Capillary Drop Penetration Method to Characterize the Liquid Wetting of Powders

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ABSTRACT: We present a method to characterize the wettability of powders, based on the penetration dynamics of a sessile drop deposited on a slightly compressed powder bed. First, we show that a direct comparison of the wetting properties of different liquids is possible without having to solve the three-dimensional liquid penetration problem, by considering the appropriate dimensionless variables. We show that the contact area between the sessile drop and the powder bed remains constant during most of the penetration process and demonstrate that as a result, the evolution of the dimensionless penetration volume is given by a universal function of the dimensionless time, with no dimensionless parameters. Then, using a reference liquid that completely wets the powder, it is possible to obtain an effective contact angle for a test liquid of interest, independent of other properties of the powder bed, such as permeability and a characteristic pore size. We apply the proposed method to estimate the contact angle of water with different powder blends, by using silicone oil as the reference liquid. Finally, to highlight the potential of the proposed method to characterize pharmaceutical powders, we consider a blend of lactose, acetaminophen, and a small amount of lubricant (magnesium stearate). The proposed method adequately captures a significant decrease in hydrophilicity that results from exposing the blend to excessive mixing, a well-known effect in the pharmaceutical industry.

INTRODUCTION

Powders are ubiquitous in the pharmaceutical industry, and the importance of characterizing their wetting properties has long been recognized.1,2,14 In solid dosage forms, for example, knowing the wetting properties of both raw excipients and the active pharmaceutical ingredient is crucial to a number of processes, ranging from formulation development to the manufacture of the final product.3 In addition, different manufacturing processes affect the surface properties of powders and could significantly change their wetting properties. Also importantly, the wetting properties of excipients can directly affect the dissolution performance and, in some cases, are also correlated with other critical quality attributes of solid dosage forms, such as tablet hardness.7,8 As a result, there are a number of techniques that have been developed to measure the contact angle of powders, from early methods based on measuring the height of large drops deposited on presaturated, compressed powders9 to more recent techniques measuring dynamic contact angles.10 Here, we focus on the drop penetration method (DPM), in which the wetting properties of a powder are characterized by the penetration dynamics of a sessile drop deposited on a powder bed.

The DPM has also been used in a number of areas, besides the pharmaceutical industry, to characterize the wetting properties of powders, granular materials, and porous media in general. In soil sciences, for example, the water-drop penetration test (WDPT) is a traditional method to characterize soil hydrophobicity.11–13 Another traditional application relates to the penetration of ink droplets into paper14,15 (thin porous media). In terms of finely divided solids and powders, the DPM is used, for example, to characterize wetting and optimize conditions in wet granulation, a process used in a variety of industries.16,17 The DPM has some comparative advantages over other methods, also based on the dynamics of liquid penetration into the powder: it is relatively fast, uses small amounts of powder to perform the experiments, and requires a relatively simple setup. It is not the objective of this work, however, to compare the DPM to other techniques that are used to characterize the wetting properties of powders, and we refer the reader to a recent review article for a detailed discussion of relative advantages and disadvantages of the DPM and alternative characterization methods.18

Although different versions of the DPM have been used for a long time, progress toward a well-established methodology to analyze the penetration dynamics and to obtain quantitative information on the capillary forces driving the flow has been limited. In some applications, such as the WDPT in soil sciences, the method remains a qualitative means to compare different soil samples.12,13,19–23 Initial modeling efforts by Denesuk et al. considered two alternative limiting cases to study...
the dynamics of capillary penetration. In one case, the area of the drop in contact with the porous substrate remains constant during the penetration, the constant drawing area (CDA) case. In the other case, it is the apparent contact angle between the drop and the substrate that remains constant, and the contact area decreases during penetration. An expression for the total penetration time, $t_p$, for a drop to be fully absorbed into a porous material was derived in each case, approximating the penetration dynamics by a one-dimensional (1D) flow into parallel bundles of cylindrical capillaries, oriented perpendicular to the interface. The same authors considered the initial spreading of the drop and showed that in many cases, the CDA approximation remains valid, as the spreading time is much shorter than the penetration time, and the drop reaches a constant contact radius before a significant amount of liquid penetrates into the porous media. In a more recent experimental work, Hapgood et al. have observed that the CDA case is in fact a good approximation to describe the penetration of droplets into powder systems, and derived a modified expression for the total penetration time that accounts for the presence of voids in the powder bed. This modified total penetration time was later used to characterize the wetting properties of different powder—liquid systems. There are also studies that have relaxed the CDA approximation and allowed the contact area to change in time. These studies, however, rely on empirical laws usually obtained on flat surfaces to describe the motion of the contact line on the surface of the powder bed. Alternatively, the presence of a precursor film has been used to describe the penetration of thin drops using lubrication theory. An important limitation of the model proposed by Denesuk et al. is the approximation of vertical imbibition into parallel capillaries, which essentially treats the powder bed (or porous media) as a 1D system. In fact, Navaz and co-workers have clearly demonstrated the importance of accounting for the fully three-dimensional (3D) nature of the penetration problem using numerical simulations. In addition, the long-time behavior of the penetration problem with a finite contact area can be approximated by the penetration of fluid from a point-source, a case that has been recently solved analytically and exhibits an asymptotically linear scaling of the penetrated volume with time, in contrast to the square-root-of-time dependence in the 1D case. Unfortunately, in the fully 3D penetration case, there is no analytical expression available for the total penetration time $t_p$.

