Micromolding as a potential manufacturing route for dry powder formulations

A technology adapted from the semiconductor industry holds promise for the development of drugs for inhalation

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This is the second in a series of articles by Purdue scientists on new technologies in inhalation drug development

As environmental concerns have led pharmaceutical companies and regulators to work towards eliminating the use of propellants in inhalation devices, much of the recent research for pulmonary drug delivery has turned towards the use of dry powder inhalers (DPIs). Developing powder formulations for use in DPI devices presents significant challenges due to the small volume of API required, the need to generate a high fine particle fraction for delivery to the appropriate part of the airway, and the extremely narrow target range of particle size. Because particle size, density, and morphology determine the API's handling and processing behaviors, including its interactions with excipients and its aerosolization properties, researchers have focused a great deal of attention on developing methods for better control of such characteristics. One new technique, microscale particle molding, also known as micromolding, represents a promising new method for achieving unprecedented control of such characteristics.

The most common and simplest way to create particles in the <10μm range necessary for delivery to the lower respiratory tract is size reduction through milling or micronization. The equipment necessary, whether a jet mill, fluid energy mill, or ball mill, uses established, well-understood technology and is widely available for commercial use; however, milling presents several serious drawbacks for the production of powders for DPIs. Milling is a high energy process that, as it converts coarse particles into fine particles, transfers significant energy into the particulate material. This process results in increased surface energy, and the resulting increases in cohesiveness and adhesiveness can make the powder difficult to handle [1]. For DPI products that use pure API, without any excipient, poor handling characteristics make metering of small doses accurately into capsules or blisters extremely problematic. When the DPI product uses a formulation with an inhalable lactose carrier or agglomerate of API and lactose, the high surface energy imparted by milling can make detaching the API from the excipient difficult, especially for COPD and asthma medications where the patient may not be able to generate sufficient inspiratory force. In addition, the reliance on fracture phenomena in milling makes processing of smaller particles challenging since both flaw size and number decrease with decreasing particle size. Milling also tends to have poor control over particle size distribution and provides no control whatsoever over the particle morphology.

Several processes currently available for creating particles in the size range necessary for delivery to the lungs allow for control over morphology, particle size distribution, and, in some cases, crystallinity. Spray drying also allows for the creation of composite or coated particles that flow freely and have reduced hygroscopicity, making them relatively easy to handle and more stable than micronized powders. However, higher operating temperatures and relatively low cyclone collection efficiency for particles below 2 μm can limit the possibilities for spray drying certain compounds. The limited solubility of many drugs also poses challenges for spray drying. The most recent approach to improving particle performance for inhalation involves creating porous particles [2] by spray drying emulsions containing a

highly volatile solvent or a blowing agent with a high vapor pressure. The low density results in larger, easier-to-handle particles with relatively small aerodynamic diameters so that they can still reach the lower respiratory tract; however, these particles may lack structural stability.

Micromolding, which builds on so-called "soft lithography" techniques adapted from the semiconductor industry, has the potential to overcome some of the limitations of these methods that have restricted their use for DPI formulations. The soft lithography technique uses castable elastomeric materials to reproduce micrometer scale features on silicon substrates created by conventional semiconductor fabrication techniques [3]. These elastomeric structures are typically inverse replicas of the original silicon master and are often used as stamps for the placement of a wide variety of materials with micrometer scale resolution and precision. In other words, the molds behave roughly like rubber stamps, and the materials they deposit are akin to the ink. Micromolding, by contrast, uses the cavities in the structures, typically made of polydimethylsiloxane (PDMS), an elastomer that can be cured at moderate temperatures, to create three dimensional forms instead of using the raised areas to transfer two-dimensional features. Although a number of groups have succeeded in micromolding particles for pharmaceutical applications, most of these efforts have targeted oral delivery or injection applications. To our knowledge, no one has yet attempted micromolding for inhalation therapy formulations.

A group led by Derek Hansford at Ohio State University has developed a number of different micromolding routes for realization of microparticles with higher surface area-to-volume ratios relative to traditionally manufactured spherical microparticles [4], including the MicroContact Hot Printing (μCHP) method, which heats the mold to cure the microparticle formulation in situ and to create better adhesion to the stamp. The μCHP process can produce particles either by stamping or by molding (Figure 1).

Hansford's group has experimented with several variables in the micromolding process to manipulate the properties of the particles created. They have shown that the viscosity of the particle formulation plays a key role in the thickness and accuracy of the resulting particles and also that coating stamps with multiple layers and types of materials leads to layered particles. More recently, they have generated particles with complex geometries, such as crosses, cylinders, and elongated bars. Non-thermal curing routes, including solvent evaporation, chemical cross linking, and UV light, have also been explored as potential methods for micromolding temperature-sensitive components such as biological therapies.

