all TASC experiments, stacks of images of the sample were collected simultaneously in a rate of 1 frame/ºC using black background to restrict the analysis to the crystalline felodipine form I particles and reduce the noise to signal ratio. These acquired images were analyzed using TASC software and the changes in the appearance of felodipine particles during the different methods were converted into normalized TASC curves against temperature or time.

Thermogravimetric Analysis (TGA)

TGA Q5000 (TA Instruments, Newcastle, USA) was used to study the thermal stability of felodipine and the polymers used in this study before the design of the TASC temperature programmes to eliminate any degradation possibility during the screening process. A heating rate of 20 ºC/min for the range 25-550 ºC was used for estimating the degradation onset of the compounds. Two replicates were tested and Universal Analysis software was used to analyze the acquired data.

Differential Scanning Calorimetry (DSC)

DSC was used to identify the thermal properties such as the melting and the glass transition temperatures of different raw materials (at 20 ºC/min heating rate). A Q-2000 MTDSC (TA Instruments, Newcastle, USA) equipped with a RC 90 cooling unit was utilized for the characterization of these materials. The instrument was calibrated prior to the sample characterization. At least three replicates of 2-3 mg of each sample were scanned using standard aluminum TA crimped pans (TA Instruments, Newcastle, USA). Universal Analysis software was used to analyze the collected data.

IR imaging

In order to understand the miscibility and diffusivity of felodipine in the polymeric spin coated films and the possibility of drug-polymer interaction, drug particles over glass coverslip as a control or representative spin coated polymer films (Eudragit E PO, PVPVA, Soluplus or HEC) representing miscible, partially miscible or immiscible binary systems respectively were heated at 20 ºC/min from 30-140 ºC and then kept isothermal slightly above the melting of the drug for 15 minutes to allow for the maximum possible interaction between felodipine and the polymeric films. The samples then analysed using Nicolet iN10MX infrared microscope (Thermo Fisher Scientific, Madison, WI, US) with 25 µm spatial resolution in transmission mode using the coverslip glass as a reference. Fast maps were acquired with 1 scan at 16 cm^{-1} resolution per pixel.

Principle component analysis (PCA)

Principal component analysis was carried out using the IBM SPSS 25 software package. Application of PCA to the whole data set of drug and polymers has the problem that the temperature range of each set of experiments is determined by the pure drug melting point. The range must run from the starting temperature (20 °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). Since 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 TR, is defined as TR= TS-TM. Where TS is the sampling temperature and TM 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 TR= +17 to -46 °C is used. PCA is applied using this normalised data.

Results and discussion

Section I Deliverable 1.1.1

Standardization of the analysis of melting point depression using TASC

A range of experiments were conducted in order to standarise the operational procedure of the screening method, including the measurement of the melting onset and the ROI selection for the data analysis. 2nd derivate method was used for identifying the onset of the melting The improvement in the reproducibility using large ROI was concluded and used in the rest of experiments. The details of these developments were described in the publication generated from IMODE project.

Drug-polymer miscibility screening using TASC

TASC analysis was used to experimentally detect the onset of melting point depression of felodipine in the presence of polymers. As seen in **Figure 3**, the polymers led to different level of depression of the melting of crystalline felodipine. The depressed melting points are summarized in **Table 1**. Based on the magnitude of depression of the onset of the drug melting, the polymers can be ranked in the order of Eudragit E PO > HPC > Soluplus > PVPVA > HPMCAS > HEC = PVP K29/32 > PAA> Na CMC = PVA, with Eudragit E PO being most miscible with felodipine. The predicted miscibility by TASC with Eudragit, Soluplus, PVPVA and HPMCAS agree well with literature data. However within literature there is no direct comparison of ten polymers. Therefore the traditional methods used for predicting the drug polymer miscibility was used to compare with the TASC results.

The miscibility of felodipine in the different polymers was ranked using the widely used solubility parameter method and the results alongside the TASC results are summarised in **Table 1**. Solubility parameter approach uses the difference in the solubility parameter (Δδ) between the drug and the polymer/drug to rank the miscibility[13-15]. Based on this approach, felodipine is expected to have good miscibility with eight of the studied polymers, including PAA, PVPVA, Eudragit E PO, HPC, Soluplus, HEC, HPMCAS, PVP K29/32. When the Δδ values are close, it is difficult to used solubility parameter to confidently rank the miscibility as it is pure theoretical method. Within these eight polymers, experimentally HEC, PVP and PAA show nearly no melting point depression when tested using TASC indicating poor miscibility. The solubility parameter method also predicts PVA and Na CMC being partial miscibility with felodipine as their Δδ values fall between 7-10. The TASC results confirmed both are at the bottom of the miscibility rank and showed no melting point depression. The comparison with the prediction based on TASC results, it is clear that solubility parameter is a fairly accurate for predicting highly miscible systems, but extremely unreliable for analysing partially and poorly miscible systems and could product highly misleading predictions in the preformulation stage.

