A material with unique physicochemical properties can often be produced by mixing two or more components (1). This fact is apparent in solid dispersion technology in which the oral bioavailability of poorly water-soluble drugs is enhanced either by molecularly dispersing the components in the carrier to form a solid solution or by dispersing them as fine crystalline particles (2). The drugs also can be partially dissolved and partially dispersed in the carrier. One common way to prepare a solid dispersion is to dissolve the drug and carrier in a chosen common organic solvent and then remove the solvent by evaporation. This kind of solvent process is attractive because it can be easily incorporated with many solvent-based particle-engineering techniques (3–10).

In addition to processing techniques, the drug–carrier compatibility and drug–carrier ratio also can influence the previously mentioned phase separation behaviors of solid dispersions (11). These two factors alone have already presented significant challenges to the traditional methods used for the accelerated development of new solid dispersion systems because of different drug–carrier ratios and various combinations of drugs and carriers (e.g., celluloses, starches, saccharides, hydrogenated saccharides, fats, glycerin, gums, lecithins, chitosans, gelatins, polymers, and surfactants). Traditional sample preparation, evaporation removal, and characterization methods such as X-ray diffraction (XRD), differential scanning calorimetry (DSC), and dissolution rate study, which often require sample crushing and pulverizing, usually take hours to complete (12). These major obstacles significantly decrease screening efficiency.

This article presents a rapid screening concept that accelerates sample preparation and characterization methods in solid dispersion technology by integrating spin casting on a silicon chip (spin-on) with optical microscopy (13). In general, spin-on requires a very small amount of sample materials (14). It involves placing only 1–2 drops of solution near the center of an ~2 × 2 cm silicon wafer chip. When the chip is spun, the solution is spread across the chip and the excess amount of solution is spun away by centrifugal force (see Figure 1). The remaining solvent evaporates by forced convection near the rotating surface, leaving a layer of dried film of solid dispersion across the chip—a process that requires ~3–10 s to complete.

In this spin-on screening process, a silicon wafer chip is chosen as a substrate because of its atomic flatness and reflective nature, which enhance constructive and destructive interference of a light wave propagating through the cast film (see Figure 2).
As a result, optical imaging of the film’s features becomes brighter and sharper in a reflective mode. The key advantage of optical microscopy, compared with XRD, DSC, and dissolution rate study, is its rapid turnaround time, usually 1–2 min, to reveal visually the effect of drug–carrier compatibility and drug–carrier ratio on phase separation behaviors of solid dispersions. Therefore, the entire screening process using spin-on and optical microscopy can be completed in <3 min/sample.

**Experimental**

The feasibility of rapid drug–carrier screening on a chip at 25 °C was tested on four precedents of solid dispersion that were characterized by XRD and DSC, including sulfisoxazole–polyvinylpyrrolidone in ethanol (16), griseofulvin–polyethylene glycol 6000 in ethanol (17), keotoprofen–phosphatidylcholine in xylene, and flurbiprofen–phosphotidylcholine in xylene (18).

For all four systems, minimum amounts of solvents chosen on the basis of their solubility data at 25 °C (see Table I) were used to codissolve the drug and the carrier to various weight (molar) ratios. Then 1–2 drops of the solution with a specific drug–carrier ratio were spun on a piece of silicon wafer chip using a spin coater (Model CB 15, Headaway Research, Inc., Garland, TX). A new chip was used for each solution. The chip was spun at a rotational speed of 2000 rpm for only 3–10 s until the solvent was totally evaporated. This procedure took place when no noticeable change existed in the film’s interference color as a result of the stabilization of film thickness. Films on the chips with different drug–carrier ratios were sequentially prepared and separately analyzed by optical microscopy.

**Results and discussion**

Optical micrographs of films (see Figures 3–6) show a medley of colors because of regional variations in film thickness (see Figure 2). Therefore, film thickness increases in the following color order: from indigo to green, yellow, orange, and red (15). Film uniformity is based on the viscosity and evaporation rate of the solution, the spin speed, the drug–carrier compatibility, and the wetting ability between the drug–carrier and the silicon chip surface (19).

**Sulfisoxazole–polyvinylpyrrolidone in ethanol.** Figure 3 shows optical micrographs of polyvinylpyrrolidone thin film; sul-
fisoxazole–polyvinylpyrrolidone thin films with weight ratios of 1:3, 1:1, 3:1, and 10:1; and sulfisoxazole thin film. As the sulfisoxazole–polyvinylpyrrolidone ratio increases, particles begin to form in the film at a ratio of 3:1 and greater. The film becomes mottled with a high population of particles at a ratio of 10:1. This morphological change agrees with the X-ray patterns of Sekikawa et al.’s samples in which the crystallization of sulfisoxazole was inhibited in polyvinylpyrrolidone at a ratio of 1:3 (coprecipitate); however, the sulfisoxazole crystal peak remained in the XRD pattern at a ratio of 10:1 (16).