Here, we show that, in the case of a constant drawing area, it is possible to compare the wetting properties of different liquids without having to solve the 3D penetration problem, by analyzing the appropriate dimensionless volume and the corresponding dimensionless penetration time for each liquid. As a result, it is also possible to obtain the effective contact angle between a test liquid and the powder, by performing supplementary experiments with a reference liquid that completely wets the powder. Using such a reference liquid decouples the properties of the porous bed from the measurement of the contact angle, a customary approach in capillary rise experiments using the Washburn method. In addition and in contrast to the traditional DPM based on the total penetration time in which the drop completely enters the powder beds, the proposed method can be applied to any penetration volume, not necessarily equal to the total volume of the sessile drop. Moreover, multiple intermediate penetration volumes can be used, as long as the same dimensionless volumes are compared between the test and reference liquids.

In fact, the proposed analysis is based on the fact that the nondimensional volume of fluid penetrating into the powder bed is a universal function of the nondimensional time. Therefore, to validate the proposed analysis method, we first investigate the penetration of water droplets of different initial volumes and show that the penetration dynamics in dimensionless units is in fact independent of the volume of the droplets. Then, we apply the proposed method to estimate the contact angle of water in different powder systems, using silicone oil as the reference fluid and lactose as the main component of the powder systems. Finally, we highlight the relevance of the proposed method for the characterization of pharmaceutical blends by detecting a dramatic decrease in the wetting of a powder system containing a hydrophobic lubricant due to overlubrication of the blend.

## DROP PENETRATION ANALYSIS

### Governing Equations

Consider a sessile drop deposited on the surface of a powder bed, as shown schematically in Figure 1. Its penetration into the powder bed has some important similarities with experiments on the capillary rise of a fluid into a porous medium. In particular, at short times, the dynamics is dominated by fluid inertia and we shall ignore these effects, limiting ourselves to larger time scales (for an estimation of the characteristic inertia time scales in our system, see section Scaling and Nondimensionalization below). In addition, we shall assume that the transport of fluid inside of the powder bed follows Darcy’s law

$$\mathbf{u} = -\frac{k}{\mu} \nabla p$$

(1)

where $\mathbf{u} = (u_x, u_y, u_z)$ is the volume-averaged fluid velocity or superficial velocity (sometimes called specific discharge), $\mu$ is the fluid dynamic viscosity, and $k$ is the permeability of the powder bed. Darcy’s law implies a macroscopic description of transport inside of the porous bed and we use boundary conditions at the same macroscopic level, as discussed below. Note that we have also assumed that the powder bed is homogeneous and isotropic at the macroscopic level, which corresponds to a scalar permeability that is uniform inside of the sample. We also ignore gravity effects on the flow.

Then, we can write the continuity equation for the averaged velocity, neglecting the liquid evaporation inside of the porous bed and assuming its incompressibility

$$\nabla \cdot \mathbf{u} = 0$$

(2)

Figure 1. Schematic view of a sessile drop penetrating into a powder bed: (1) air; (2) porous bed; (3) sessile drop on the surface of the powder bed with volume $V_d(t)$; and (4) wet region inside of the powder bed, with volume $V_w(t)$. The position of the interface between the wet and dry regions inside of the powder bed is given by $z = -h_p(x, y, t)$.

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which in combination with Darcy’s law yields the Laplace equation for the pressure field
\[ \nabla^2 p = 0 \quad (3) \]

In principle, we should also write governing equations that describe the evolution of the fluid inside of the drop. However, we shall approximate the pressure inside of the drop to be uniform and equal to the atmospheric pressure, \( p_0 \), at all times. Note that we ignore the pressure drop that develops because of the fluid motion inside of the drop. We assume that such pressure differences are small compared to the pressure differences that are required to move the fluid inside of the powder bed because of the confinement of the fluid inside of the microscopic pore space. We also assume that the drop is much larger than the pore size to neglect the pressure difference across the drop–air interface compared to the capillary pressure at the liquid–air interface inside of the porous medium. Similarly, we neglect gravity effects on the pressure inside of the drop. On the other hand, it is not necessary to assume that the drop size is below the capillary length, as long as both gravity and capillary effects are small compared with the capillary pressure inside of the porous bed. In other words, the analysis could still apply for a drop that deforms under gravity.

