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AMORPHOUS SOLID DISPERSIONS OF BCS CLASS II DRUGS: A RATIONAL APPROACH TO SOLVENT AND POLYMER SELECTION

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ABSTRACT

Miniaturised solvent casting (MSC) has been developed as a method for screening the stability of amorphous solid dispersions (ASD) of BCS class II drugs. The aim of the work was to further develop a rapid screening technique for drug-polymer amorphous dispersions made by solvent removal techniques. A second aim was to assess the impact of varying dissolution solvent on the resultant ASD stability. The technique was rapid, repeatable and practically straightforward. Storage stability of resultant ASD films was monitored over 4 weeks. The method is suited to pre-formulation as a risk-reduction tool during the formulation of drug product. Four drugs, seven polymers and five solvents have been examined. The resultant ASD films were monitored for stability and homogeneity over a four week period using polarised light microscopy (PLM), X-ray powder diffraction (XRD) and photography. A qualitative scoring system indicating the approximate proportion of amorphous and crystalline content of the films was developed. Results were rationalised against the physiochemical properties of the drugs, the functionality of the polymeric excipients and the physical properties of the solvents.

KEYWORDS

Poorly water soluble drugs, formulation, solvent casting, amorphous solid dispersions, stability

1. INTRODUCTION

Combinatorial chemistry and robotics have left a challenging legacy to the drug product formulation scientist. Up to 70% of new chemical entities (NCE) and 40% of marketed drugs are poorly soluble in water.[1] A number of strategies such as salt-formation, co-crystals, particle size reduction, micro emulsions, etc. have been successfully deployed to counteract low *in vivo* solubility.[2] In selected cases, amorphous solid dispersions (ASD) have been found to be excellent solutions. However, despite decades of research in the area and the pioneering work of Zografi[3] and co-workers,[4] relatively few examples of commercialised ASD pharmaceuticals exist.[5] This is at least partly attributable to the reputation of such systems towards spontaneous crystallisation, but also due to the perception that crystalline drug products are less risky.[6] Nevertheless, ASD offer order-of-magnitude better solubility than their pure crystalline counterparts and remain a highly active area of research.

When generating amorphous solid dispersions of drugs, polymeric excipients have often been used to stabilise the systems.[7] Due to their high molecular weight and high entropy, polymers often resist the ordered stacking required for spontaneous crystallisation. They can form a matrix around a substance, hence reducing the likelihood of molecular motion. Physical properties of the polymer like glass transition temperature (Tg) are a function of molecular weight. Polymers are more likely to be glassy solids than the active pharmaceutical ingredient (API) and dispersions of the drug-

polymer are also more likely to be glassy. The miscibility of the drug-polymer ASD is a key factor[8] in maintaining stable dispersions. Intermolecular forces such as hydrogen bonding are critical in maintaining a homogenous phase. Reliable methods for predicting the stability of drug-polymer dispersions are of great value.

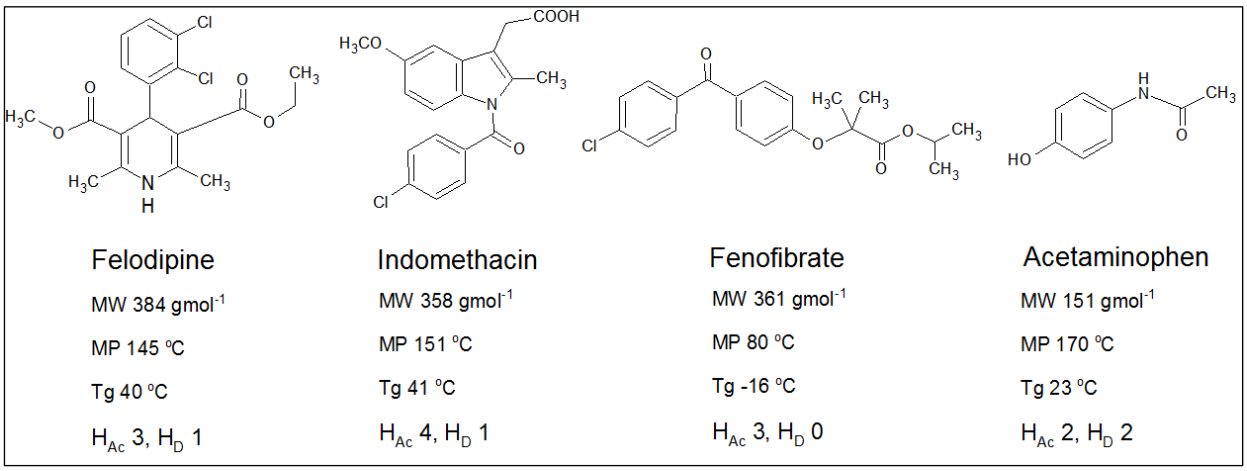


Fig 1: Drugs involved in the study and their selected physical properties: molecular weight (MW), melting point (MP), glass transition temperature (Tg), number of hydrogen bond acceptors (H_{Ac}) and donors (H_D).