**Griseofulvin–polyethylene glycol 6000 in ethanol.** Figure 4 shows optical micrographs of a polyethylene glycol 6000 thin film; griseofulvin–polyethylene glycol 6000 thin films with w/w % ratios of 5, 10, 20, and 40; and a griseofulvin thin film. Dewetting occurred at 10 w/w %. Dendritic morphology, most likely a result of the crystallization of polyethylene glycol 6000, was observed at 20 w/w %. Colloids were found in the terrace region at 20 w/w %, and the film was filled with a large number of colloids at 40 w/w %. These optical micrographs are consistent with Chiou et al.’s report about a decreasing dissolution-rate order of griseofulvin in the griseofulvin–polyethylene glycol 6000 system as the ratio increases from 5 to 40 w/w % (17). Apparently, griseofulvin is molecularly dispersed in the polyethylene glycol 6000 matrix at a low weight-per-weight percent.

**Table I: Solubilities for drugs and carriers in different solvents at 25 °C and 1 atm.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Solvent</th>
<th>Solubility (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfisoxazole</td>
<td>Ethanol</td>
<td>16</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>Ethanol</td>
<td>3</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>Xylene</td>
<td>40</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Xylene</td>
<td>140</td>
</tr>
<tr>
<td><strong>Carrier</strong></td>
<td><strong>Solvent</strong></td>
<td><strong>Solubility</strong></td>
</tr>
<tr>
<td>Polyvinylpyrrolidone</td>
<td>Ethanol</td>
<td>46</td>
</tr>
<tr>
<td>Polyethylene glycol 6000</td>
<td>Ethanol</td>
<td>24</td>
</tr>
<tr>
<td>Phosphotidylcholine</td>
<td>Xylene</td>
<td>125</td>
</tr>
</tbody>
</table>

**Figure 4:** (a) Polyethylene glycol 6000 thin film. Griseofulvin–polyethylene glycol 6000 thin films with a w/w % of (b) 5, (c) 10, (d) 20, and (e) 40. (f) Griseofulvin thin film.

**Figure 5:** (a) Phosphatidylcholine thin film. Keptoprofen–phosphatidylcholine thin film with a mol % of (b) 25, (c) 50, and (d) 75. (e) Keptoprofen thin film.
and are more readily dissolved than a colloidal dispersion at a high weight-per-weight percent.

Flurbiprofen–phosphatidylcholine in xylene and keptoprofen–phosphatidylcholine in xylene. Figures 5 and 6 show optical micrographs of thin films of keptoprofen–phosphatidylcholine and flurbiprofen–phosphatidylcholine, respectively, with molar ratios of 25, 50, and 75 mol %. Although dewetting and nonuniformity were observed, numerous particles were not detected in any one of those films. These observations concur with the X-ray diffractograms in Fujii et al.’s studies in which flurbiprofen and keptoprofen were in an amorphous state when the molar ratio of the solid dispersion system was $<75$ mol % (18). A better film uniformity at 50 mol % may also suggest a more homogeneous dispersion of flurbiprofen and keptoprofen in phosphatidylcholine matrix; therefore, the dissolution rates of flurbiprofen and keptoprofen were enhanced as observed by Fujii et al. (18).

Although these experiments (see Figures 3–6) were performed at 25 °C with various drug–carrier ratios, all the chip-based films can be further annealed at different temperatures in a vacuum oven to a desired temperature, $T$. If all the optical micrographs are arranged in a mosaic array with $T$ versus $f$, a phase diagram can be constructed (13). This kind of phase diagram shows the effect of temperature and drug–carrier ratio on phase separation behaviors of solid dispersions. This diagram can serve as a road map for selecting conditions in which to process solid dispersion systems. Furthermore, the evaporation rate of solvents in the spin-on method can be varied in a chamber with partial solvent pressure or under vacuum pressure to simulate the effect of rapid evaporation on the quality of solid dispersion systems during the spray-drying process. Spun-cast films on silicon chips may also provide an approximate cross-sectional view of the solid dispersion materials. Besides optical microscopy, other analytical tools such as Raman–IR spectroscopy, atomic force microscopy, transmission electron microscopy (14,20–23), nanoindenter (24), microthermal analysis (25), and dielectric analysis (26,27) can also be used to examine the drug–carrier spatial distribution, high-resolution lattice image, local mechanical properties, polymorphism, and film curing of the chip-based solid dispersion thin films. Therefore, rapid screening by spin-on based on good science seems to have the potential to be used as process analytical technology to increase process automation, reduce analytical costs, and provide faster investigations with more results (28).

Solutions of various drug–carrier ratios used for spin-on were prepared and kept separately in various vials. This batch-wise process can be expedited by a mixed composition-gradient column developed in polymer science (29). If desired, this technique can be easily integrated with the spin-on method.

Conclusions

The authors have presented a rapid drug–carrier screening technique integrated with optical microscopy on silicon chips (spin-on). Desired drug–carrier ratios that provide the amorphous or crystalline state are identified visually and verified in the literature. The fast evaporation rate of solvents and the short image-acquisition time make this method appealing for accelerated development of new solid dispersion materials. This method also can be automated and integrated with many combinatorial methods in polymer science and other spectroscopic and microscopic techniques to obtain the drug–carrier spatial distribution, local mechanical properties, polymorphism, and dielectric constant of the chip-based solid dispersion thin films. Thus, it has a potential to be facilitated as a process analytical technology in the pharmaceutical industry.

References


