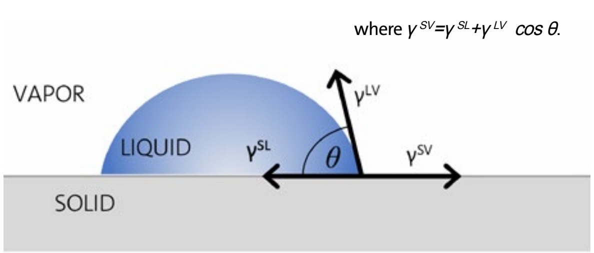
TECHNICAL NOTE

Wetting of Corning® Valor® Glass Vial Surfaces by Aqueous Solutions

Pharmaceutical manufacturers primarily use glass containers (vials, cartridges, syringes) and elastomeric closures (stoppers, plungers, and septa) to package and protect their products. Glass is an ideal material for these applications because of its hermeticity, thermal stability, and chemical durability. Its optical transparency enables direct visual inspection of the drug product and any defects therein. But the visual inspection of the container can be limited if the drug product is non-uniformly distributed upon the container walls (e.g., fogging of a lyophilized powder onto the container walls, or droplets of liquid on the glass walls above the liquid surface, etc.). Also, the delivery of an accurate dosage can be affected by product hold-up (drug volume that wets the surface and is not delivered to the patient). The origins of these behaviors are described here from a materials- and surface-science perspective.

The way a liquid spreads out (or draws together) on a solid surface refers to its wetting behavior, and this interaction is governed by the chemistry and energetics of the solid-liquid-vapor interface. The response is described by the contact angle (θ) which reflects the balance of 3 interfacial energies (Figure 1).



∠Θ ≈ <5°		Perfect wetting, spreading
∠Θ ≈ >5°		Good wetting
∠Θ ≈ 45°		Partial wetting, de-wetting
∠Θ ≈ 90°		De-wetting
∠Θ ≈ 180°		No wetting

Figure 1. Schematic showing a liquid droplet on a solid surface and the balanced forces that determine the contact angle. This table shows examples of varying wetting behavior, relating contact angle to the appearance of the liquid.

The table in Figure 1 shows the full range of responses from spreading (perfect wetting) to no wetting (occasionally called de-wetting). This behavior is most easily observed in pharmaceutical containers at the liquid's meniscus.

In Figure 2, the glass vial at left shows water wetting all surfaces and exhibiting low contact angle, whereas the vial at right shows water de-wetting all surfaces and exhibiting high contact angle.

Figure 2. Glass vials with water showing perfect wetting (left) and de-wetting (right) behavior.

From the perspective of the solid, wetting behavior is an extrinsic property that is influenced by the interfacial roughness, surface energy, defects, solution chemistry, and solution polarity among others. It is not inherent to the bulk solid composition, but rather it reflects the chemistry of the topmost approx. 10 nanometers of its surface. All flat, multicomponent silicate glass fracture surfaces will have high surface energy and demonstrate indistinguishably low contact angles (θ <5°) with water. Figure 3 shows indistinguishable wetting behavior (perfect wetting) for borosilicate (left) and Valor (right) vials after depyrogenation and filling with high purity water.

However, as any glass surface ages (even in clean air environments), adventitious carbon compounds will adsorb upon the glass surface within hours, altering its energetics and polar character. Monolayer coverage by adventitious carbon can be enough to reduce the wetting behavior relative to the clean, carbon-free glass surface. Figure 4 shows the two extremes: uniform wetting with spreading meniscus (left) and uniform de-wetting (right). Non-uniform organic coverage can lead to mixed wetting and de-wetting behavior on the same surface as shown in Figure 5.

Figure 3. Recently depyrogenated borosilicate (left) and Valor (right) vials filled with high purity water showing indistinguishable wetting behavior.

Figure 4. Glass vials with high purity water showing uniform wetting (left) and uniform de-wetting (right).

Figure 5. Non-uniform wetting and de-wetting behavior in a glass vial headspace.

ASSESSING WETTING BEHAVIOR

There are many methods to qualitatively and quantitatively probe the wetting behavior of a surface. The simplest methods expose the glass surface to water and examine the meniscus. In one specific method, high purity water is added to a container lying horizontally on its side (Figure 6, left). The container is rotated to wet the sidewall regions with liquid, then stood upright (Figure 6, right).

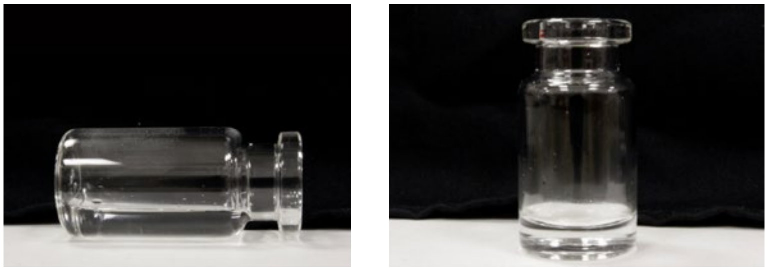


Figure 6. Steps in a wetting assessment. At left, a horizontal vial is filled with water then rotated to initially wet all surfaces. At right, the vial is stood upright and the behavior of the meniscus is monitored.

