Highly efficient miniaturized coprecipitation screening (MiCoS) for amorphous solid dispersion formulation development

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ABSTRACT

Microprecipitated bulk powder (MBP) is a novel solid dispersion technology to manufacture amorphous formulations of poorly soluble compounds that cannot be processed by spray drying or melt extrusion. An efficient high-throughput screening method has been developed to aid the selection of polymer type, drug loading and antisolvent to solvent ratio for MBP formulation development. With a 96-well platform, the miniaturized coprecipitation screening (MiCoS) includes mixing of drug and polymer in dimethylacetamide, controlled precipitation to generate MBP, filtration/washing, drying and high-throughput characterization. The integrated MiCoS approach has been demonstrated with a model compound, glybenclamide. Based on the solid state stability and kinetic solubility of the MBP, hydroxypropylmethylcellulose acetate succinate polymer with 40% or lower drug loading, and antisolvent (0.01 N HCl) to solvent (dimethylacetamide) ratio of 5:1 or higher were selected to make glybenclamide MBP. MiCoS can be applied to both early and late stage formulation processing. In early stage research programs, the system can be used to enable efficacy, pharmacokinetics or mini-toxicology studies for poorly water soluble molecules using minimal amount of drug substance (2–10 mg). In late stage development programs, MiCoS can be used to optimize MBP formulation by expanding the experimental design space to include additional formulation variants.

1. Introduction

Amorphous solid dispersion (ASD) is a revolutionary formulation technology that enables in delivery of poorly water-soluble drugs. Successful ASD formulations generally show faster dissolution rates and higher apparent solubility, thereby resulting in improved bioavailability (Hancock and Zografi, 1997). Several ASD drug products are currently on the market, such as Kaletra®, Norvir®, Prograf®, Sprax®, Zelboraf®, Intelence®, Incivek®, and Kalydeco® (Miller et al., 2012).

For drug discovery research, commonly used small-scale ASD methods (Padden et al., 2011) include rotary evaporation, coprecipitation, spin-coating, melt-quenching, co-grinding, etc. For mid to large scale ASD drug manufacturing, common pharmaceutical processes include spray-drying, hot-melt extrusion (HME), coprecipitation and lyophilization. The selection of ASD manufacturing method is often based on drug properties (Shah et al., 2012a). For example, lyophilization, often used to process molecules with high aqueous solubility such as peptides or proteins, is not suitable for insoluble small molecules. Drugs with high melting point are usually not amendable to HME processing, as high processing temperature may increase the degradation risk for both drugs and excipients. Drugs with low solubility in volatile solvents are not good candidates for spray drying due to low spray efficiency and high crystallization risk.

In recent years, more and more lead molecules in drug discovery and development have poor drug-like properties, such as high molecular weight (>500), high melting point, low solubility, and high lipophilicity (Ku and Dulin, 2012). To make ASD for these drug molecules, spray-drying can be used if the molecules have good solubility in volatile solvents, and HME is applicable if the molecules have low melting points and thermal stability. But for molecules with both high melting point and low solubility in volatile solvents, ASD manufacturing by conventional processing techniques (spray-drying, HME or lyophilization) is challenging.
Recently, a novel solvent controlled precipitation (SCP) technology to manufacture ASD, known as microprecipitated bulk powder (MBP), has been successfully developed by Shah and coworkers (Albano et al., 2008; Shah et al., 2012b). For high-melting and low solubility compounds that are not amenable to be processed by spray drying or HME, MBP technology provides an alternative to make ASDs. During MBP manufacturing, drug and polymer are co-dissolved in water miscible solvents such as DMA, DMSO or DMF, and added to chilled acidic water (eq. 0.01 N HCl) in a controlled manner to produce fine MBP, as shown in Fig. 1. The resulting MBP is uniform and homogeneous ASD. MBP is distinct from general coprecipitation in its use of enteric polymers and aqueous antisolvents. Furthermore, MBP can be manufactured consistently from laboratory to pilot scale.