DSC has generally been considered the gold-standard technique for assessing the stability of amorphous dispersions. Predictive aids like *In Silico* modelling,[1] data mining,[8] high throughput screening[9] and design of experiments have been powerful approaches in the quest to reduce risk and define a robust design space for amorphous dispersions. The beneficial effect of polymers on the stability of supersaturation, granulation and storage have all been investigated.[10] A wide range of analytical techniques such as FTIR, XRD, PLM, ssNMR, DSC, AFM, Raman and many others have been utilised to monitor stability of the dispersions over time.

In this work, we have focused on expanding upon a miniaturised solvent casting (MSC) method as a predictive tool for ASD stability. In particular, the ability of the technique to screen BCS class II drugs and also chemically diverse GRAS polymers was investigated. Similar techniques have previously been used, but are often focused on one specific model system, or detailed spectroscopic analysis of same. We herein assess the method itself and look at four drugs, seven polymers and five solvent systems. We have also considered the effect of the dissolution solvent on the stability of the resultant solid. To the best of our knowledge, the effect of a 'legacy' solvent on the stability of ASD has not been previously investigated.

Rather than identifying a 'design space' for formulation, we focused only on developing solvent casting as a screening technique. The practical simplicity of the technique is part of the inherent advantage. It does not rely on the significant time or expense required for *in silico* software programming, data mining licences nor capital expenditure. It can be seen as a pre-formulation tool for the solvent removal synthesis of ASD.

MSC can aid decision-making with polymer selection, solvent selection and be used to investigate the potential stability of novel amorphous drug-drug combinations. Furthermore it is a realistic screening technique, as it involves the physical removal of a selected solvent from a given drug-polymer combination. Real-world solutions help to circumnavigate potential pitfalls or subtle interactions which can be omitted in computed models. Such unforeseen omissions can be extremely costly in the formulation development of highly valuable NCE. The authors therefore strongly recommend the use of MSC in series with simulation research.

The downside to the technique is the rather repetitive practical work: involving accurate weighing, accurate pipetting and most importantly, meticulous record keeping. In our case, it was found that Excel worksheets were a good way of managing the volume of data. Handling amorphous films during stability trials and carrying out the analytical work without contaminating the samples was challenging. Any careful and competent scientists could complete the tasks, but the risk of handling or data errors is significant, particularly with less experienced operators. Automation is a potential solution, particularly for the synthesis steps, but perhaps also for the analysis.

The objectives of this study are to expand and improve upon existing methods for miniaturised solvent casting (MSC) of ASD. Within the sphere of consideration are BCS class II drugs, GRAS excipient polymers and a variety of low toxicity solvents. The effects of the physical properties of the drug (e.g. Tg) and its quotient of hydrogen bonding acceptor and donors are of interest. The type and substitution patterns of polymers are relevant. The effect of the solvent system used is interesting. The work can be described in three different parts: (a) the effect of drug physiochemical properties, (b) the effect of polymer properties and (c) the effect of solvent choice in the resultant ASD. We are casting the net wide, to look for patterns in successful and unsuccessful ASD. The nature of these patterns will funnel our future work direction and may provide further insight into these elusive structures.

2. MATERIALS AND METHODS

2.1 Materials

Solvents were purchased from Sigma-Aldrich, Fluka and Fisher and were >99% purity in all cases. Polymers Kollidon 25, Kollidon 30, Kollidon VA 64, Kollidon SR and Soluplus were donated by BASF. Polymers AQOAT AS-HG (HPMC-AS), HPMCP HP-55 (HPMC-P) and Metolose 90SH-4000 (HPMC) were donated by Shin Etsu. Drugs indomethacin and fenofibrate and polymer PVP 10 were purchased from Sigma-Aldrich. Felodipine was purchased from King Stone and acetaminophen was donated by GSK.

2.2 Preparation of Amorphous Solid Dispersions:

In a typical experiment, felodipine (50 mg) and Soluplus (50 mg) were weighed into a sample vial and dissolved in acetone-methanol (30:7, 4.0 ml) by vortex spinning at room temperature. The appearance of the solution was noted (i.e. clear, hazy, suspension or insoluble). A microscope slide (1 mm thick) was cut to size (for XRD mounting), labelled and heated on a hotplate (T = 60 ^{o}C). A small volume of the solution (60 µl) was pipetted dropwise onto the heated slide and the solvent was removed over 2 minutes. The slide was stored at ambient temperature (18-24 ^{o}C) and RH (25-35%) for 4 weeks.