**Boundary Conditions.** Following the notation used in ref 38, we define the penetration profile or the wetting front, \( h_p(x, y, t) \) by an implicit equation
\[ F(x, y, z, t) = h_p(x, y, t) + z = 0 \quad (4) \]
The kinematic condition then couples the evolution of the wetting front to the flow field inside of the powder bed
\[ \frac{DF}{Dt} = \frac{\partial F}{\partial t} + (\mathbf{v} \cdot \nabla) F = \frac{\partial h_p}{\partial t} + v_x \frac{\partial h_p}{\partial x} + v_y \frac{\partial h_p}{\partial y} + v_z = 0 \quad (5) \]
where \( \mathbf{v} \) is the interstitial or seepage velocity, \( u = \overline{\mathbf{v}} \), where \( \epsilon \) is the porosity of the medium. As we mentioned before, the description of the penetration profile has to be consistent with the description of the flow and therefore performed at the same macroscopic level as Darcy’s law. As a result, the kinematic condition does not account for the complex pore space of the powder bed. Similarly, the dynamic boundary condition inside the media is the normal-stress balance
\[ p_{F=0} - p_0 = -p_c \quad (6) \]
where we assume that the pressure inside of the dry powder is equal to the atmospheric pressure, \( p_0 \) and \( p_c \) is the capillary pressure (we use the convention that \( p_c \) is positive if the liquid wets the powder\(^{30}\)). We note that any pressure build-up because of the displacement of air by the penetrating liquid is small compared with the corresponding pressure drop driving the fluid penetration, as a result of the viscosity contrast between the penetrating fluids and air. The macroscopic nature of the equation above makes it necessary to write the capillary pressure explicitly in terms of the wetting properties of the powder and the geometry of the powder bed. Specifically, we write an effective Young–Laplace equation for the normal stress condition
\[ p_{F=0} - p_0 = -p_c = -\frac{2\gamma \cos(\theta)}{r_{\text{eff}}} \quad (7) \]
where \( \gamma \) is the surface tension, \( \theta \) is the contact angle of the liquid on the powder, and \( r_{\text{eff}} \) is the effective pore radius, that is, the radius of a capillary made of the powder material that would result in the same capillary pressure as that in the macroscopic description. We shall also assume that the capillary pressure is independent of the position of the wetting front, which is consistent with our previous assumption of a homogeneous system.

Finally, as we mentioned in the introduction, we shall assume that the contact radius \( r_c \) of the sessile drop in contact with the surface of the powder bed (see Figure 1) is constant during the penetration, or at least, during a significant portion of the penetration process. This first part of the penetration in which the contact area is constant is used to calculate the contact angle. In this case, the boundary conditions at the powder bed–sessile drop interface correspond to continuity conditions in both pressure and velocity fields. Recalling that the pressure inside of the sessile drop is approximated as equal to the atmospheric pressure, we write
\[ p(x, y, z, t)|_{t=0} = p_0 \quad \text{for} \quad r \leq r_c. \quad (8) \]

On the other hand, because we are not describing the flow inside of the drop, the continuity on the velocity is immaterial, and for simplicity, we can impose a no-slip condition for the tangential velocity.

**Scaling and Nondimensionalization.** Let us first identify the appropriate characteristic scales for the drop penetration problem given the conditions and approximations discussed above. First of all, we have argued that the flow and pressure fields inside of the sessile drop can be ignored. Similarly, the capillary pressure resulting from the sessile drop–air interface can also be neglected, compared with the capillary pressure inside of the powder bed. As a result, the initial radius \( R_0 \) and volume \( V_0 = V_0(t=0) \) of the sessile drop have no influence on the penetration process, except through the contact radius \( r_c \). In fact, only the contact radius enters the governing equations, setting the area of the inlet region in eq 8. Therefore, we use the contact radius as the characteristic length, \( l_c = r_c \). The characteristic scale for the pressure field inside of the powder bed is given by the capillary pressure in eq 7 and the characteristic velocity \( u_c \) can subsequently be obtained from Darcy’s law \( \text{eq 1} \), \( u_c = k_p/\mu r_c \). Finally, we write the characteristic time for the convective transport inside of the powder bed
\[ t_c = \frac{r_c}{u_c} = \frac{r_c}{k_p/\mu r_c} = \frac{\mu r_c^2}{k_p} \quad (9) \]
We note that an alternative time scale in this problem is given by the initial penetration phase, dominated by inertia effects. This inertial flow transitions to the viscous-dominated regime on a time scale \( t_i = r_{\text{eff}}^2/4\mu \).\(^{45}\) We shall see that in our system, this time is orders of magnitude smaller than the time scale of the penetration process.