Similar to ASD development by spray drying or HME, successful MBP development requires extended timeline and resources. The selection of the right polymer and drug loading (DL) are fundamentally critical in MBP manufacturing. In addition, other processing parameters such as antisolvent to solvent ratio (AS/S), shear force, precipitation temperature and time are also very important. Conventionally, lab-scale MBP preparation was used to screen polymer, DL, AS/S and optimization of processing parameters. Each individual lab-scale experiment requires at least 100 mg of API and can only test one condition. A simple screening of three polymers, three DL and three AS/S would require 27 experiments, costing at least 2.7 g of material and substantial time and resources. Such low throughput screening is highly inefficient and may not even be feasible in early phases of development due to the availability of the compound. Clearly, a need exists for high-throughput MBP formulation screening.

A few methods have been published for ASD screening in recent years. These methods focused on miniaturization of spray-drying (Mansky et al., 2007; Shanbhag et al., 2008) and screened polymer and drug loading with high-throughput experiments (Chiang et al., 2012; Van Eerdensbrugh and Taylor, 2010). These screening methods use volatile solvents and generate ASD by solvent casting which may be representative of the spray drying process but does not simulate coprecipitation. For this reason, the current screening methods are only limited to the application of spray-drying processing. At present there is no high throughput screening method to guide the MBP development. Thus an efficient screening tool to guide MBP formulation development is not only helpful, but also required to shorten the formulation development timeline.

This study presents a novel miniaturized coprecipitation screening (MiCoS) method to guide MBP development. The two major components of MiCoS are — parallel MBP preparation and high-throughput MBP characterization. Parallel MBP preparation, mimicking large-scale MBP manufacturing process, dissolves drug and polymer in DMA and coprecipitates the MBP solid in acidic water (e.g. 0.01 N HCl) at 96-well format. High-throughput characterization includes MBP solid property evaluation by HT-XRPD and Raman spectroscopy. MBP biopharmaceutical performance assessment is also determined by measuring kinetic solubility in biorelevant media. Based on both MBP solid and biopharmaceutical properties, MiCoS is capable of selecting polymer type, DL, AS/S with high-throughput experiments using minimum amount of API. The system has been validated by mid to large scale MBP manufacturing. Currently MiCoS has been applied to both early and late stage R&D programs in formulation research.

In this study, nifedipine and felodipine were used as testing compounds to validate the MiCoS system. Glybenclamide (glibenclamide or glyburide), a BCS II compound, served as a model compound to demonstrate MiCoS capabilities of MBP formulation development. Tremendous research efforts have focused on ASD to increase the solubility and dissolution of glybenclamide (Chauhan et al., 2005; Cirri et al., 2007; Manimaran et al., 2010). Here MiCoS was applied to select the polymer type, DL, AS/S to make successful glibenclamide ASD.

2. Materials and methods

2.1. Materials

All chemicals used were of ACS analytical grade. Commercial crystalline glybenclamide (>99%) and felodipine (>99%) were purchased from Sigma–Aldrich. Crystalline nifedipine was obtained from RIA International. HPMCAS LF and HPMCP HP-55 were purchased from Shin-Etsu Chemical Co. Eudragit L100 and Eudragit L100-55 were purchased from Evonik. FaSSIF media was freshly prepared using SIF powder from Biorelevant. All other chemicals were used as received without any further treatment. Solvent DMA (>99%) was purchased from Sigma–Aldrich.

Three drug molecules, nifedipine, felodipine and glybenclamide, were tested in MiCoS. The basic physico-chemical properties of these drug molecules are listed in Table 1.

2.2. MiCoS

A schematic representation of the MiCoS is shown in Fig. 2. The MiCoS includes five major steps – mixing of drug and polymer stock solutions, SCP in 1-ml glass vials, filtration/washing on a 96-well filter plate, drying, and characterization.

Initially, stock solutions of polymers (140 mg/ml of HPMCAS, HPMCP, Eudragit L100 and Eudragit L100-55) and the drug (70 mg/ml) were prepared in DMA. Polymer stocks and drug stocks were mixed accordingly to make 10–50% DL solutions. Total solid content in each drug and polymer mixture is about 9–13%.

SCP was carried out in 1-ml glass vials with magnetic stirrers in a 96 position insert (VP Scientific Inc.). The glass vials were filled with 700 µl of acidic water (0.01 N HCl) and chilled at 5 °C. The tumbler stirrer (VP Scientific Inc.) was set to 800 rpm. The polymer/drug mixture (70 µl) was added drop-wise by a multi-channel pipette to the acidic water while keeping stirrer speed at 800 rpm to generate precipitation. The suspensions were kept stirring for 2 additional min at 5 °C.