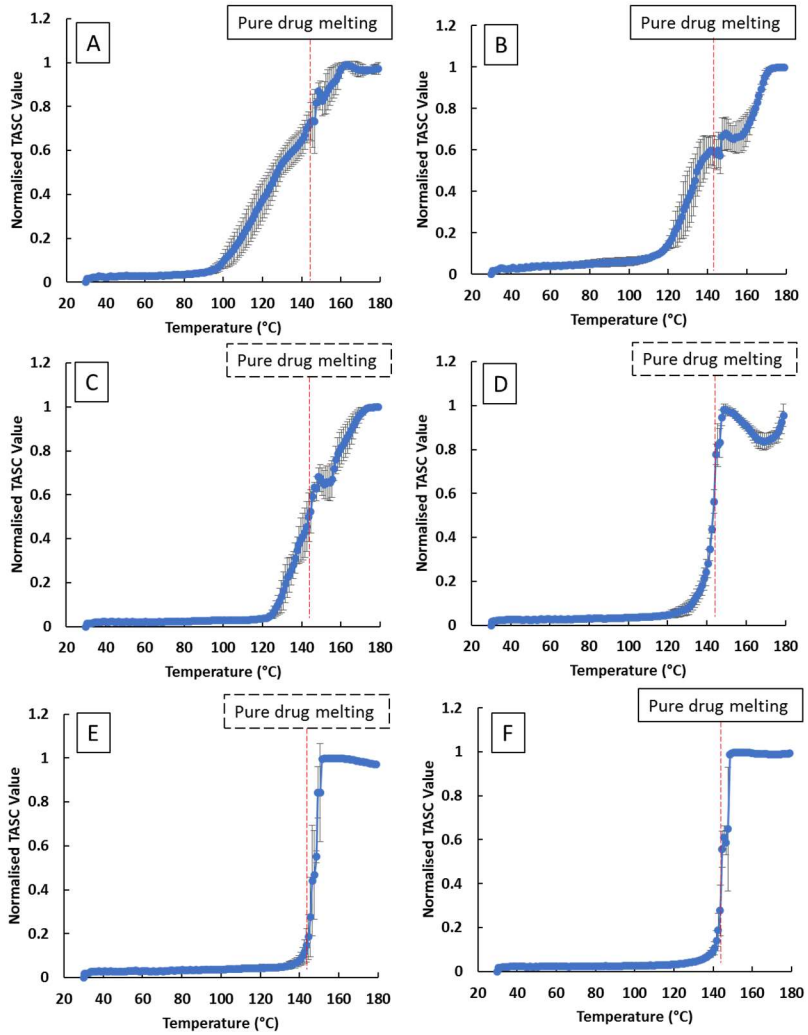


Figure 3. Melting point depression of felodipine form I particles caused by different polymeric spin coated substrates detected by TASC analysis using 20 °C/min and large ROIs; A) felodipine-Eudragit E PO, B) felodipine-Soluplus, C) felodipine- PVP VA, d) felodipine- HPMC AS E) felodipine- Na CMC and F) felodipine-PAA

Table 1. Solubility parameter values, thermal transitions (melting, glass transition and the measured depression in melting) with different methods of ranking for the compounds used in this study

Compound	δ	Δδ	TASC T_m depression (°C)	Δδ ranking	TASC T_m depression ranking
Felodipine	20.8	---	---	---	---
Soluplus	24.3	3.5	121.9	5	3
Eudragit E PO	18.8	2.0	98.1	3	1
PVP K29/32	26.3	5.5	141.6	8	6-7
PVPVA	22.3	1.5	123.8	2	4
HPMCAS	25.7	4.9	132.7	7	5
HPC	23.2	2.4	119.8	4	2
HEC	25.0	4.2	141.6	6	6-7
PAA	21.3	0.5	142.5	1	8
PVA	30.5	9.7	144.6	10	9-10
Na CMC	28.9	8.1	144.6	9	9-10

Confirming miscibility using IR imaging

In order to further validate the screening method and confirm the between the different polymers with felodipine, the samples were analyzed using IR imaging after TASC heat-isotherm screening. The hypothesis for the investigation is based on noticing the possible mixing and diffusion the drug into the soften polymer due to the miscibility. If this is the case, IR imaging should show the chemical mapping of both drug and polymer at the original location of the molten drug particle. On the other hand, if there is no diffusion or interaction, the mixture is more likely immiscible and high drug concentrated should be detected by the IR. As shown in **Figure 4A** and **B**, felodipine form I converted into its amorphous form after melting as indicated by the blue shift in its NH stretching from 3372 to 3339 cm^{-1} due to the stronger intermolecular hydrogen bonding between its molecules in the amorphous form as reported in the literature[29-32]. Compared to the pure drug without any polymeric substrate, felodipine showed diffusion in Eudragit E PO film with the outer boundary circles were mixture of the two compounds (**Figure 4C** and **D**). In addition, monitoring the NH stretching of the drug, revealed a shift in its NH stretching to higher wave number as the drug diffuses away from the center of the molten drug particle 'green zones showed the shift compared to the central red zone'. This indicates that the intermolecular interactions between the drug and Eudragit E PO are weaker compared to the drug in its amorphous or even the crystalline states. In contrast to Eudragit E PO, the drug also showed a noticeable diffusion in PVP VA film with more stronger interaction as indicated by the presence of a shoulder in the IR spectra of the blend in the outer zones of the mixture to lower wave number 3290 cm^{-1} (**Figure 4E** and **F**). For Soluplus, as seen in **Figure 4G** and **H,** it was noticed that felodipine diffused in the polymer and the presence of shoulder at approximately 3000 cm^{-1} which may indicate stronger interaction between Soluplus and felodipine compared to the drug alone but it may be due to the spectral interference between the two compounds. Finally, felodipine doesn't seem to diffuse in HEC film and there is no interaction between the two compounds as seen in **Figure 4I** and **J**. The overall results of IR imaging were consistent with the data collected from TASC screening. In both methods the drug showed interaction (melting point depression, diffusion in the polymer film and shifting in the IR bands).

Drug-drug co-amorphous screening using TASC

The data on drug-polymer miscibility set the foundation of the TASC method for screening. Drug-drug co-amorphous screening was then explored using TASC method. The co-amorphous drug delivery systems have been widely investigated in pharmaceutical community as an alternative formulation strategy for delivery poorly soluble drugs. A co-amorphous system can be described as a multi-component single phase amorphous solid system which lacks periodicity in lattice and is associated by weak and discrete intermolecular interactions between the components. There are two types of co-amorphous systems that have been reported recently, drug–drug combinations and drug–excipient mixtures. For drug-drug co-amorphous systems, two pharmacologically relevant drugs intended for multidrug therapies are combined, where one of drugs stabilize other one in the amorphous form. Both drugs act as an active component and stabilizing excipient at the same time. In this study, felodpine and paracetamol were selected as the model system.