The container is then visually inspected to observe when the meniscus de-wets (falls, retreats, etc.). The results are commonly expressed in 2 ways: either the fraction of vials de-wetting within the 20-second window, or the time required for individual vials to de-wet. Surfaces that are more de-wetting will exhibit shorter times, whereas more wetting surfaces will remain wetting after 20 seconds.

OBSERVATIONS OF COMMERCIAL PHARMACEUTICAL CONTAINERS

Bulk-packed glass containers (both borosilicate and Valor glass containers) exhibit slight de-wetting by water as-received. This is caused by adventitious carbon that adsorbs onto the glass surface after manufacture. This response can increase by extended storage and certain transportation materials (shrink wrap, glues, etc.) as additional organics adsorb and build up.

Thermal depyrogenation is generally adequate to remove these adventitious carbon deposits and then observe uniform wetting. Lower temperature, short cycles (e.g., 280°C for 10 minutes) may be inadequate to remove these organics. In one study, Valor vials, stored approx. 5 years in white plastic corrugated trays in a lab environment, were uniformly wetted by water after minimal depyrogenation (320°C for 15 minutes).

Internal surfaces of depyrogenated vials that are filled with simple organic-free solutions (i.e., WFI diluent, NaCl, or KCl) and subsequently capped should remain wetted by the solution for some time. However, silicones and other organics migrate from elastomeric closures to the glass surface and impart increasing de-wetting behavior over time (days to years at room temperature).

PDMS (polydimethylsiloxanes) is the material most commonly measured in de-wetting regions. Increasing temperature decreases the time needed to observe de-wetting; for example, terminal sterilization by autoclave can immediately impart de-wetting. Silicone-free closures (such as aluminum foil or PTFE-lined septa) better preserve the wetting behavior of the freshly-depyrogenated glass surface.

As organic material migrates from the elastomeric closures onto the glass surface, it prefers to adsorb at the glass: air interface – occasionally forming lines (or rings) of de-wetting behavior (Figure 7). These behaviors can be highly variable from lot-to-lot and within an elastomer lot – due to varying silicone levels.

Figure 7. Glass vial exhibiting non-uniform wetting in defined rings or bands around the vial and isolated areas. This was produced by filling a depyrogenated glass vial with water and closing with an elastomeric stopper and aluminum cap, then terminally sterilizing (60 minutes at 121°C).

SPECIAL CONSIDERATIONS

Some drug products contain components (API, surfactants, other amphiphilic molecules) that directly affect the wetting behavior. Specifically, surfactants (such as polysorbate 80) serve to disperse particles and prevent agglomeration, create emulsions for non-soluble formulations, and/or reduce the energy of packaging component surfaces. In these cases, the added components may change the interfacial energetics and impart specific wetting (or de-wetting) behavior. Similarly, functional coatings may be applied to internal glass surfaces to control the wetting behavior, or to serve a mechanical benefit (such as improved plunger lubricity) and unintentionally affect the wetting behavior.

SUMMARY

- Wetting, fogging, or product hold-up behaviors reflect the chemistry of the topmost approx. 10 nm of surface. All pharmaceutical glass surfaces (free of organics) are perfectly wetting; showing a contact angle with water that is less than 5°. Depyrogenated borosilicate and Corning® Valor® (aluminosilicate) glass vials show indistinguishable wetting (liquid spreading) behavior.
- Valor glass and typical bulk-packed borosilicates may exhibit slight de-wetting behavior as received due to trace levels of organics adsorbing from the surrounding environment and packaging materials.
- Silicones (including PDMS) commonly impart de-wetting behavior. Other organics (slip agents from plastic bags, shrink wrap volatiles) also impart de-wetting, but are less common.
- Thermal depyrogenation (such as 320°C for 15 minutes) is generally adequate to remove adventitious carbon. Minimal cycles (such as 280°C for 10 minutes) may be inadequate to remove many of these.
- An initially wetting glass surface may become de-wetting over time as organic components adsorb at the glass surface.
- Non-liquid contact surfaces will adsorb organics preferentially over liquid contact surfaces. This leads to variation in wetting performance of the glass surface in the container headspace. Non-uniform wetting behavior can increase rejects during visual inspection.
- Elastomeric closure components (stoppers, plungers, septa, etc.) provide the material necessary to impart de-wetting after depyrogenation and filling. Variation in wetting performance is commonly linked to variation in elastomer manufacturing, not glass chemistry or manufacture.
- De-wetting is effectively inevitable for filled containers sealed with most elastomeric closures.

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