After SCP, the suspension was filtered onto two 0.45 µm polycarbonate 96-well filter plates (Millipore). Wide-bore tips were used for suspension transfer. On the first filter plate, different
Table 1
Model compounds used in MiCoS study.

<table>
<thead>
<tr>
<th>Drug (structure from Sigmaaldrich.com)</th>
<th>Physico-chemical properties (from Drugbank.ca)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine</td>
<td>Molecular weight: 346.3</td>
</tr>
<tr>
<td></td>
<td>pK_a: 3.93 (Plumley et al., 2010)</td>
</tr>
<tr>
<td></td>
<td>Melting point: 172–174 °C</td>
</tr>
<tr>
<td></td>
<td>T_g: 42 °C</td>
</tr>
<tr>
<td></td>
<td>Solubility: 0.02 mg/ml in water, &gt;70 mg/ml in DMA</td>
</tr>
<tr>
<td>Felodipine</td>
<td>Molecular weight: 384.3</td>
</tr>
<tr>
<td></td>
<td>pK_a: 5.39</td>
</tr>
<tr>
<td></td>
<td>Melting point: 145 °C</td>
</tr>
<tr>
<td></td>
<td>T_g: 47 °C</td>
</tr>
<tr>
<td></td>
<td>Solubility: 0.007 mg/ml in water, &gt;70 mg/ml in DMA</td>
</tr>
<tr>
<td>Glybenclamide</td>
<td>Molecular weight: 494.0</td>
</tr>
<tr>
<td></td>
<td>pK_a: 13.7</td>
</tr>
<tr>
<td></td>
<td>Melting point: 169–170 °C</td>
</tr>
<tr>
<td></td>
<td>T_g: 65 °C</td>
</tr>
<tr>
<td></td>
<td>Solubility: 0.002 mg/ml in water, &gt;70 mg/ml in DMA</td>
</tr>
</tbody>
</table>

Volumes of the suspensions (90, 50, 35, 30 and 25 µl for 10–50% drug loading suspensions, respectively) were filtered to ensure each well contains 0.1 mg of API. This plate was washed with water, dried at 40 °C in an air flow oven for 2 h and used for kinetic solubility test. The rest of the suspensions were filtered onto a second filter plate. The filtrate was collected on a clean 96-well receiver plate for HPLC analysis. The solid content on the second plate was also washed with water, and dried at 40 °C oven for 2 h before solid state characterization by HT-XRPD and Raman spectroscopy and stability assessment.

In kinetic solubility test, to each well 300 µl freshly prepared FaSSIF buffer at pH 6.5 was added, and stirred at 200 rpm at room temperature. A fraction of 120 µl at 1 h and 3 h were filtered onto a 0.45 µm polycarbonate 96-well filter plate. The filtrate were collected and diluted in FaSSIF buffer before HPLC analysis. All samples were run in triplicates.

2.3. HPLC
Analysis was performed on a Waters Acquity UPLC H-class system, equipped with an Acquity UPLC BEH C18 column (2.1 mm × 100 mm, 1.7 µm). Mobile phase A and B consisted of 0.05% trifluoroacetic acid in water and acetonitrile, respectively. The flow rate was 0.5 ml/min and the total run time was 3 min. The wavelength was set at 230 nm for

Fig. 2. A schematic representation of the MiCoS.
monitoring glybenclamide, and 234 nm for nifedipine and felodipine.

2.4. HT-XRPD

XRPD patterns were recorded on a STOE-Stadi P Combi diffractometer using a Cu Kα radiation source operating at 40 keV and 40 mA. The diffractometer was equipped with a linear PSD detector in transmission mode. Corundum was used as a calibration standard. For HT-XRPD analysis, a 96-well plate stage was used. The diffraction patterns were recorded 2θ range of 5–30 for nifedipine and felodipine, and 10–24 for glybenclamide with step width of 0.5° and a measurement time of 20 s per step. The samples in 96-well polycarbonate filter plate were measured directly without additional sample preparation. The polycarbonate membrane filter was selected as it gives minimal amorphous XRPD background comparing with other membrane filters such as PVDF or Teflon. The minimal background of the polycarbonate membrane was subtracted by batch processing in WinXpow software for each diffractogram.