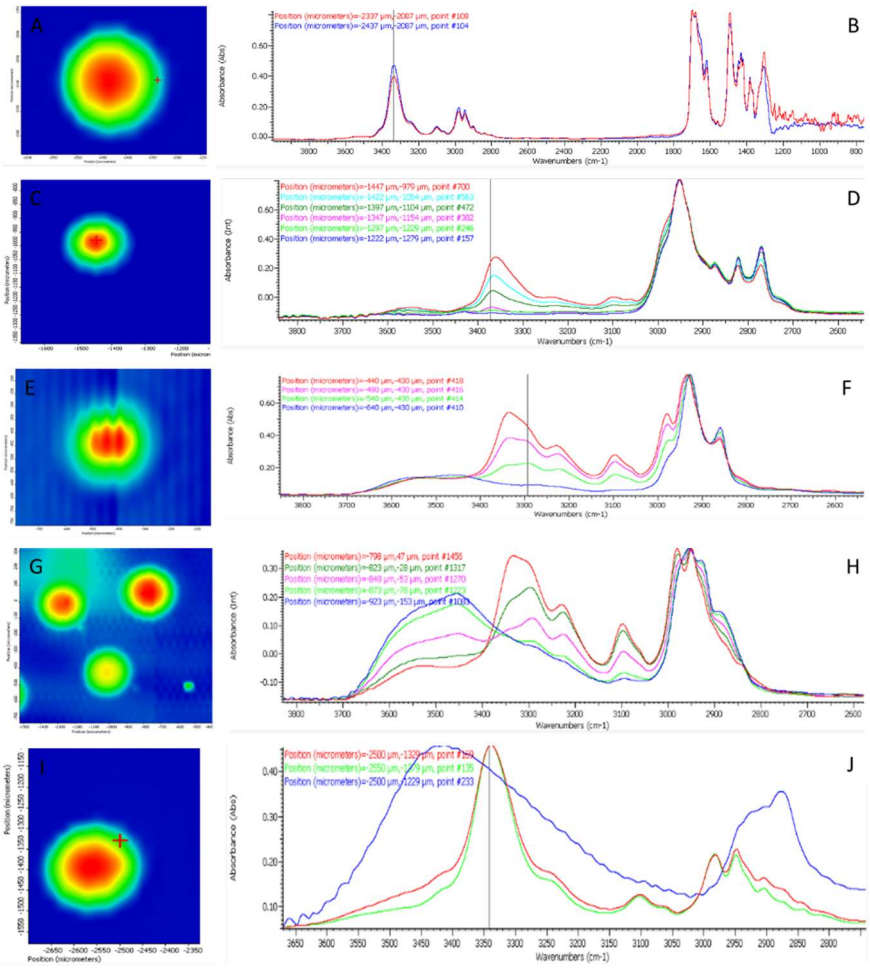


Figure 4. IR imaging of pure felodipine particles on representative polymeric substrates of miscible and immiscible blends; A and B are the 2D IR image and spectra of different boundary circles of molten felodipine 'amorphous form'; C and D are the 2D IR image and spectra of different boundary circles of molten felodipine over Eudragit E PO film; E and F are the 2D IR image and spectra of different boundary circles of molten felodipine over PVP VA film; G and H are the 2D IR image and spectra of different boundary circles of molten felodipine over Soluplus film and I and J are the 2D IR image and spectra of different boundary circles of molten felodipine over HEC film

Structural-wise, the model drugs of this study, felodipine and paracetamol show multiple potential hydrogen bonding sites. However the interaction affinity between paracetamol and felodipine is highly depended on the competition with paracetamol-paracetamol and felodipine-felodipine interactions. The Hansen solubility parameters can be used as a crude prediction measure of such affinity. The solubility parameter of paracetamol and felodipine are reported as 29.9 and 21.76, respectively, indicating poor miscibility. Therefore, it is expected that when different proportion of the felodipine and paracetamol was mixed to form co-amorphous system, the result co-amorphous would have different stability. As seen in **Figure 5**, the physical mixtures of the two drugs with different ratios exhibit clear different TASC response, indicating different level of miscibility when different felodipine to paracatamol ratios were used.

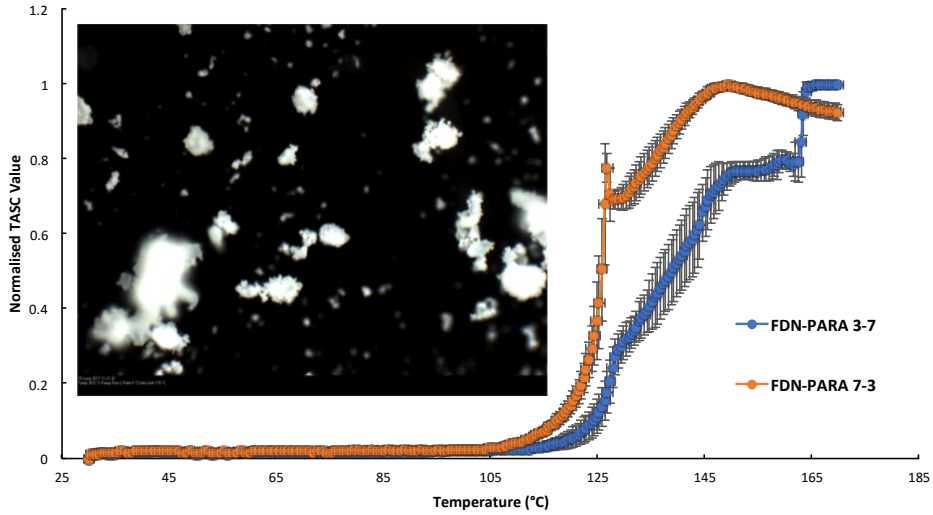


Figure 5. TASC results of felodipine-paracetamol with mixture ratios of 3:7 and 7:3 with inserted TASC image acquired during the test

As predicted, different real-time physical stabilities of the co-amorphous systems with different felodipine-paractamol ratios were observed. As seen in **Figure 6**, the co-amorphous of paracetamol-felodipine with 1:2 molar ration (= 3:7 weight ratio) show the best physical stability on aging even under stressed conditions.