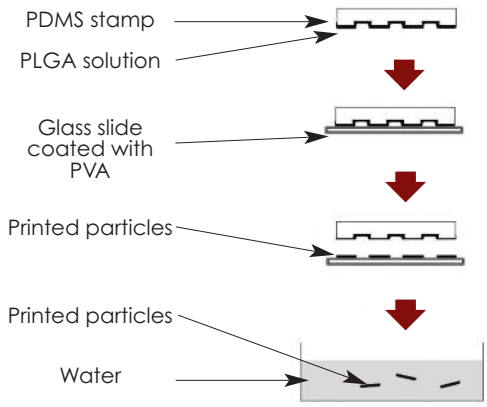
Despite these successes, PDMS-based micromolding is not without its limitations. For example, the process cannot handle temperatures over 200°C or high aspect ratio geometries where particles have greater thickness than lateral dimension. Moreover, PDMS is prone to swelling in many organic solvents, limiting its utility in non-aqueous formulations. Finally, finite wetting of the molding material often results in thin "flashing" that connects the particles to one another, a problem that can be mitigated to some extent through novel process adaptations such as Hansford's μCHP but that may impact the cost-effectiveness and reproducibility of such processes. As a result, more robust and versatile alternatives are required.

One such alternative has been demonstrated recently by a group at the University of North Carolina led by

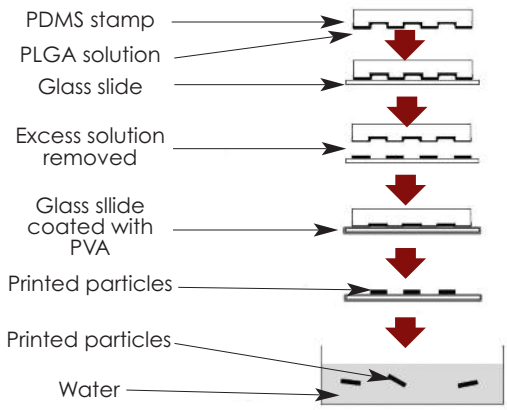
Figure 1

PDMS microparticle molding methods

(a) Particles are created from protruding stamp geometries



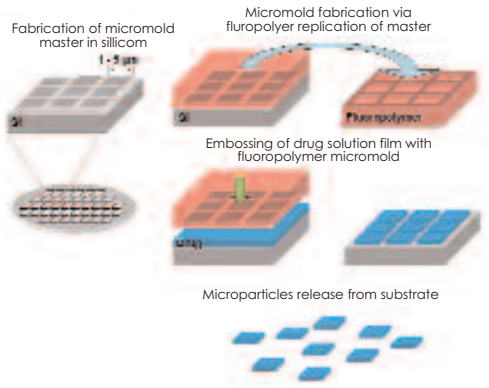
(b) Particles are molded in recessed stamp geometries (adapted from Hansford)



Joseph DeSimone that developed photocurable perfluoropolyethers (PFPEs) as an alternative to PDMS [5]. PFPEs serve as the basis for a new micromolding technique called PRINT, an acronym for Particle Replication In Nonwetting Templates. The PRINT process shows the potential for greater reliability and scalability than other micromolding processes developed thus far due to its simplicity (Figure 2). PFPE retains most of the beneficial properties of PDMS, while also providing greater resistance to organic solvents and wetting. This last property is particularly beneficial with regard to micromolding because it increases molding fidelity, improves particle release, and eliminates interparticle flashing. Using the PRINT process, the DeSimone group has demonstrated fabrication of particles with nanometer scale resolution and precisely controlled size, size distribution, shape, and composition.

Figure 2

"PRINT" fabrication method (adapted from DeSimone)



While micromolding offers significant promise for the realization of precision-engineered particles for pharmaceutical applications in a number of areas, the technique holds special promise for DPI formulations beyond the fact that the process can tightly control particle size and size distribution, so that nearly all of the particles are the same size, ensuring uniformity of flow and deposition characteristics. Recent studies have demonstrated that elongated particles produce better deposition behavior than equivalent spherical particles, presumably due to smaller effective aerodynamic diameter [6], and micromolding provides a means for controlling shape with a degree of precision and sophistication that is otherwise impossible with conventional techniques.

Finally, micromolding holds promise for far greater control of particle composition, drug loading, and crystalline morphology, among others, thus providing the opportunity for creation of new formulations with greater efficacy and stability. Although additional research is needed to verify this hypothesis and to explore whether the formation of drug particles without excipients is possible, in theory, a well-mixed solution of drug and excipient at a particular concentration should retain the same composition and drug loading when forming particles through micromolding. Such control would provide exciting options for the development of new DPI formulations.

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