An ASD of felodipine-Soluplus was synthesised by weighing felodipine (5.0g) and soluplus (5.0g) into a round-bottomed flask and dissolving in acetone-methanol (30:7, 100ml) then evaporating to dryness by rotary evaporation. The solid was further dried on a high-vacuum line (4 x 10^{-3} mBar) for 2 hours to give a yellow-white foam (9.90g, 99%).

2.3 ASD Analysis

Non-invasive techniques PLM and XRD were used. Analysis was typically performed at Day 0, Week 1 and Week 4.time points In general, there was excellent qualitative agreement between the techniques used.

2.3.1 Polarised Light Microscopy

A Zeiss Imager A1m microscope, equipped with an AxioCam MRc 5 camera, linked to a computer running AxioVision software (release 4.7) was used for polarised light microscopy (PLM). All micrographs were taken at x50 magnification.

2.3.2 X-ray diffraction

A PANalytical Empyrean X-ray diffractometer attached to a computer running High Score Plus was used to collect and process X-ray data. Diffraction patterns were collected *in-situ*, by spinning the glass slide samples within the X-ray beam. Plasticine™ was used to mount the slide in the holder at the correct height. The radiation was generated by Cu filter at 40 kV and 40 mA. Data was collected over the 2θ range of 5-50º, with a step size of 0.026º and a step time of 56 s.

2.3.3 Solid state nuclear magnetic resonance spectroscopy

^{13}C solid state NMR spectra were recorded on a Bruker Avance III instrument operating at a carbon frequency of 125.8 MHz. Samples were spun at the magic angle (54.7º) at a frequency of 37.5 kHz at temperature 295 K. The spectra were obtained using the cross polarisation magic angle-spinning (CP/MAS) method. The contact time was 3 ms and the pulse delay between scans was 5 s.

3. RESULTS AND DISCUSSION

MSC is compatible with a wide variety of analytical techniques. Herein we focused on PLM and XRD along with photographic records of films on glass slides. These techniques are non-invasive, i.e. they require no physical or chemical manipulation of the sample prior to analysis. This was important as invasive techniques can potentially disturb or damage the molecular structure of the samples. During a stability study this is particularly important. The attraction of PLM and XRD is that only electromagnetic radiation passes through the samples. DSC is an informative technique, but in these experiments it would have required the removal of an aliquot of sample to place in a DSC pan. The passage of heat through the sample would also disrupt the structure. Nevertheless, DSC is a widely-employed technique and will be utilised in ongoing work in tandem with these analyses.

Here we have focused on PLM as a clear and concise method for visualising a sample. Birefringence is very clear in thin films when crystals are present. X-ray diffractograms can be recorded directly by mounting the glass slides at the surface of a holder using Plasticine™ or other such mouldable amorphous materials. Bragg peaks were very clear (even with low quantities of crystals) and gave information which could potentially be quantitated or used to identify polymorphs. A matching of Bragg peaks with (for example) the Cambridge structural database or the quantitation of crystalline fraction of the films by relating to the intensity of the peaks is possible and could be investigated in future work. When no crystals were present, only an amorphous 'halo' was recorded. Blank slides or Plasticine™ only also gave the 'halo' result. As both techniques are sensitive and non-invasive, they are very well suited to monitoring the qualitative structure of the samples.

In this work, four drugs, seven polymers and five solvents were studied. The effects of the drug, the polymer and the solvent on stability have been considered. The physical properties of the drugs in Figure X will affect their solubility. Generally, higher molecular weights will tend to have higher melting points and higher glass transition temperatures. However the functionalisation (number and nature of functional groups) of the molecule will have a significant impact on its melting point, in particular hydrogen bonding functional groups. Felodipine and indomethacin both have hydrogen acceptor (H_{AC}) and hydrogen donor (H_D) groups. In contrast, fenofibrate has no hydrogen donor. Intermolecular hydrogen bonding is therefore not possible for pure felodipine and this is illustrated in the low melting point (80 ºC) and very low glass transition temperature (-16 ºC).