2.5. HT-Raman spectroscopy

Raman spectra were recorded on Kaiser Raman WorkStationTM. It consisted of a dispersive Raman spectrometer equipped with a diode laser source (785 nm) and a charge-coupled device (CCD) detector. A PhAT probe was used with 1 mm imaging size. The Raman spectral range was 142–1898.4 cm⁻¹.

The MiCoS samples were measured directly in 96-well polycarbonate filter plates. For each well, with laser power at 400 mW, 5 scans were accumulated with 0.2 s/scan. Each well was measured at 7 different 1 mm-spots (6 spots in the shape of hexagon and one spot in the middle) to get the average Raman spectrum. The Raman spectral background of the polycarbonate membrane was negligible.

3. Results and discussion

3.1. MiCoS development

SCP is a complex process in which the intrinsic properties of drug and polymer and processing parameters contribute to make successful MBP. From miniaturized experiments to large scale MBP manufacturing, the intrinsic properties of drug and polymer remain constant whereas processing parameters may vary. The intrinsic properties include drug crystallization tendency (Baird et al., 2010), drug and polymer miscibility, and solubility in solvent and antisolvents. For instance, if the drug has high crystallization tendency and it easily crystallizes in miniaturized experiments, it will also crystallize easily at large scale manufacturing. On the other hand, processing parameters, such as the drying time for MBP products, may vary from small scale to large scale experiments. The scope of the MiCoS is to evaluate the intrinsic properties of drug and polymer contributing to MBP formation in miniaturized but high-throughput experiments under adequate engineering support.

Similar to the large scale coprecipitation process, MiCoS has five major steps, as shown in Fig. 2. The key technical challenges in developing this small scale screening technique are the selection of the coprecipitation apparatus and high-throughput characterization.

3.1.1. Coprecipitation

Coprecipitation is the most critical step in MBP manufacturing. During coprecipitation, drug and polymer solution is added to antisolvent to induce rapid but controlled precipitation of drug and polymer simultaneously. For successful MBP generation, drug and polymer not only have to precipitate together, but are also dispersed to fine powders after rapid diffusion of DMA out of MBP matrix. Poorly controlled precipitation, such as inadequate mixing or poor temperature control, will result in failure of amorphous MBP.

To achieve adequate mixing, overhead propeller mixer or high shear mixer are employed in lab and commercial MBP manufacturing. While efficient and strong mixing is also required in miniaturized coprecipitation, mechanical overhead mixer for 96-well plate is not commercially available. To mimic the lab scale precipitation, magnetic stirring has been evaluated. Conventional magnetic stirring was found to be not efficient for mixing, and the precipitates tended to settle and aggregated on the stir elements due to high viscosity of the polymers. Consequently, for 96-well plate high-shear mixing, a magnetic tumble mixer, providing strong mixing and similar magnetic force across all positions by vertical spinning of the magnets was selected. The efficient mixing was also optimized by using stir sticks or V-shaped stirring elements.

To confirm adequate mixing in miniaturized coprecipitation, two model compounds, nifedipine and felodipine were tested for the proof-of-concept study. Nifedipine has high crystallization tendency (Aso et al., 2000; Baird et al., 2010) and it is difficult to render amorphous, while felodipine is a ‘slow crystallization’ compound (Van Eerdenbrugh et al., 2010) and can readily form ASDs at high drug loading. Nifedipine and felodipine were both tested in MiCoS at 20, 35 and 50% of drug loadings with three polymers, HPMCAS LF, Eudragit L100 and L100–55. Fig. 3 summarizes the primary XRPD screening of the MBP from MiCoS. Nifedipine showed mainly crystalline dispersion and felodipine showed all amorphous MBP. The results confirmed that MiCoS provides adequate mixing for making ASD by coprecipitation.

3.1.2. Characterization

Generally, ASDs can be characterized by XRPD, thermal techniques such as DSC, polarized light microscopy, spectroscopy, solid state NMR, etc. (Newman and Munson, 2012). To accommodate the high throughput MiCoS, automated characterization tools compatible with 96-well plate format and requiring minimal sample preparation were highly desired. HT-XRPD and Raman spectroscopy were adopted for MiCoS. XRPD measures the long range order of material, and was used as the primary characterization tool to identify physical form of the solid dispersion. The API amount was designed to have ≥1 mg in each well so that it meets the detection limit of the HT-XRPD instrument (Wyttenbach et al., 2007). Raman spectroscopy, as a secondary characterization tool, focuses on molecular arrangement with adjacent molecules and it is less affected by the amount of material in each screening well. As such Raman spectroscopy can provide sensitive and alternative outcome on chemical and physical identity of MBP. ASDs usually have broad and weak bands while crystalline solid dispersion gives sharp and intense bands. Raman spectral differences could be further utilized to quantitate the crystalline amount in the MBP, if needed.