Using the characteristic velocity, time, length, and pressure scales to render the governing equations nondimensional, we obtain
\[ \mathbf{u} = -\nabla \mathbf{p} \quad (10a) \]
\[ \nabla^2 \mathbf{p} = 0 \quad (10b) \]
where $X = x/r_o$, $Y = y/r_o$, $Z = z/r_o$, and $p = p/p_c$. Similarly, we obtain the nondimensional boundary condition for the wetting front

$$\frac{\partial \tilde{h}_p}{\partial \tilde{t}} + \tilde{u}_x \frac{\partial \tilde{h}_p}{\partial \tilde{x}} + \tilde{u}_y \frac{\partial \tilde{h}_p}{\partial \tilde{y}} + \tilde{u}_z = 0$$

(11)

where $\tilde{h}_p = h_p/r_o$ and $\tilde{t} = t/t_o$, and we have replaced the seepage velocity $\tilde{v}$ by the average velocity $\tilde{u}$ to have a close set of equations on $\{\tilde{u}, \tilde{p}\}$. In addition, this also eliminated the porosity $\varepsilon$ from the equation. Finally, we write the nondimensional boundary condition for the pressure field, both at the inlet (contact area)

$$\tilde{p}(\tilde{x}, \tilde{y}, \tilde{z}, \tilde{T})|_{\tilde{t}=0} = 0 \quad \text{for} \quad \tilde{r} \leq 1$$

(12)

where $\tilde{r} = r/r_o$ and at the wetting front

$$\tilde{p}|_{\tilde{p}=0} = -1$$

(13)

where the nondimensional pressure is now measured with respect to the ambient pressure, which is equivalent to set $p_0 = 0$.

A fundamental aspect of these nondimensional equations is that they do not depend on any dimensionless parameter. That is, the nondimensional solution to the penetration problem is independent of the contact radius $r_o$, the capillary pressure inside of the powder bed $p_0$, the permeability of the powder bed $k$, or the effective pore radius $r_{de}$, the viscosity $\mu$, and the surface tension $\gamma$ of the liquid or the contact angle $\theta$. In addition, we have shown that the penetration dynamics is also independent of the initial sessile drop volume $V_o$ and the radius $R_0$ as well as the apparent contact angle between the drop and the powder bed $\theta_0$. Therefore, under the assumptions and approximations discussed above, there is a universal solution that applies to any powder—liquid system. It follows that any quantity of interest is given by a universal function of the dimensionless variables in the problem. For example, the position of the wetting front $h_p$ and the corresponding volume of the region wet by the fluid $V_p$ can be written as $h_p = r_f(x, y, \tilde{T})$ and $V_p = r_f^3 g(\tilde{T})$, respectively. Then, taking into account that the volume of liquid inside of the wet region is given by $V_p(t) = e V_c(t)$ (adsorbed volume or penetration volume), we derive a similar expression for the total penetration time $\tau_p$ such that $V_p(t = \tau_p) = V_0 = V(t = 0)$

$$\tau_p = t_f \left( \frac{V_o}{e r_c^3} \right) = \frac{\mu \varepsilon r^2}{k_p} \left( \frac{V_o}{e r_c^3} \right)$$

(14)

for some function $f$. It is important to note that, given that the penetration front dynamics and thus $V_p(t)$ are independent of the initial drop volume, we can use the equation above to define the penetration time of an arbitrary nondimensional volume of fluid. For example, the penetration time $\tau_a$ for a volume of fluid equal to a fraction $\alpha$ of a hemisphere of radius $r_o V_o = \alpha^2/8 \pi r_o^3$, is

$$\tau_a = \frac{\mu \varepsilon r^2}{k_p} \left( \frac{2/3}{\pi} \alpha^2 \varepsilon_r \right)$$

(15)

In the following section, we discuss how to take advantage of this result to measure the contact angle for a powder—liquid system at intermediate penetration volumes. That is, at intermediate times during the penetration of the drop, when the volume of fluid that has penetrated is smaller than the total drop volume.

## Penetration Time Measurements

We present a simple method to measure the contact angle of a given powder—liquid system, based on the results discussed above. To this end, we assume that we have a reference liquid $R$, with viscosity $\mu_R$ and surface tension $\gamma_R$, and, most important, zero contact angle with the powder under consideration, that is, complete wetting $\gamma_R = 0$. Then, we would like to determine the contact angle $\theta_T$ of a test liquid $T$ (viscosity $\mu_T$ and the surface tension $\gamma_T$) with the same powder. The experiments with the reference and test liquids are performed using the same powder bed, with permeability $k$, porosity $\varepsilon$, and effective pore radius $r_{de}$.

Next, using eq 15, we write the ratio of penetration times $\tau_a$ for both reference and test liquids

$$\frac{\tau_{aR}}{\tau_{aT}} = \frac{\mu_T}{\mu_R} \left( \frac{r_{de}^2}{r_{de}^2} \right) \frac{1}{\gamma_T \cos(\theta_T)}$$

(16)

Note that the function $f$ cancels out because it has the same value in both cases. Then, using eq 7 and the fact that the transport properties of the medium ($k, r_{de}, \varepsilon$) are the same in both cases, we obtain

$$\frac{\tau_{aR}}{\tau_{aT}} = \frac{\mu_T}{\mu_R} \left( \frac{r_{de}^2}{r_{de}^2} \right) \frac{1}{\gamma_T \cos(\theta_T)}$$

(17)

Rearranging the previous equation, we obtain an expression for the contact angle of the test liquid as a function of the penetration times

$$\cos(\theta_T) = \frac{\tau_{aR}}{\tau_{aT}} \frac{\mu_T}{\mu_R} \left( \frac{r_{de}^2}{r_{de}^2} \right) \gamma_T$$

(18)

Note that the equation for $\cos(\theta_T)$ above has no explicit dependence on the transport properties of the powder bed. It is also clear that the derivation of this equation is independent of the actual form of the solution to the penetration problem. In particular, it does not depend on the shape of the region inside of the powder bed that is wet by the liquid. In addition, we could repeat the same procedure for any dimensionless volume and the corresponding penetration times obtained experimentally.