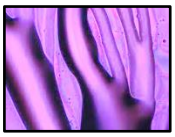
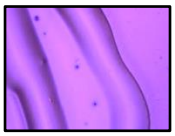
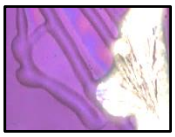
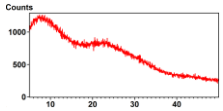
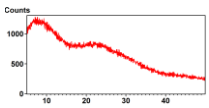
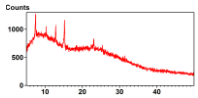
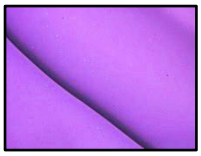
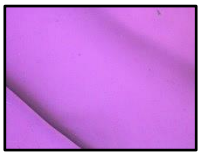
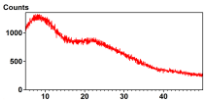
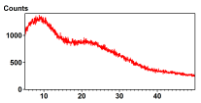
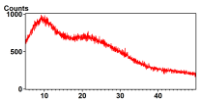
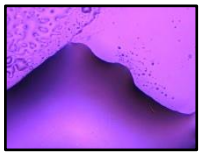
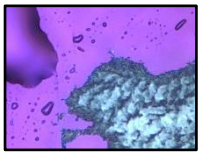
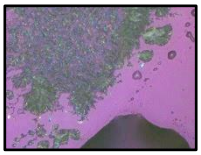
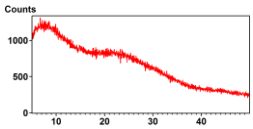
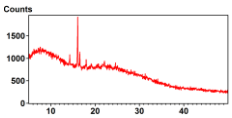
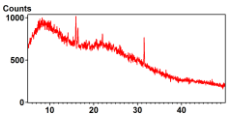
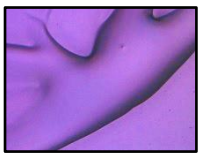
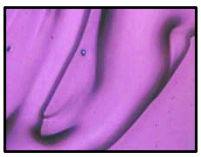
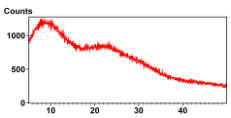
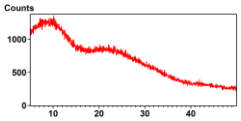
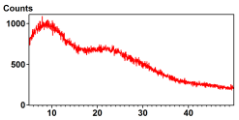
Experiment	Analysis			
	Timepoint	Day 0	Week 1	Week 4
Pure felodipine, no polymer, acetone-methanol solvent	PLM			
	XRD			
	Rating	AAAA	AAAA	AACC
Felodipine, Soluplus, acetone-methanol solvent	PLM			
	XRD			
	Rating	AAAA	AAAA	AAAA
Pure fenofibrate, no polymer, acetone-methanol solvent	PLM			
	XRD			
	Rating	AAAA	ACCC	ACCC
No drug, Kollidon K25 polymer, acetone-methanol solvent	PLM			
	XRD			
	Rating	AAAA	AAAA	AAAA

Table 1, Polarised light microscopy (PLM) and X-ray diffraction (XRD) data of some selected ASD during the 4 week stability trial. PLM and XRD were taken at time points day 0, week 1 and week 4. The ratings qualitative in nature and indicate fully amorphous (AAAA), mostly amorphous (AAAC), half-and-half (AACC), mostly crystalline (ACCC) and completely crystalline (CCCC) films of material.

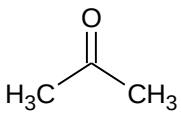
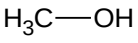
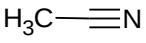
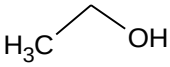
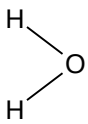
Structure					
Solvent	Acetone	Methanol	Acetonitrile	Ethanol	Water
ICH (ppm)	Class 3	3000	410	N/A	N/A
B.P. (^oC)	56.3	64.7	81.6	78.3	100
$\Delta H_{V\ (kJmol^{-1})}$	29.1	35.3	33.8	38.7	40.7
ε	20.7	32.6	37.5	24.3	78.5
KT_α	0.08	0.98	3.44	0.86	1.17
KT_β	0.43	0.66	-	0.75	0.47

Table 2: Selected physical properties of the 'legacy' solvents used in the solvent casting study. Properties considered most relevant to evaporation, solvation and hydrogen bonding have been included.[12]

This belies the fact that fenofibrate has a comparable molecular weight (361 $gmol^{-1}$) to felodipine (384 $gmol^{-1}$) and indomethacin (358 $gmol^{-1}$), but the melting points of the three drugs vary considerably (80, 145 and 151 ^oC respectively). Felodipine and indomethacin both have one H_D each, and similar numbers of H_{AC} (3 and 4 respectively). However, felodipine contains a primary amine and two ester groups, whereas indomethacin has a tertiary amine, an ether and a free carboxylate. Therefore the interactions of the two API with the same polymeric excipient will differ. Acetaminophen has different physical properties: it is BCS class III, with a far higher solubility in water (1.4×10^4 $mg.ml^{-1}$). The melting point is 170 ^oC and glass transition is 22.6 ^oC. Acetaminophen has two H-bond acceptors and two H-bond donors, making it a different example to the other drugs, but interesting due to the hydrogen bonding possibilities. Acetaminophen was also a faster crystalliser that the other three drugs.