The performance and stability are the two major concerns of MBP. In MiCoS, the performance of the MBP was estimated by high throughput kinetic solubility test in biorelevant FaSSIF media. Successful MBP not only promotes the drug solubility/dissolution, but also maintains the supersaturation over extended period of time. Therefore two time-point (1 h and 3 h) solubility is required to select the MBP with the best performance. To evaluate the stability of the MBP from MiCoS, one week stress condition at 40°C/75% RH is recommended. The screening process may also be accelerated by 24 h exposure of MBP to 40°C/100% RH conditions.
3.2. MiCoS application to glybenclamide ASD development

Sequential MiCoS has been applied to glybenclamide ASD screening. The first screening focused on the selection of polymer and drug loading, and the second screening was applied to AS/S selection.

3.2.1. Polymer type and drug loading recommendation by MiCoS

Four enteric polymers, HPMCAS LF, HPMCP HP-55, Eudragit L100 and Eudragit L100-55 and five drug loadings, 10, 20, 30, 40 and 50% were evaluated for each polymer in the first screening. The AS/S was kept at 10:1. The MiCoS design map of the triplicate samples on a 96-well plate is illustrated in Fig. 4.

To ensure the drug precipitation in MBP, all filtrate were analyzed by HPLC. Fig. 5 indicates that the glybenclamide concentration of the filtrate ranged 0−22 μg/mL, equivalent of 0−17 μg drug loss per well. With an average of 2 mg API per well, the theoretical glybenclamide recovery from the coprecipitation was over 99%.

The solid state characterization and solid state stability (after 24 h storage at 40 °C/100% RH) of MBP were primarily characterized by HT-XRPD. Fig. 6 shows the XRPD pattern of the MBP at initial and after storage. Eudragit L100−55 yielded stable amorphous MBP at 10−50% drug loading. HPMCAS LF and HPMCP HP-55 formed stable amorphous MBP with glybenclamide up to 40% drug loading, while Eudragit L100 was not able to form stable amorphous MBP with glybenclamide. Based on the capability of forming high DL amorphous MBP, the polymer selection for glybenclamide MBP was ranked as Eudragit L100−55 > HPMCAS LF > HPMCP HP-55 > Eudragit L100.

After primary characterization by HT-XRPD, Raman spectroscopy was used as a secondary characterization tool to further confirm the physical and chemical identity of the MBP. Crystalline glybenclamide and its crystalline MBP presented distinctive spectral features from amorphous MBP. As shown in Fig. 7, the carbonyl group in the crystalline glybenclamide has a small but sharp peak at 1714 cm−1, while this peak disappeared in the amorphous MBP. Similar spectral difference was also observed on FT-IR with glybenclamide crystal and ASD (Bartsch and Grieser, 2004). In Fig. 7, the carbonyl stretch at 1714 cm−1 reappears when the amorphous MBP with HPMCAS at 50% DL was unstable and recrystallized after 40 °C/100% RH storage. The physical form characterization from Raman spectra was in good agreement with the XRPD results.

The performance of the MBP, as indicated by 1 h and 3 h kinetic solubility in FaSSIF media, are shown in Fig. 8. HPMCAS LF maintained the glybenclamide supersaturation for 3 h at all five drug loadings. HPMCP HP-55 maintained the glybenclamide supersaturation for only 1 h. Surprisingly, Eudragit L100−55, the most favorable polymer from the solid state characterization, was also not able to maintain the glybenclamide supersaturation at 3 h. The drug concentration dropped significantly at 3 h, especially for high DL samples. Eudragit L100, the least favorable polymer by the solid state characterization, only provided good supersaturation with 10 and 20% DL samples at h. Based on the degree of supersaturation and during of maintaining supersaturation, the polymer ranking for making glybenclamide MBP was HPMCAS LF > HPMCP HP-55 > Eudragit L100−55 > Eudragit L100.