### Materials and Methods

#### Powders and Blends

Three different powder systems with increasing number of components were studied. The first one is 100% lactose powder, using $\alpha$-lactose monohydrate (Foremost Farms USA). Lactose is a typical excipient found in pharmaceutical formulations. The composition of the second powder system is a blend of 91% lactose powder and 9% acetaminophen (APAP) by weight, that is, a 10:1 ratio by weight. Acetaminophen is a model active ingredient that we have used in previous studies (semi APAP, Mallinckrodt Pharmaceuticals). The powder was mixed in a V-blender (without intensifier bar) for 15 min. The maximum capacity of the V-blender was used is 1 kg, and we mixed 700 g of lactose with 70 g of APAP. Lubricated blends, with the same 10:1 ratio as between lactose and APAP but adding 1% by weight of magnesium stearate (MgSt), a widely used lubricant, were also investigated. The composition of the lubricated blends was approximately 90% lactose, 9% APAP, and 1% MgSt. In this case, lactose and APAP powders were first mixed in the V-blender as before (700 g lactose and 70 g APAP; 15 min; no intensifier bar). Then, 7.78 g of MgSt was added, and the blend was mixed for an additional 2 min. The $D$-values characterizing the particle size distribution of the raw materials were measured using a laser-diffraction analyzer with a
Table 1. Particle Size Distribution D-Values for the Raw Materials

<table>
<thead>
<tr>
<th>Material</th>
<th>Mean (µm)</th>
<th>D10 (µm)</th>
<th>D50 (µm)</th>
<th>D90 (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>72</td>
<td>10</td>
<td>64</td>
<td>158</td>
</tr>
<tr>
<td>Acetaminophen (APAP)</td>
<td>49</td>
<td>6</td>
<td>33</td>
<td>123</td>
</tr>
<tr>
<td>Magnesium stearate (MgSt)</td>
<td>9</td>
<td>2</td>
<td>8</td>
<td>17</td>
</tr>
</tbody>
</table>

Mixing and Controlled Shear Strain. Some of the blends were then exposed to a controlled amount of mechanical shear strain using an ad hoc modified Couette shear cell. The shearing rate used was 80 rpm. First, the un lubricated blend was sheared for 16 min (1280 revolutions) to use it as a control system when studying the combined effect of lubricant and shear strain on the blends. The lubricated blend was sheared for either 8 or 16 min, corresponding to 640 and 1280 revolutions, respectively. The particle size distributions of both lactose and APAP powder were not affected by the shear. A summary of the composition and exposure to mechanical shear of the five powder systems under consideration is provided in Table 2.

Powder Bed Preparation and Characterization. The drop penetration experiments were performed using powder beds contained in a cylindrical vessel of 25 mm diameter and 20 mm height. The powder beds were prepared using an FT4 Powder Rheometer (Freeman Technology) in three steps. First, the powder system was conditioned by a blade to improve the uniformity. Then, the powder was compressed by a vented piston at a compression pressure of 15 kPa. Finally, the compressed powder was scraped to produce a flat and (relatively) smooth surface to perform the drop penetration experiments. In Table 2, we report the porosity of different powder beds, calculated from the total mass and the density of the individual powders as provided by the manufacturer.

Fluids. As we discussed before, to measure the contact angle of water with different powder systems, we also use a reference liquid that completely wets the powders. Specifically, we use silicone oil (Cannon Instrument Co.) as the reference liquid and deionized water as the test liquid. The viscosity, density, and surface tension of both liquids are listed in Table 3. It is also important to note that, although lactose dissolves in water, characteristic penetration times in our experiments are significantly shorter than dissolution times, an advantage of DPM over alternative penetration methods that typically require longer times.

Experimental Setup. Droplets were generated with a manual syringe (volume 1 mL). The droplet size was controlled by changing the diameter of the syringe needle. In the case of water, the volume of the droplets investigated were 6, 12, 20, and 30 µL. The volume of the silicone oil droplets was approximately 3 µL in all experiments. A maximum of four droplets were deposited in a single powder bed to avoid any interaction between the penetration of different droplets. In addition, a minimum center-to-center separation of 15 mm was ensured between any two droplets deposited in the same powder bed, which corresponds to more than six droplet radii (contact radii) for the largest droplets considered here. The drops were delivered from a controlled height close to the upper surface of the powder bed, with a gap of approximately 5 mm between the bottom of the syringe needle and the upper surface of the powder bed, to minimize any effect due to the momentum of the droplets as they were deposited. At least three penetration experiments and two powder beds were used for each powder system—fluid combination.