Polymers were chosen based on GRAS status and structural features. In particular, vinyl-derived, cellulose-derived and specialist polymers were investigated. The povidones are vinyl derivatives showing excellent general solubility and stability. They are known to be very hygroscopic and different grades will vary in average molecular weight, viscosity, glass transition temperature and bulk density. The examples chosen in this study were PVP 10, K25 and K30. Also included were Kollidon VA64, which is a copovidone containing amide and acetate functional groups in a 6:4 ratio and Kollidon SR: a spray-dried polyvinyl acetate-containing povidone. The specialised polymer Soluplus was designed to withstand the heat of hot melt extrusion and also to form stable homogenous dispersions. It contains amide, acetate and ether functional groups and can also be formulated by the solvent method. In contrast to these synthetic polymers, cellulose derivatives are formed from a natural product. HPMC contains polyol, methyl ether and hydroxyisopropyl ether functionality, along the cellulose backbone. HPMCAS contains the previous functional groups, but also includes acetate and succinate derivatives. HPMCP is similar to HPMC, but with phthalate esters. Already the variety of functionalisation and the difference in backbone flexibility will have a significant impact on the nature of the dispersions. Polymer polarity, flexibility and the ability to donate and accept hydrogen bonds will be of critical importance.

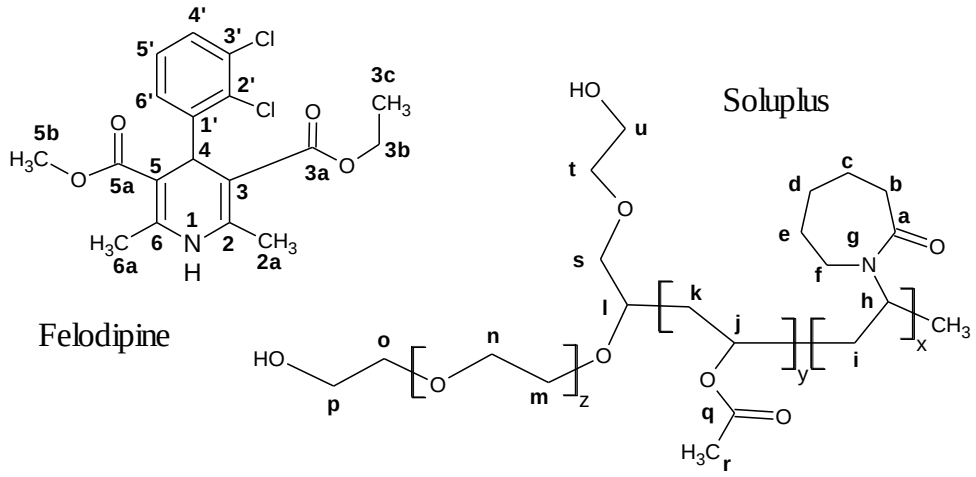
Solvents chosen were acetone-methanol mixture, acetonitrile mixture, acetonitrile, ethanol and ethanol-water mixture. Only solvents with superior ICH limits were included, therefore chloroform and dichloromethane were not considered on this occasion. Mixtures were utilised in order to broaden the likelihood of solubility of a certain combination. The solvation requirements of the system, in particular polymers, will differ. Favour was given to solvents with low boiling points and favourable ICH limits (e.g. acetone b.p. 56.3 ^{o}C ICH class 3). The solvent mixture of acetone-methanol (30:7) was carefully chosen, firstly because of the ability to solubilise a wide range of chemically diverse species, but also because it forms an azeotropes at mole fraction 0.75% acetone, that boils at 54.5-55.5 ^{o}C. Such azeotropes represent cost reductions should such processes be scaled-up. Furthermore, both acetone and methanol are inexpensive and low in toxicity.

A second goal of the work was to investigate the effect of legacy solvents on the stability of ASD made by solvent-casting. Consider ASD DxPyA, made from a drug X and polymer Y dissolved in solvent A., Will DxPyA have the same stability as ASD DxPyB made by casting of drug X and polymer Y from a solution in solvent B? It might be assumed that DxPyA and DxPyB are identical and will therefore behave identically on stability. However, it is very possible that differences in the physiochemical properties of the solvent will impact on the stability of the resultant ASD.