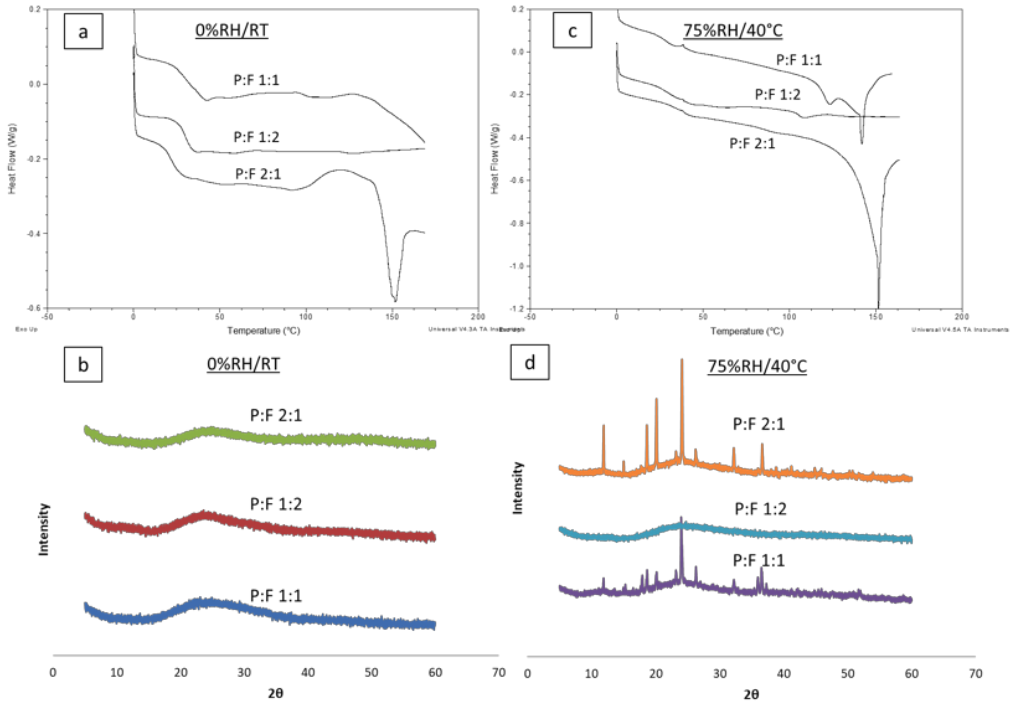


Figure 6. 7 days physical stability data of P-F co-amorphous 1:1, 1:2 and 2:1 (a) DSC and (b) PXRD of the samples aged under under 0% RH/RT; (c) DSC and (d) PXRD data of the samples aged under 75%RH/40ºC

Drug-drug co-crystal screening using TASC

Ibuprofen co-crystals with co-forms nicotinamide and saccharin were tested for exploring the potential of using TASC to screen co-crystals materials. These are well-documented co-crystals and well suited as examples to validate the TASC screening results. As seen in **Figure 6**, the TASC results correlate extremely well with DSC results of identifying the formation of co-crystals of the two pairs.

Section I Deliverable 1.1.2

Classification of the curves by principal component analysis (PCA) is rapid, allows the use of the whole data set and a may be automated. 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/polymer interactions. The first two components (P1 and P2) separate the data quite well and the second component correlates well with the reduced melting point. Using the combined data it is possible to put any drug/polymer combination on a universal scale so that 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) is shown in **Figure 7**.

Using IMC as the example, the P2 component separates clearly the highly soluble pair of IMC-Eudragit EPO from the poorly soluble pair of IMC-PVA, which agree well with the existing literature data obtained by 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 Eudragit EPO and PVA, possibly indicating different degree of solubility. The TASC data of the pure drugs crystals on non-polymer coated 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 insoluble and the higher P2 values on the scale the pair has the higher likelihood of being soluble. However, as discussed below, some degree of caution is necessary

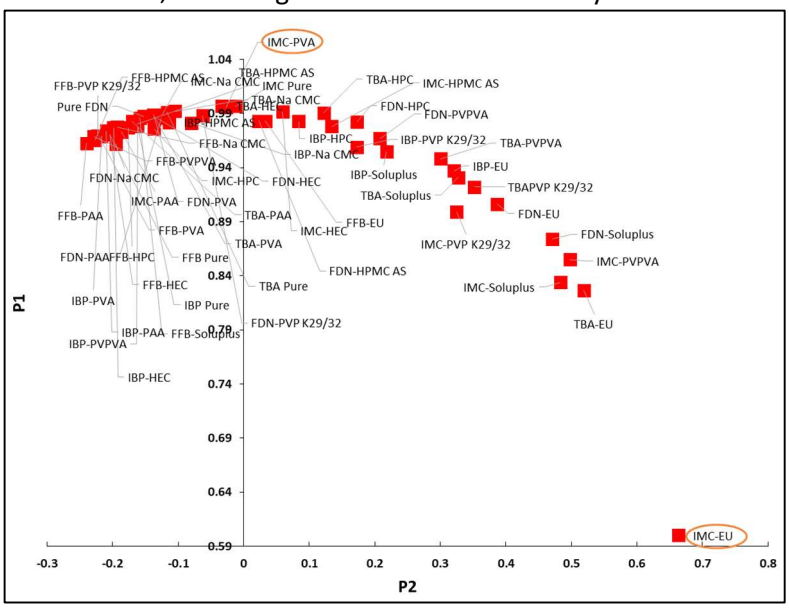


Figure 7 A plot of the first and second principal components, P1 versus P2 of the TASC full curve data of 5 drugs with 10 polymers.