Based on both the solid state properties and kinetic solubility, HPMCAS LF was recommended to make glybenclamide ASD up to 40% of drug loading. MBP at higher drug loadings up to 50% with HPMCAS was achievable, but the risk of instability increased with elevated API concentrations in the dispersions.

3.2.2. AS/S recommendation by MiCoS

Once the polymer type and drug loading were selected, the second screening was to optimize the AS/S. In industrial MBP manufacturing lower AS/S can significantly reduce manufacturing cost. However, as AS/S decreases the apparent solubility of the API in the AS/S mixture increases, reducing stability and recovery from the process.

In general drug solubility at different AS/S provides a metric for selecting AS/S in MBP development. However, the solid property of drug substance may be different from that of the solid dispersion.
Fig. 4. The glybenclamide MiCos design map of the triplicate samples on a 96-well plate.

Fig. 5. Glybenclamide concentration in the MiCos filtrate.

Fig. 6. XRPD characterization of glybenclamide MBP at T₀ and 24 h at 40°C/75%RH.
after coprecipitation, resulting in different solubility in the same AS/S. For this reason, AS/S needs to be experimentally determined. For early development with a limited API supply, 10:1 has been used as the default AS/S for SCP. At late stage, the AS/S is determined experimentally in batch mode by trying different AS/S to balance drug recovery and physicochemical properties of the dispersion. Such a study costs grams to kilograms of material and takes weeks to complete. MiCoS uses minimum amount of API and can be used to optimize AS/S much more efficiently.

In this screening, four AS/S from 5:1 to 12:1 were tested with HPMCAS LF at 10–40% DL. The concentration of glybenclamide in filtrates was analyzed by HPLC and the calculated recovery is listed in Table 2. With AS/S from 5:1 to 12:1, the drug recovery was above 97%. An AS/S of 5:1 was found to be acceptable for glybenclamide MBP manufacturing.

The solid state stability and kinetics solubility of the MBP at different AS/S was also evaluated. No noticeable difference was observed on the amorphous stability and solubility for all the MBP from different AS/S (Figs. 9 and 10). However, sufficient washing was critical when AS/S was low, as residual solvent could potentially lead to crystal seeds upon solvent evaporation and serve as a source for amorphous instability.

3.2.3. MiCoS perspectives

MiCoS has been confirmed and validated by mid to large scale MBP manufacturing with several commercial and Roche internal compounds. It has been successfully applied to both early and late stage amorphous formulation development. The general MiCoS paradigm is shown in Fig. 11.

The screening strategy is slightly different for early and late stage drug candidates. For early stage programs formulation intervention is required to enable efficacy or toxicology studies with limited API supply (such as 1 g) while meeting aggressive timelines. Typically all available drug substance is used to supply the material for PK studies, thus leaving very limited amounts for actual formulation development. Such a strategy has no guarantee of success, and frequently leads to failed amorphous products. MiCoS, on the other hand, can run a feasibility study with only 10 mg of API and provide useful insights in the manufacturing of MBP. The screening usually includes a few polymers at a conservative drug loading such
Table 2
Glybenclamide concentration in coprecipitation filtrates and the calculated recovery at different AS/S.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Conc. (µg/ml)</th>
<th>Total V (µl)</th>
<th>API amount in filtrate (mg)</th>
<th>Total API/well (mg)</th>
<th>Recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS/S = 5/1, 10%DL</td>
<td>55.2</td>
<td>420.0</td>
<td>0.023</td>
<td>0.89</td>
<td>97.4</td>
</tr>
<tr>
<td>AS/S = 5/1, 20%DL</td>
<td>47.7</td>
<td>420.0</td>
<td>0.020</td>
<td>1.6</td>
<td>98.8</td>
</tr>
<tr>
<td>AS/S = 5/1, 30%DL</td>
<td>52.3</td>
<td>420.0</td>
<td>0.022</td>
<td>2.3</td>
<td>99.0</td>
</tr>
<tr>
<td>AS/S = 5/1, 40%DL</td>
<td>55.8</td>
<td>420.0</td>
<td>0.023</td>
<td>2.8</td>
<td>99.2</td>
</tr>
<tr>
<td>AS/S = 8/1, 10%DL</td>
<td>21.1</td>
<td>630.0</td>
<td>0.013</td>
<td>0.89</td>
<td>98.5</td>
</tr>
<tr>
<td>AS/S = 8/1, 20%DL</td>
<td>22.3</td>
<td>630.0</td>
<td>0.014</td>
<td>1.6</td>
<td>99.1</td>
</tr>
<tr>
<td>AS/S = 8/1, 30%DL</td>
<td>23.7</td>
<td>630.0</td>
<td>0.015</td>
<td>2.3</td>
<td>99.3</td>
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<tr>
<td>AS/S = 8/1, 40%DL</td>
<td>24.4</td>
<td>630.0</td>
<td>0.015</td>
<td>2.8</td>
<td>99.5</td>
</tr>
<tr>
<td>AS/S = 10/1, 10%DL</td>
<td>15.0</td>
<td>770.0</td>
<td>0.012</td>
<td>0.89</td>
<td>98.7</td>
</tr>
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<td>AS/S = 10/1, 20%DL</td>
<td>18.2</td>
<td>770.0</td>
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<td>99.1</td>
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<tr>
<td>AS/S = 12/1, 10%DL</td>
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<td>98.8</td>
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<td>930.0</td>
<td>0.012</td>
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<td>AS/S = 12/1, 30%DL</td>
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<td>0.012</td>
<td>2.3</td>
<td>99.5</td>
</tr>
<tr>
<td>AS/S = 12/1, 40%DL</td>
<td>13.6</td>
<td>930.0</td>
<td>0.012</td>
<td>2.8</td>
<td>99.6</td>
</tr>
</tbody>
</table>