Table 3. Liquid Properties

<table>
<thead>
<tr>
<th>Liquid Combination</th>
<th>Density, (\times 10^{-3}) (kg/m³)</th>
<th>Viscosity, (\times 10^{-5}) (Pa·s)</th>
<th>Surface Tension, (\times 10^3) (N/m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Liquid/Water</td>
<td>0.93</td>
<td>9.35</td>
<td>20</td>
</tr>
<tr>
<td>Reference Liquid/Silicone Oil</td>
<td>1.00</td>
<td>0.89</td>
<td>72</td>
</tr>
</tbody>
</table>

The penetration of the droplets was recorded using an AVT Gige camera (AVT StreamPix video recorder) with a frame rate of 58 frames/s and an exposure time of 0.3 ms. The videos were analyzed using ImageJ (NIH), first removing the background and then converting the pictures into binary images, as shown in Figure 2b,c. The volume was then calculated assuming that the shape of the droplets is axisymmetric.

RESULTS

First, in Figure 3, we present the contact radius of three water and three silicone oil droplets as they penetrate into a powder bed made with the Unlub. blend—1280 rev. In both cases, the radius remains nearly constant during the penetration process. The only exception occurs when the height (and volume) of the sessile drop is relatively small compared with the contact radius, leading to small apparent contact angles and a possible retraction of the contact area. The curves presented in Figure 3 are representative of the behavior observed in all of our experiments and validate the assumption of a constant drawing area. Next, we performed a series of experiments to validate the prediction that there is a universal function that describes the penetration process in nondimensional units. Specifically, we compare the penetration curves of water drops of different volumes (6, 12, 20, and 30 µL) using powder beds made with Lubricated blend—640 rev. The objective is to show that the nondimensional penetration curves are independent of the initial volume (and contact radius) of the drops, as predicted by our analysis. Note, however, that the properties of the powder system, including the capillary pressure inside of the powder bed, do not change in these experiments, and as a result, an accurate estimation of these values is not necessary. In fact, we have not determined the value of the contact angle in this case and hence cannot accurately estimate the capillary pressure driving the penetration process. For every droplet size, we performed four independent experiments measuring the droplet volume as a function of time and calculated the corresponding penetration volume \(V_p\) (see Figure 4a). In each experiment, we measure both the initial
volume as well as the contact radius, which remains relatively constant throughout the penetration process. Then, we use the hemispherical volume \( \alpha = 1 \), \( \frac{2}{3} \pi r_c^3 \), to make the penetration volume nondimensional. The time is made nondimensional using the characteristic time given by eq 9 using the following values for the fluid and powder properties: (i) the viscosity and surface tension of water listed in Table 3 (25 °C), (ii) the average porosity of the powder bed given in Table 2, (iii) the characteristic size of the particles approximated as \( d_p = 100 \, \mu m \), (iv) the capillary pressure estimated using eq 7 with \( r_{ef} = d_p/2 \) and \( \cos(\theta) = 1 \), and (v) the permeability of different powder beds listed in Table 2, as estimated using Kozeny–Carman’s formula. Finally, the contact radius is measured for each drop from the drop penetration videos. Let us note that, using these values to estimate the inertial time scales, we obtain \( t_i \approx 0.5 \) ms for water and \( t_i \approx 0.05 \) ms for silicone oil. By contrast, approximating the contact radius \( r_c \) to 1 mm, we obtain \( t_c \approx 20 \) ms for water and \( t_c \approx 0.5 \) s for silicone oil. As a result, we use the convective time \( t_c \) as the characteristic time of the penetration process.