In order to compare P2 with the onset of melting, a parameter, ΔT, has been defined as the difference between the melting point of the pure drug and the onset temperature of melting. A plot of ΔT versus P2 is shown in **Figure 8**. P2 is negative for all systems having a value of ΔT between 0 and -6 °C. Greater depressions have a positive value of P2. It is important to compare the depression of the onset of melting measured by the TASC method with the more conventional calorimetric method. In the calorimetric method an intimate mixture of the drug and polymer is made and conditions as near possible to thermodynamic equilibrium are sought (26). This necessarily involves a very slow heating regime of typically 0.5 or 1 °C per minute. 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 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 melting point.

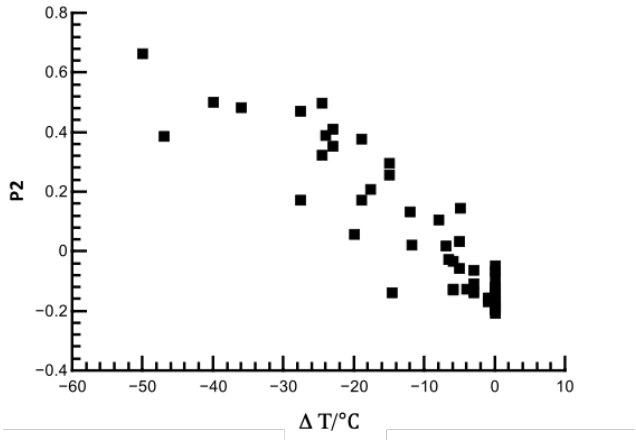


Figure 8 Plot of the second principal component (P2) versus the depression of onset of the melting temperature (ΔT)

In the experiments described here the ratio of drug to polymer is very low. If the drug is soluble in the polymer at room temperature, then 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 behaviour is not possible. So as the system is heated two things happen, the polymer becomes more mobile 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 the 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 and the consequent observation of crystal melting. The lower the melting point of the drug the less energy will be required to overcome the internal bonding of the crystal. The ΔT observed in our experiments is not easily compared to the ΔT observed in calorimetric experiments. The consequence of this is that variations of the ΔT may not carry an implication about 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.

Our methodology therefore sorts drug/polymer pairs into soluble and insoluble but does not necessarily carry an implication of how soluble the drug is in the polymer. In order to explore the predictive capacity of the TASC method, initial literature search was carried out. It became clear that in the literature the conditions of formation of drug polymer combinations and storage conditions were very variable or not well defined therefore experiments were carried out with sample of drug polymer combinations stored at a unified condition, 40 °C and 75% RH. The system was classified as stable if there was no crystallization after one month's storage. Two drug loadings: 30% and 60% were used. Table 1 compares the stabilities with principal component two of the PCA (P2) and the depression of the onset of the melting point (ΔT) measured using TASC. It is assumed that if the measured ΔT is less than 6 °C there is no evidence of miscibility.

Table 2 Summary of the TASC predicted stability and 1-month real-time physical stability data of 14 pairs of drug-polymer dispersions. The dispersions with 30% and 60% drug loading were tested.

Drug-polymer dispersions	**ΔT (°C)**	**P2 value from PCA**	**Predicted stability**	**1-month real-time stability:30% drug load**	**1-month real-time stability: 60% drug load**
FFB-PVP VA	0	-0.22	no	no	no
IBP-PAA	-1	-0.21	no	no	no
IMC-PAA	0	-0.18	no	**yes**	no
TBA-PAA	-6	-0.17	no	no	no

FFB-HPC	0	-0.17	no	no	no
IMC-HPC	-1	-0.13	no	**yes**	**yes**
FDN-PAA	-6	-0.12	no	no	no
TBA-HPMCAS	-5	-0.01	no	no	no
FFB-Eudragit E PO	-8	0.03	yes	yes	**no**
IBP-PVP K29/32	-15	0.17	yes	**no**	**no**
FDN-Soluplus	-28	0.47	yes	yes	yes
IBP-Eudragit E PO	-19	0.32	yes	yes	**no**
TBA-Eudragit E PO	-40	0.51	yes	yes	yes
IMC-Eudragit E PO	-50	0.66	yes	yes	yes

It is clear from the data in **Table 2** that ΔT and P2 correlate very strongly in prediction of miscibility but it is notable the two IMC samples show anomalous behaviour; being stable when the TASC results suggest instability. This may be the formation of stable supersaturated solutions. In some cases, the 60% system is not stable but the 30% system is this is probably simply a miscibility limit for the system. It seems clear that the prediction of shelf life under extreme storage conditions is not easy to predict and that sample history may play an important role so that simple comparisons are not straight forward.
In the case of IMC-HPC, the ΔT of IMC is 44 °C below the T_g of HPC. This may help with kinetic stabilisation. In addition, crystallisation requires the presence of the appropriate nuclei. If these are absent, crystallisation will not take place unless supersaturation is so high that homo-nucleation occurs. Both of these might lead to kinetic stability as opposed to thermodynamic stability. These results indicate one of the limitations of using thermodynamic measurement for solubility is that kinetically stabilised systems are inherently unstable and slight changes in storage conditions may result in crystallisation.

An interesting sub-group of drug/ polymer systems are listed in **Table 3**. In these the onset 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. It must be colluded therefore that the mobility at the interface is much greater than in the bulk allowing crystal polymer interactions to take place.