Formulation	Day 0	Wk 1	Wk 4	Formulation	Day 0	Wk 1	Wk 4
Pure felodipine	AAAA	AAAA	AACC	Fenofibrate-HPMCP	AAAA	AACC	AACC
Felodipine-PVP10	AAAA	AAAA	AAAA	Pure indomethacin	AAAA	AAAC	AAAC
Felodipine-K25	AAAA	AAAA	AAAA	Indomethacin-PVP10	AAAA	AAAA	AAAA
Felodipine-K30	AAAA	AAAA	AAAA	Indomethacin-K25	AAAA	AAAA	AAAA
Felodipine-Soluplus	AAAA	AAAA	AAAA	Indomethacin-K30	AAAA	AAAA	AAAA
Felodipine-VA64	AAAA	AAAA	AAAA	Indomethacin-Soluplus	AAAA	AAAA	AAAA
Felodipine-KSR	AAAA	AAAA	AAAA	Indomethacin-VA64	AAAA	AAAA	AAAA
Felodipine-HPMCAS	Not soluble			Indomethacin-KSR	AAAA	AAAA	AAAA
Felodipine-HPMCP	AAAA	AAAA	AAAA	Indomethacin-HPMCAS	Not soluble		
Pure fenofibrate	AAAA	ACCC	ACCC	Indomethacin-HPMCP	AAAA	AAAA	AAAA
Fenofibrate-PVP10	AAAA	CCCC	CCCC	Pure acetaminophen	ACCC	CCCC	CCCC
Fenofibrate-K25	Not soluble			Acetaminophen-	AAAA	-	AAAA

				PVP10			
Fenofibrate-K30	Not soluble			Acetaminophen-K25	AAAA	-	AAAA
Fenofibrate-Soluplus	AAAA	AAAA	AAAC	Acetaminophen-K30	AAAA	-	AAAA
Fenofibrate-VA64	AAAA	ACCC	CCCC	Acetaminophen-Soluplus	AAAA	-	AAAA
Fenofibrate-KSR	AAAA	AAAA	AACC	Acetaminophen-VA64	AAAA	-	AAAA
Fenofibrate-HPMCAS	Not soluble			Acetaminophen-KSR	AAAC	-	AACC

Table 3, Drug-Polymer ASD stability results at Day 0, week 1 and week 4 (All films made from acetone:methanol (30:7) solvent). K25 is Kollidon 25, VA64 is Kollidon VA64, KSR is Kollidon SR. The ratings qualitative in nature and indicate fully amorphous (AAAA), mostly amorphous (AAAC), half-and-half (AACC), mostly crystalline (ACCC) and completely crystalline (CCCC) films of material. Ratings shown are the mean of XRD and PLM values.



δC Felodipine: 15.05 (3c); 18.98 (6a); 20.40 (2a); 38.33 (4); 50.36 (5b); 58.83 (3b); 103.78 (5); 104.88 (3); 127.89 (5', 4'); 129.40 (2'); 133.0 (6', 3'); 146.03 (2); 147.33 (6); 151.12 (1'); 166.61 (3a); 168.69 (5a).

δC Soluplus: 21.51 (c); 23.00 (r); 30.84 (e, d); 37.74 (b, i, k); 42.86 (f); 46.33 (h); 67.93, 71.18 (j, l, m, n, o, p, s, t, u); 170.31 (q); 175.51 (a).

δC Felodipine-Soluplus ASD: 14.73 (fel 3c); 18.91 (fel 6a); 21.08 (Sol c, fel 2a); 23.20 (Sol r); 30.38 (Sol e, d); 38.16 (fel 4, Sol b, i, k); 42.83 (Sol f); 46.49 (Sol h); 50.80 (fel 5b); 59.71 (fel 3b); 68.45, 70.95 (Sol j, l, m, n, o, p, s, t, u); 103.60 (fel 5, 3); 129.08 (fel 5', 4', 2'); 133.00 (fel 6', 3'); 146.66 (fel 2, 6, 1'); 167.50 (fel 3a, 5a); 170.11 (Sol q); 176.56 (Sol a).

Figure 2, Numbering system for felodipine and for Soluplus. Assignment of 13-C NMR spectra