In Figure 4b, we observe that all curves approximately collapse into a single nondimensional penetration curve, as anticipated. The largest deviation is observed for some of the smallest droplets. We also observe that the penetration time is relatively long in nondimensional units. Given that we have not considered the actual contact angle in the estimation of the capillary pressure inside of the powder bed, the results suggest that \( \cos(\theta) = O(10^{-2}) \). In terms of the penetration dynamics, in Figure 5a, we plot the nondimensional volume of fluid inside of the powder bed, \( \bar{V}_p \) as a function of \( \bar{t} \). The nonlinear behavior highlights the limitations of the traditional DPM analysis, in which the penetration process is approximated as 1D, following the work of Denesuk et al., and should therefore scale linearly with \( \sqrt{\bar{t}} \). In Figure 5b, we show that, in fact, the evolution of the penetration volume is \( \bar{V}_p \approx \bar{t}^{0.8} \) (solid line), markedly different from the 1D case, \( \bar{V}_p \approx \bar{t}^{0.5} \) (dashed line). We note that the radial imbibition from a source-point into a homogeneous porous media predicts that the penetrated volume of fluid would asymptotically scale linearly in time.
Next, we used silicone oil as our reference fluid, assuming \( \cos(\theta_R = 1) \) to measure the contact angle of water in various powder systems listed in Table 2. We performed multiple penetration experiments for both the reference and test liquids as indicated in Table 4 (\( n \) indicates the number of drops analyzed in each case). First, we consider the case of Pure Lactose. Figure 6a shows two sets of penetration curves corresponding to water and silicone oil drops, as indicated. From each penetration curve, we measure two penetration times, \( \tau_{\alpha=0.50} \) and \( \tau_{\alpha=0.75} \). The average and standard deviations obtained for each powder system and fluid combination are reported in Table 4. In Table 4, we also report the measured contact radius (average and standard deviation). Once the dimensional penetration times (and contact radii) are measured for both fluids, we can calculate the water contact angle using eq 18. In Table 4, we report the average value (and standard deviation) of the cosine of the contact angle obtained using both penetration times (\( \tau_{\alpha=0.50,0.75} \)). Finally, in Figure 6b, we plot the penetration curves of both water and silicone oil in Pure Lactose powder beds in nondimensional units. The characteristic time in the case of water drops is calculated using eqs 7 and 9, together with the average cosine of the contact angle listed in Table 4. Again, we observe that, as predicted by the proposed model, all curves collapse into a universal penetration curve when plotted in dimensionless units. Note that, as expected, the nondimensional time of the penetration process is \( O(1) \) and we obtain \( \cos(\theta) \approx 0.1 \), which is consistent with the values reported in the literature for monohydrate lactose powder. A small deviation from the universal behavior is observed for long times, when the drop volume becomes small (penetration volume nearing its final

Table 4. Drop Penetration Results

<table>
<thead>
<tr>
<th>system name</th>
<th>liquid</th>
<th>( n )</th>
<th>( \tau_{\alpha=0.50} ) (s)</th>
<th>( \tau_{\alpha=0.75} ) (s)</th>
<th>( r_c ) (mm)</th>
<th>( \cos(\theta) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure Lactose</td>
<td>water</td>
<td>4</td>
<td>0.14 ± 0.04</td>
<td>0.28 ± 0.08</td>
<td>1.50 ± 0.07</td>
<td>0.10 ± 0.03</td>
</tr>
<tr>
<td>Pure Lactose</td>
<td>PDMS</td>
<td>6</td>
<td>0.31 ± 0.07</td>
<td>0.49 ± 0.10</td>
<td>1.10 ± 0.08</td>
<td></td>
</tr>
<tr>
<td>Unlab. blend—0 rev</td>
<td>water</td>
<td>4</td>
<td>0.13 ± 0.02</td>
<td>0.25 ± 0.04</td>
<td>1.41 ± 0.19</td>
<td>0.13 ± 0.06</td>
</tr>
<tr>
<td>Unlab. blend—0 rev</td>
<td>PDMS</td>
<td>3</td>
<td>0.35 ± 0.11</td>
<td>0.50 ± 0.14</td>
<td>1.19 ± 0.15</td>
<td></td>
</tr>
<tr>
<td>Unlab. blend—1280 rev</td>
<td>water</td>
<td>4</td>
<td>0.14 ± 0.08</td>
<td>0.24 ± 0.10</td>
<td>1.32 ± 0.13</td>
<td>0.09 ± 0.05</td>
</tr>
<tr>
<td>Unlab. blend—1280 rev</td>
<td>PDMS</td>
<td>3</td>
<td>0.28 ± 0.05</td>
<td>0.46 ± 0.05</td>
<td>1.17 ± 0.13</td>
<td></td>
</tr>
<tr>
<td>Lab. blend—1280 rev</td>
<td>water</td>
<td>3</td>
<td>7.31 ± 1.77</td>
<td>13.9 ± 1.6</td>
<td>1.33 ± 0.13</td>
<td>0.004 ± 0.003</td>
</tr>
<tr>
<td>Lab. blend—1280 rev</td>
<td>PDMS</td>
<td>4</td>
<td>0.57 ± 0.29</td>
<td>1.10 ± 0.72</td>
<td>1.08 ± 0.08</td>
<td></td>
</tr>
</tbody>
</table>

*\( n \) indicates the number of drops analyzed in each case.

Figure 5. Nondimensional volume of fluid inside of the powder bed, \( \bar{V}_p \) as a function of nondimensional time \( \bar{t} \) for the cases shown in Figure 4. (a) \( \bar{V}_p \) vs \( \sqrt{\bar{t}} \). (b) \( \bar{V}_p \) as a function of \( \bar{t} \) plotted in the log–log scale. The solid line corresponds to \( \bar{V}_p \approx \bar{t}^{0.8} \). The dashed line corresponds to \( \bar{V}_p \approx \bar{t} \).