Table 3 Drug/polymer systems in which the onset temperature is below the T_g of the polymer

System	T_o (°C)	T_g (°C)	ΔT (°C)	T_g-T_o (°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

Conclusion

This study described the development of the development of a rapid drug-polymer and drug-drug miscibility screening method based on TASC. The TASC screening method is 20-40 times faster in terms screening speed compared to the conventional DSC method for melting point depression detection without any reduction in the analytical sensitivity. The results of this study demonstrated the clear potential and advantages (such as fast and inexpensive and user-friendly) of using TASC as a screening method of drug-polymer and drug-drug miscibility

during the preformulation phase of pharmaceutical product development. The next stage of the project will focus on further development and validation of the screening method for co-crystals and identify possible method to develop the high throughput capability of this technique.

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 TASC method for rapid formulation screening, the full TASC plots of all drug-polymer pairs were analysis using PCA instead of comparing the depressed onset of melting as a single point measurement. The PCA results confirmed the ability of TASC to sort the drug-polymer combinations based on the degree of the melting depression which is directly related to the degree of miscibility of the drug in the polymer. This demonstrated the clear potential of TASC being developed into an automatic rapid formulation screening tool for drug-polymer based formulations.

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 cost. Their tube-like shape is with a 6mm diameter means an array of 10x10 could easily be achieved. Creating a hot stage of 60x60 mm is also straightforward. This would increase throughput by x100. Within each field of view is conceivable 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.

References:

1. Baghel S, Cathcart H, O'Reilly NJ. Polymeric Amorphous Solid Dispersions: A Review of Amorphization, Crystallization, Stabilization, Solid-State Characterization, and Aqueous Solubilization of Biopharmaceutical Classification System Class II Drugs. Journal of Pharmaceutical Sciences. 2016;105(9):2527-44.
2. Frank DS, Matzger AJ. Probing the Interplay between Amorphous Solid Dispersion Stability and Polymer Functionality. Molecular pharmaceutics. 2018;15(7):2714-20.
3. Jermain SV, Brough C, Williams RO. Amorphous solid dispersions and nanocrystal technologies for poorly water-soluble drug delivery – An update. International Journal of Pharmaceutics. 2018;535(1):379-92.
4. DiNunzio JC, Miller DA, Yang W, McGinity JW, Williams RO, 3rd. Amorphous compositions using concentration enhancing polymers for improved bioavailability of itraconazole. Molecular pharmaceutics. 2008;5(6):968-80.
5. Hancock BC, Parks M. What is the True Solubility Advantage for Amorphous Pharmaceuticals? Pharmaceutical Research. 2000;17(4):397-404.
6. Brouwers J, Brewster ME, Augustijns P. Supersaturating drug delivery systems: the answer to solubility-limited oral bioavailability? J Pharm Sci. 2009;98(8):2549-72.
7. Craig DQM. The mechanisms of drug release from solid dispersions in water-soluble polymers. International Journal of Pharmaceutics. 2002;231(2):131-44.
8. Tran PH, Tran TT, Park JB, Lee BJ. Controlled release systems containing solid dispersions: strategies and mechanisms. Pharm Res. 2011;28(10):2353-78.
9. Van den Mooter G. The use of amorphous solid dispersions: A formulation strategy to overcome poor solubility and dissolution rate. Drug Discovery Today: Technologies. 2012;9(2):e79-e85.
10. Marsac PJ, Li T, Taylor LS. Estimation of drug-polymer miscibility and solubility in amorphous solid dispersions using experimentally determined interaction parameters. Pharm Res. 2009;26(1):139-51.
11. Qian F, Huang J, Hussain MA. Drug-polymer solubility and miscibility: Stability consideration and practical challenges in amorphous solid dispersion development. J Pharm Sci. 2010;99(7):2941-7.
12. Tian Y, Booth J, Meehan E, Jones DS, Li S, Andrews GP. Construction of drug-polymer thermodynamic phase diagrams using Flory-Huggins interaction theory: identifying the relevance of temperature and drug weight fraction to phase separation within solid dispersions. Molecular pharmaceutics. 2013;10(1):236-48.