Fig. 9. HT-XRPD characterization of the glybenclamide MBP at different AS/S.

as 20% and AS/S of 10:1. It also provides experimental evidence on amorphous processing feasibility. MiCoS either confirms the experimental condition for making amorphous MBP, or concludes a failure using only 10 mg of API, rather than exhausting the entire drug substance batch. It also worth noting that MBP has great advantage over other amorphous technology such as HME or spray drying, as it is able to process few milligram of ASD with over 95% yield. In late stage research programs, amorphous development usually focuses on the optimization of the formulation. MiCoS, with broader experimental design space including more experimental parameters, can be applied efficiently to select the polymer, drug loading and AS/S to optimize the MBP formulation. In one 96-well plate, it can evaluate 96 experimental conditions using only 200 mg of material. Within a week, it can select the best performing polymer, DL and AS/S. Such
a comprehensive screening would require about 9.6 g of material and substantial time/resources by a tradition lab-scale screening method. Thus, the MiCoS process can significantly reduce cost and shorten the timeline for MBP formulation development.

While MiCoS has been developed specifically for MBP formulation screening, it can be expanded to ASD screening with general coprecipitation method. MBP preparation is limited by using enteric polymer, non-volatile solvent and acidic aqueous antisolvent. MiCoS, on the other hand, has been expanded to screening non-enteric polymers, volatile solvents, basic aqueous or organic antisolvents. For example, with MiCoS it is possible to prepare an ASD of BCS II drug candidate using the basic polymer Eudragit E PO by coprecipitation at pH 11 (data not shown). Water-soluble polymer povidone-10, coprecipitated with drugs in hexane. Volatile solvents such as acetone or methanol (Karnachi et al., 1995) could also be used in MiCoS, if good solubility could be achieved with both drug and polymer.

4. Conclusions

An integrated MiCoS system has been developed using commercially available components and devices based on a 96-well plate format. The MiCoS system composed of miniaturized coprecipitation with high-throughput solid state characterization and product performance assessment can be used to screen polymer types, drug loading, and AS/S at milligram scale. Other important coprecipitation parameters, such as solvent, antisolvent and coprecipitation temperature could also be evaluated in MiCoS. 300 mg of the model compound, glybenclamide was screened against four polymers, five drug loadings and four AS/S in triplicates. The results clearly suggest the choice of polymer as HPMCAS, with drug loading up to 40%, and AS/S of 5:1 to prepare stable glybenclamide ASD by coprecipitation.

MiCoS can be used in both early and late stage formulation development. In early stage research programs, MBP formulation could be quickly screened with minimal amount of API to enable efficacy and toxicology studies. In late stage development programs, MBP formulation optimization could be realized through wide experimental design space.

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