Figure 6. Drop penetration in Pure Lactose powder beds. (a) Penetration volume \( V_p(t) \) as a function of time for water and silicone oil drops. (b) Same as (a) but in nondimensional units.
value). We note that in most cases, the contact radius is not constant at long times, as the drop contact line seems to recede, as observed in Figure 3. Therefore, at long times, near the end of the penetration, the assumption of a constant contact radius is no longer valid. For this reason, we use $\tau_{\alpha=0.75}$ as the maximum penetration time to compute the contact angle, even when the initial volume of the drop is larger than $V_{\alpha=0.75}$.

Finally, to highlight the potential applications of the proposed method, we investigate powder blends including an active pharmaceutical ingredient (acetaminophen) with and without an added lubricant. The addition of a hydrophobic lubricant is particularly relevant because of its reported effects on altering the hydrophilicity of the blend depending on the processing conditions. In particular, it has been shown that exposing the blend to large shear strains leads to overlubrication, that is, a large decrease in its hydrophilicity. First, we performed experiments with the unlubricated blend, both exposing it and not exposing it to additional shear strain, that is, Unlub. blend$—0\ rev$ and Unlub. blend$—1280\ rev$. In both cases, we observed that the penetration curves and the measured contact angles are similar to those of Pure Lactose. In all cases, $\cos(\theta) = O(10^{-1})$, as reported in Table 4. Then, we consider the case of a lubricated blend that was exposed to significant shear strain. In Figure 7a we show the penetration curves obtained for both water and silicone oil. We observe that the trend is now reversed and water droplets take significantly longer to penetrate into the powder bed. In fact, repeating the same procedure discussed above, we determine that the cosine of the contact angle is an order of magnitude smaller than in the unlubricated case, $\cos(\theta) = O(10^{-3})$. This is consistent with the previous work showing the effect of overlubrication in blends containing magnesium stearate that forms a nonwetting coating on the particles of the other excipients in the blend.7 Figure 7b shows that in fact, using such a small value for the cosine of the contact angle, curves nearly collapse into a universal curve when plotted in nondimensional units.

**DISCUSSION AND CONCLUSIONS**

We presented a drop penetration method that can be used to compare the wetting of a given powder blend by different liquids. The same approach can be used to calculate the effective contact angle between a test liquid and a powder system by using a reference liquid that completely wets the powder. One of the key advantages of the proposed method is that solving the penetration dynamics is not required. Instead, it is based on comparing the penetration times. In fact, in contrast to traditional drop penetration methods, it is possible to use multiple intermediate penetration volumes to compare the corresponding penetration times. That is, it is not necessary to use the total penetration time when the droplet is fully adsorbed into the powder bed, which is usually difficult to determine experimentally. In addition, the sessile drops usually recede when the apparent contact angle with the powder beds becomes small and the constant area approximation is not usually valid near the end of the penetration process. Therefore, the possibility to compare intermediate penetration times has significant benefits. In addition, it would be possible to use the entire penetration curve or part of it to obtain the cosine of the contact angle by comparing the rescaled curves.

To validate the proposed method, we first investigated the penetration of water droplets of different volumes in a fixed powder blend (Lub. blend$—640\ rev$) and demonstrated that the evolution of the nondimensional penetration volume is independent of the volume of the droplets, and follows a universal function of the nondimensional time. In these initial experiments, we worked with a single fluid and as a result, we did not account for the contact angle in calculating the characteristic time. As a result, we observed large values of the nondimensional penetration times, suggesting an effective contact angle consistent with $\cos(\theta) = O(10^{-2})$ for water.

Then, we used silicone oil as our reference liquid to investigate the contact angle of water with different powder systems. In particular, we showed that either Pure Lactose or lactose with APAP, resulted in similar contact angles. Moreover, exposing these blends to a significant amount of shear strain did not affect the measured contact angles. In all cases, we obtained $\cos(\theta) \approx 0.1$ (see contact angle values for Pure Lactose, Unlub. blend$—0\ rev$ and Unlub. blend$—1280\ rev$ in Table 4). On the other hand, when we added a small amount of lubricant and distributed it by shearing the blend (Lub. blend$—1280\ rev$), the cosine of the contact angle decreases more than an order of magnitude to $\cos(\theta) \approx 0.004$. This demonstrates that the proposed drop penetration method is able to capture the well-studied overlubrication effect, in which excessive shearing of a lubricated blend leads to hydrophobic blends.7 This result also emphasizes that the cosine of the contact angle should be interpreted as an effective force driving the penetration process, and not representing a physical contact angle between the drop and the powder system.

Finally, we note that some of the powder systems investigated in this work are intrinsically heterogeneous. Moreover, the presence of a hydrophobic lubricant could enhance the contrast between the wetting properties of...
different excipients. Even for a given excipient, the presence of a lubricant could result in heterogeneities from powder grains that are coated by the lubricant and those that are not. These heterogeneities could lead to differences in the penetrating front of different liquids and need to be further investigated to validate the use of the proposed model, which is based on the similarity of the penetrating front for both test and reference liquids.

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