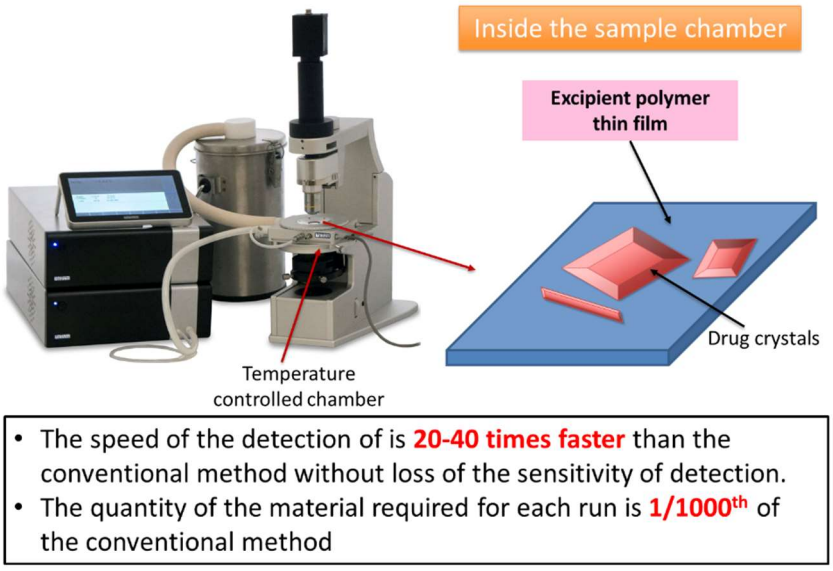
13. Qi S, Belton P, Nollenberger K, Clayden N, Reading M, Craig DQ. Characterisation and prediction of phase separation in hot-melt extruded solid dispersions: a thermal, microscopic and NMR relaxometry study. Pharm Res. 2010;27(9):1869-83.
14. Ghebremeskel AN, Vemavarapu C, Lodaya M. Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: Selection of polymer–surfactant combinations using solubility parameters and testing the processability. International Journal of Pharmaceutics. 2007;328(2):119-29.
15. Alhijjaj M, Bouman J, Wellner N, Belton P, Qi S. Creating Drug Solubilization Compartments via Phase Separation in Multicomponent Buccal Patches Prepared by Direct Hot Melt Extrusion–Injection Molding. Molecular pharmaceutics. 2015;12(12):4349-62.
16. Baghel S, Cathcart H, O'Reilly NJ. Theoretical and experimental investigation of drug-polymer interaction and miscibility and its impact on drug supersaturation in aqueous medium. European Journal of Pharmaceutics and Biopharmaceutics. 2016;107:16-31.
17. Marsac PJ, Shamblin SL, Taylor LS. Theoretical and practical approaches for prediction of drug-polymer miscibility and solubility. Pharm Res. 2006;23(10):2417-26.
18. Mahieu A, Willart J-F, Dudognon E, Danède F, Descamps M. A New Protocol To Determine the Solubility of Drugs into Polymer Matrixes. Molecular pharmaceutics. 2013;10(2):560-6.
19. Knopp MM, Olesen NE, Holm P, Lobmann K, Holm R, Langguth P, et al. Evaluation of drug-polymer solubility curves through formal statistical analysis: comparison of preparation techniques. J Pharm Sci. 2015;104(1):44-51.
20. Knopp MM, Tajber L, Tian Y, Olesen NE, Jones DS, Kozyra A, et al. Comparative Study of Different Methods for the Prediction of Drug–Polymer Solubility. Molecular pharmaceutics. 2015;12(9):3408-19.
21. Alhijjaj M, Reading M, Belton P, Qi S. Thermal Analysis by Structural Characterization as a Method for Assessing Heterogeneity in Complex Solid Pharmaceutical Dosage Forms. Analytical chemistry. 2015;87(21):10848-55.
22. Alhijjaj M, Belton P, Fábián L, Wellner N, Reading M, Qi S. Novel Thermal Imaging Method for Rapid Screening of Drug-Polymer Miscibility for Solid Dispersion Based Formulation Development. Molecular pharmaceutics. 2018;15:5625-36.
23. Liu H, Zhang X, Suwardie H, Wang P, Gogos CG. Miscibility studies of indomethacin and Eudragit(R) E PO by thermal, rheological, and spectroscopic analysis. J Pharm Sci. 2012;101(6):2204-12.
24. Chokshi RJ, Shah NH, Sandhu HK, Malick AW, Zia H. Stabilization of low glass transition temperature indomethacin formulations: impact of polymer-type and its concentration. J Pharm Sci. 2008;97(6):2286-98.
25. Mori Y, Motoyama K, Ishida M, Onodera R, Higashi T, Arima H. Theoretical and practical evaluation of lowly hydrolyzed polyvinyl alcohol as a potential carrier for hot-melt extrusion. Int J Pharm. 2019;555:124-34.
26. Knopp MM, Tajber L, Tian Y, Olesen NE, Jones DS, Kozyra A, et al. Comparative Study of Different Methods for the Prediction of Drug-Polymer Solubility. Molecular pharmaceutics. 2015;12(9):3408-19.

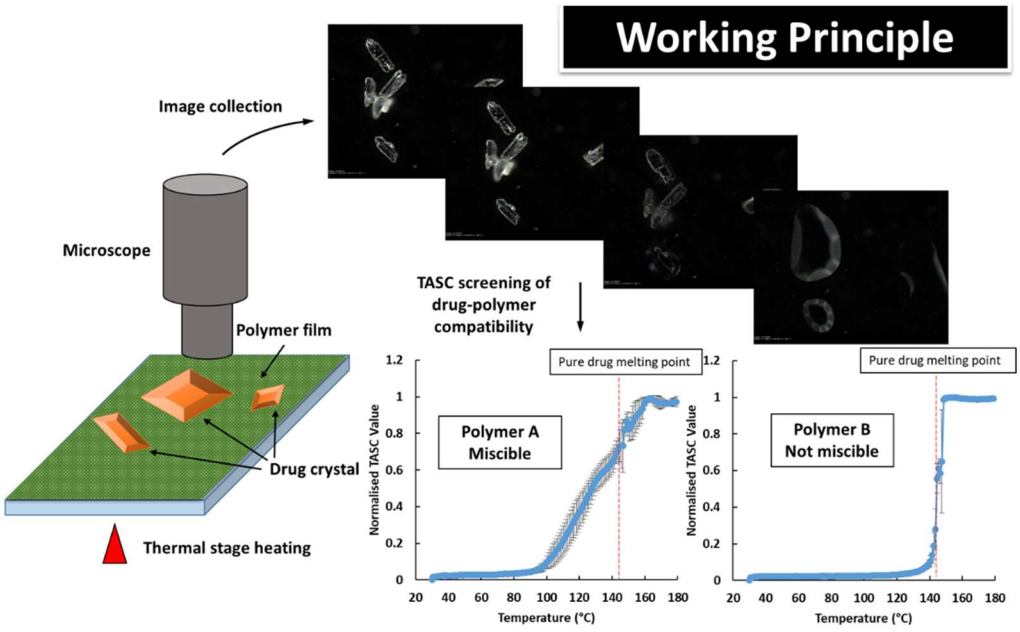
2) Description of the results obtained for the output in term of specific results category and specific result type