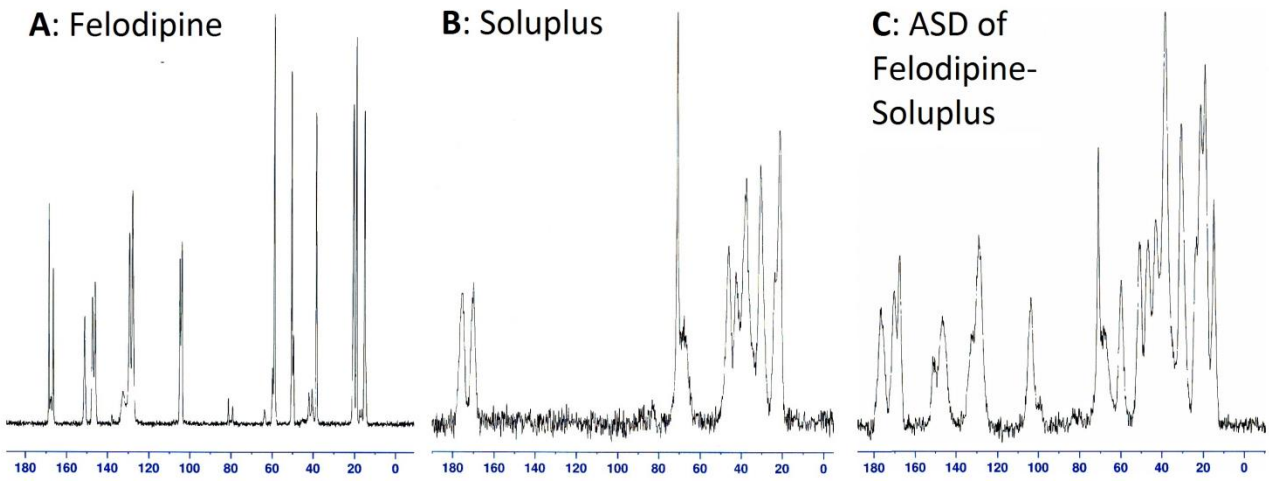


Figure 3, The 13-C solid-state NMR spectra of (A) crystalline felodipine, (B) amorphous Soluplus and (C) an amorphous solid dispersion of felodipine-Soluplus. The data compared well with that previously reported.[11]

Felodipine was solvent casted as the pure drug and in combination with seven polymers from acetone-methanol mixture. The pure drug crystallised between weeks one and four. All polymeric systems stabilised felodipine for the full four weeks of the test. The stability of these systems could be partly attributable to the favourable molecular weight (384 $gmol^{-1}$), Tg (40 ^{o}C) and number of hydrogen accepting groups (3) and donating groups (1) in felodipine. The miscibility with polymers PVP10, K25, K30, VA64, KSR, Soluplus and HPMCP may be favourable.

Indomethacin was solvent casted as the pure drug and in combination with seven polymers from acetone-methanol mixture. The pure drug crystallised between day 0 and week 1. All polymeric systems stabilised felodipine for the full four weeks of the test. The stability of these systems could be partly attributable to the favourable molecular weight (357 $gmol^{-1}$), Tg (41 ^{o}C) and number of hydrogen accepting groups (4) and donating groups (1) in indomethacin. The miscibility with polymers PVP10, K25, K30, VA64, KSR, Soluplus and HPMCP appeared favourable.

Acetaminophen was solvent casted as the pure drug and in combination with six polymers from acetone-methanol mixture. The pure drug crystallised between on day 0. Five of the drug-polymer ASD remained stable over the 4 week test. Kollidon SR crystallised on day 0. The reason for this result is not understood. The molecular weight (151 $gmol^{-1}$), Tg (23 ^{o}C) and number of hydrogen accepting groups (2) and donating groups (2) in acetaminophen will influence the system stability. The miscibility with polymers PVP10, K25, K30, VA64, and Soluplus appeared favourable.

Fenofibrate was solvent casted as the pure drug and in combination with seven polymers from acetone-methanol mixture. The pure drug crystallised between week 1 and week 4. Three of the drug-polymer dispersions crystallised between day 0 and week 1: PVP10, VA64 and HPMCP. Two dispersions crystallised between week 1 and week 4: KSR and Soluplus. Surprisingly, fenofibrate did not dissolve in the acetone-methanol mixture when combined with K25 or K30, but did dissolve PVP10. This result is not completely understood, but may be due to the viscosity or molecular weight difference between the PVP10 and the higher molecular weight povidone solutions. The stability of fenofibrate dispersions is influenced by the molecule's molecular weight (361 $gmol^{-1}$), Tg (-16 ^{o}C) and number of hydrogen accepting groups (3) and donating groups (0). In particular the lack of any hydrogen bond donors makes this molecule very difficult to stabilise by amorphous solid dispersion. The absence of intermolecular H-bonds in the pure drug is also a contributing factor to the low glass transition temperature.

Acetaminophen was solvent casted from five 'legacy' solvents: acetone-methanol mixture, acetonitrile-methanol mixture, pure acetonitrile, pure ethanol and ethanol-water mixtures. Acetaminophen was solvent casted in six ASD with different polymers from acetone-methanol mixture. Five of these ASD remained fully amorphous for the full 4 week test: PVP10, K25, K30, VA64 and Soluplus. The exception was acetaminophen-KSR which crystallised on day 0. This is probably due to a weaker interaction between KSR and acetaminophen than with the other polymers.

Acetaminophen was also solvent casted into seven ASD by combination with polymers from acetonitrile-methanol. Only three of these ASD remained stable over the four week test: the povidones PVP10, K25 and K30. Two of the systems crystallised on day 0: KSR and HPMCP. Two polymers, VA64 and Soluplus, crystallised between day 0 and week 4.

Acetaminophen was solvent casted into seven ASD by combination with polymers from pure acetonitrile. Two ASD remained stable for the four weeks: PVP10 and K25. Two polymers crystallised between day 0 and week 4: VA64 and Soluplus. Three polymers crystallised on day 0: K30, KSR and HPMCP.