Specific results category And Specific result type	Description of the specific results
Knowledge - Created/Increased skill and capacities	1 new technique for formulation screening that allows: i) significant time saving for multicomponent formulation screening (expected save 75% testing time) and ii) reducing costs since it requires very low quantities of drug (expected reduction of 75% in products quantities needed for screening). Based on this new technique for formulation screening, we published 1 high impact publication and with 2 more in the preparation. We presented this research work at multiple international conferences and 2 of them were selected being given as podium presentations to the international pharmaceutical audience. Dr Qi has presented the work as a part of her research work in leading Universities in Germany, Jordan, China, Thailand, and Brazil between 2016 to 2019. In addition to this screening research, inspired by the results, we also applied the knowledge to development of the pharmaceutical application of 3D printing and published 1 peer-reviewed publication. • Reports & high impact scientific publications targeting both academic and industrial users. The publications will show 1) the working principle; 2) validation – Alhijjaj, M., Belton, P., Fabian, L., Wellner, N., Reading, M. & Qi, S. Novel thermal imaging method for rapid screening of drug-polymer miscibility for solid dispersion based formulation development. 2018, Molecular Pharmaceutics. 15, 12, p. 5625–5636 – Muqdad Alhijjaj, Peter Belton, Laszlo Fabian, Mike Reading, Sheng Qi*. The automation potential of a new, rapid, microscopy based method for screening drug-polymer miscibility, ACS Omega, submitted Jan 2020. – Muqdad Alhijjaj, Peter Belton, Laszlo Fabian, Nikolaus Wellner, Mike Reading and Sheng Qi*. A new approach for rapid formulation development of solid dispersion based pharmaceutical products. In preparation – Alhijjaj, M., Nasereddin, J., Belton, P. & Qi, Impact of processing parameters on the quality of pharmaceutical solid dosage forms produced by fused deposition modelling (FDM). 2019, In : Pharmaceutics. 11, 12, 633. – IMODE Deliverable reports D1.1.1 and 1.1.2 • The number of viewing/downloading and citation of the publications will be used as evidence for measuring the increased knowledge (at the end of the project)

	• Detailed description of the target groups contacted that we have been actively engage with targeted end users via conference presentation and 1-1 meetings (IMODE engagement forms and the list as Appendix I at the end of this document) • Within 2019 alone, the research work generated has been presented at MedFit, PharmSci 2019, CRS 2019 and will be presenting at BioFit, AAPS PharmSci 360 2019.
Socio-Economic -Increased business activities/capacities (new products, processes, services, techniques)	The developed technology will be ready-to-use and increase the competitiveness of SME(s). The technology will be developed in collaboration with SME with the aim to be implemented as a part of their future advanced product/service to increase the competitiveness of the SME. We have contacted the following companies and communicated our research with them: • AstraZeneca • UroPharma • Health Innovation Ltd. • PCE Automation • i-BOXit • Consort Medical • Neucine Design • The FlowMakers • LinkedNutri • Janssen, a division of Johnson&Johnson • CooperVision • Hethel Innovation Center • IWIC-Ipswich Waterfront Innovation Center • Chiang Mai medical plant innovation center • CHM Chiang Mai Holding • Bee product Co.Ltd. • Micropsray Technology • ARBURG • Bionica S.L. • Hovione FarmaCiencia SA • Genentech Linkham has used our research in their latest marketing material and provided us a letter of support.
Socio-Economic -Patent applications 1 Patent filling in preparation	Patent prior art search and patent filing preparation with external patent agencies, Haseltine Lake LLP, European Patent & Trade Mark Attorneys. 1 EU patent has been identified which covers one of the area of our invention within 1 of their claims, but has no direct data. We are working on collected more sophisticated data to allow us to be significantly different from the existing patent.

List of documents enclosed as annex

Images	4 images 1. Image of the physical instrumental setup and the technological advancements of the new screening technique. 2. Working principle of the new screening technique 3. Validation of the effectiveness of the new screening method and the advancements in speed of screening 4. The patentable set up of drug printing technology for medical devices.  **Figure 1**. Image of the physical instrumental setup and the technological advancements of the new screening technique.



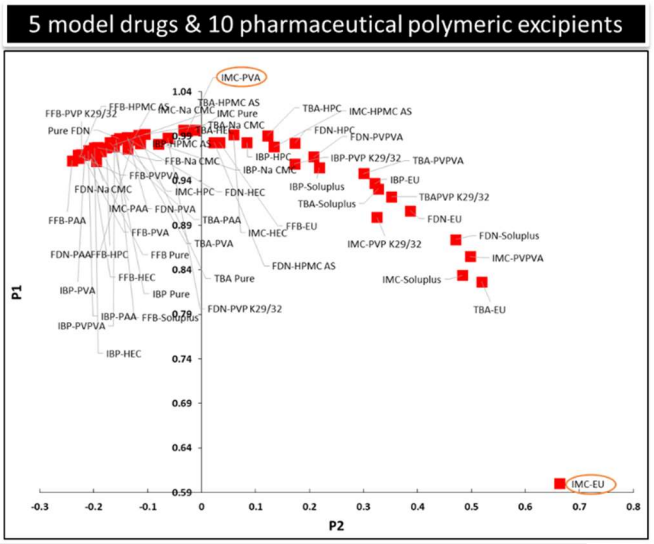
Novel thermal imaging method for rapid screening of drug-polymer miscibility for solid dispersion based formulation development. Alhijjaj, M., Belton, P., Fabian, L., Wellner, N., Reading, M. & Qi, S., 3 Dec 2018, In : *Molecular Pharmaceutics*. 15, 12, p. 5625–5636

Figure 2. Working principle of the new screening technique

Improvement in efficiency/productivity:

TASC method:
8 minutes per pair
7.5 hours in total

Conventional DSC method:
Average 160 minutes per pair
16 days (working hour lab time)



In Preparation for submission 2019: The automation potential of a new microscopy based rapid screening method of drug-polymer miscibility. Muqdad Alhijjaj, Peter Belton, Laszlo Fabian, Mike Reading, Sheng Qi, RSC Materials Horizon

Figure 3. Validation of the effectiveness of the new screening method and the advancements in speed of screening.

Reports and high impact publications	1 published 1 submitted and 1 in preparation
Communications in European and/ or international events	APS, CRS and AAPS
Patent prior art	In preparation for filing (1 filing data for the patent attorney attached)

search & patent preparation	
Patent	None
Official letters from company(ies)	1