The difference in results between acetone/methanol and acetonitrile/methanol is not due to the boiling point or enthalpy of vaporisation differences, because evaporation is performed above the boiling point and the films are held at this temperature for 2 minutes. There may be a contribution from the Kamlet-Taft differences between acetone and methanol. Kamlet-Taft is a separate measure of the hydrogen bond donor, hydrogen bond acceptor and polarisability of a solvents as contributors to the overall solvent polarity.[8] The cyano functional group in acetonitrile and the carbonyl of acetone are both polarised. There are also structural differences between the solvents: acetonitrile is linear but acetone is planar. Many complex factors are affecting the interaction of these solvent with drug and polymers solutes. Considering all relevant factors is beyond the scope of this manuscript, but it may be possible to better understand these systems using computational methods.

Future work may involve longer testing conditions or higher humidity levels. DSC analysis of the formulations would add valuable information on the presence of domain structure.

Formulation/ Solvent	Day 0	Wk 4	Formulation/ Solvent	Day 0	Wk 4
Ace-PVP10/ Solv B	AAAA	AAAA	Ace-KSR/ EtOH	AAAC	ACCC
Ace-K25/ Solv B	AAAA	AAAA	Ace-HPMCAS/ EtOH	ACCC	CCCC
Ace-K30/ Solv B	AAAA	AAAA	Ace-HPMCP/ EtOH	ACCC	CCCC
Ace-Sol/ Solv B	AAAA	ACCC	Ace-HPMC/ EtOH	CCCC	CCCC
Ace-VA64/ Solv B	AAAA	AACC	Ace-K30/ EtOH(80):H_2O(20)	AAAA	AAAA
Ace-KSR/ Solv B	AAAC	CCCC	Ace-K30/ EtOH(90):H_2O(10)	AAAA	AAAA
Ace-HPMCAS/ Solv B	Not soluble		Ace-K30/ EtOH(95):H_2O(5)	AAAA	AAAA
Ace-HPMCP/ Solv B	AAAC	CCCC	Ace-K30/ EtOH(70):H_2O(30)	AAAA	AAAA

Ace-HPMC/ Solv B	Not soluble		Ace-K30/ EtOH(60):H_2O(40)	AAAA	AAAA
Ace-PVP10/ ACN	AAAA	AAAA	Ace-K30/ EtOH(50):H_2O(50)	AAAA	AAAA
Ace-K25/ ACN	AAAA	AAAA	Ace-K30/ EtOH(40):H_2O(60)	AAAA	AAAA
Ace-K30/ ACN	AAAC	AAAC	Ace-K30/ EtOH(20):H_2O(80)	AAAC	ACCC
Ace-Sol/ ACN	AAAA	AAAC	Ace-K30/ EtOH(10):H_2O(90)	AAAC	CCCC
Ace-VA64/ ACN	AAAA	AACC	PVP10/Solv A	AAAA	AAAA
Ace-KSR/ ACN	AAAC	CCCC	K25/Solv A	AAAA	AAAA
Ace-HPMCAS/ ACN	Not soluble		K30/Solv A	AAAA	AAAA
Ace-HPMCP/ ACN	AAAC	CCCC	Sol/Solv A	AAAA	AAAA
Ace-PVP10/ EtOH	AAAA	AAAA	VA64/Solv A	AAAA	AAAA
Ace-K25/ EtOH	AAAA	AAAA	KSR/Solv A	AAAA	AAAA
Ace-K30/ EtOH	AAAA	AAAA	HPMCAS/EtOH-CH_3Cl	AAAA	AAAA
Ace-Sol/ EtOH	AAAA	AAAA	HPMCP/Solv A	AAAA	AAAA
Ace-VA64/ EtOH	AAAA	AAAA	HPMC/EtOH-H_2O(1:1)	AAAA	AAAA

Table 4, Formulations from 'legacy' solvents: Acetone-methanol (Solv A), acetonitrile-methanol (Solv B), acetonitrile (ACN), methanol (MeOH), ethanol (EtOH), chloroform (CH_3Cl); Acetaminophen (Ace), Polyvinylpyrrolidone (PVP), Kollidon 25 (K25), Kollidon 30 (K30), Soluplus (Sol), Kollidon VA64 (VA64), Kollidon SR (KSR)

5. CONCLUSIONS

Miniaturised solvent casting (MSC) is a useful tool in the pre-formulation of drug product amorphous solid dispersions. A range of drugs, polymers and solvents are suited to this screening technique. A rational ASD selection should take physiochemical properties of drug, polymer and solvent into account. The properties of the solvent will affect the stability of the amorphous film even after solvent has been removed.

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