COSOLVENT FORMULATIONS

# Seeing When and Where Cosolvent Cakes Lift, From Outside the Vial

Using LyoVision™ infrared imaging of the vial wall, we tracked an ethanol-containing frozen cake as it lifted from the vial base at the start of primary drying, rose to about 75% of the way to the vial shoulder within an hour, and stayed there until primary drying finished.

LyoWave, Inc. | Lab-scale cosolvent formulation study | November 2026

**50 to 75%**
Cake height, as a share of the distance from vial base to shoulder, from lift-off to one hour later

**~18 h**
Elapsed run time by which the wall temperature profile had become uniform

## The challenge

Nonaqueous solvents such as ethanol are often added to lyophilized formulations to improve the solubility of the drug. They also make the formulation harder to freeze dry. High solvent vapor pressure and freezing point depression combine, at high concentrations, to create large pressure gradients through the cake and to detach it from the vial.

The result is cake lifting: the frozen solid rises off the vial base during primary drying and settles in the barrel. Once it lifts, heat from the shelf no longer flows directly into the cake, which can compromise the batch.

When a formulation needs a cosolvent, developers have to design a cycle to prevent lifting without making it so conservative it runs far longer than needed. That requires knowing when and where lifting happens.

## The approach

**Equipment.** A LyoVision™ long-wave infrared camera (8 to 14 µm) mounted to a standard 3- or 4-inch sanitary port on a Millrock Stellar® laboratory freeze-dryer with a single 10 x 18 inch shelf, imaging the edge vials facing it.

**Product and container.** 10% v/v ethanol and 3% w/v sucrose in 20 mL vials with a 5 mL fill. Five edge vials were monitored.

**Primary drying conditions.** Shelf temperature -27°C, chamber pressure 10 mTorr.

**Method.**

1. Draw a rectangular region of interest along the wall of an edge vial.
2. Extract the temperature profile along the vial's vertical axis from each frame.
3. Compare profiles across frames. The cake's position shows as a feature in the wall temperature profile, so a shift in that feature marks cake movement.

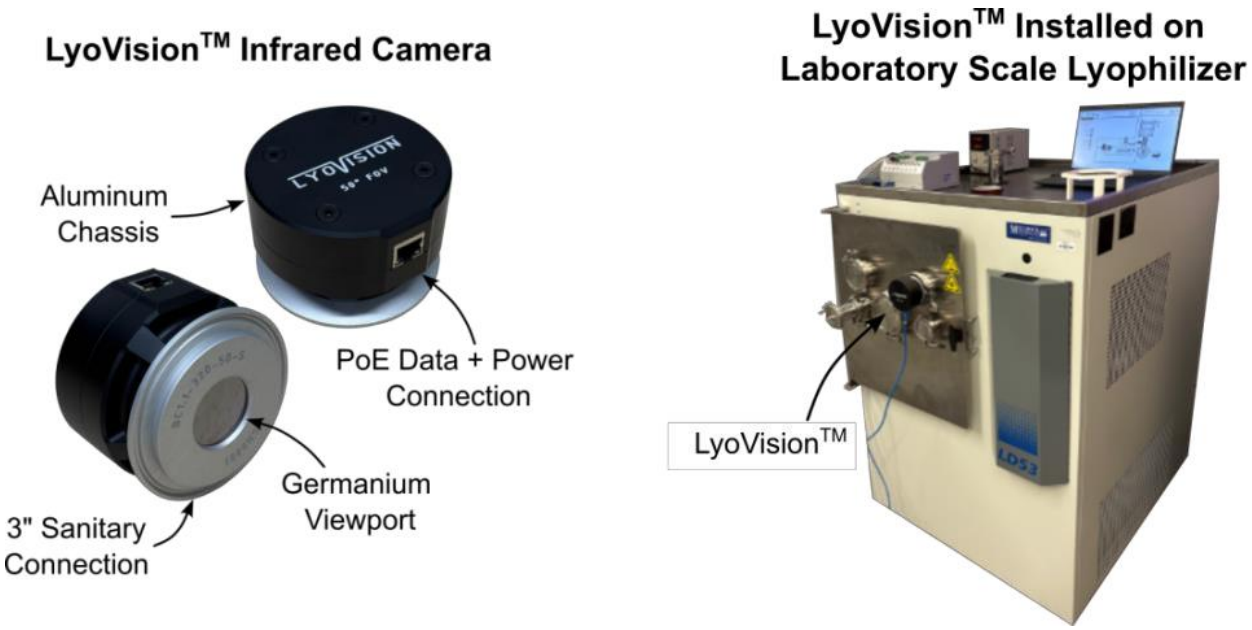


*Figure 1. LyoVision™ camera (left) and a representative installation on a laboratory-scale freeze-dryer (right).*

## Results

All five monitored vials lifted, to differing degrees. In the tracked vial, the frozen cake lifted at the onset of primary drying and moved up the barrel within the first hour.

- **Lift-off.** At the onset of primary drying, the ethanol-containing frozen solid lifted to about 50% of the distance from the vial base to the shoulder.
- **Continued rise.** Within one hour, the thermal profile showed the cake had moved further, settling at about 75% of the same distance.
- **End of primary drying.** By about 18 hours of elapsed run time, the wall temperature profile had become approximately uniform over the vial height, marking the end of primary drying.

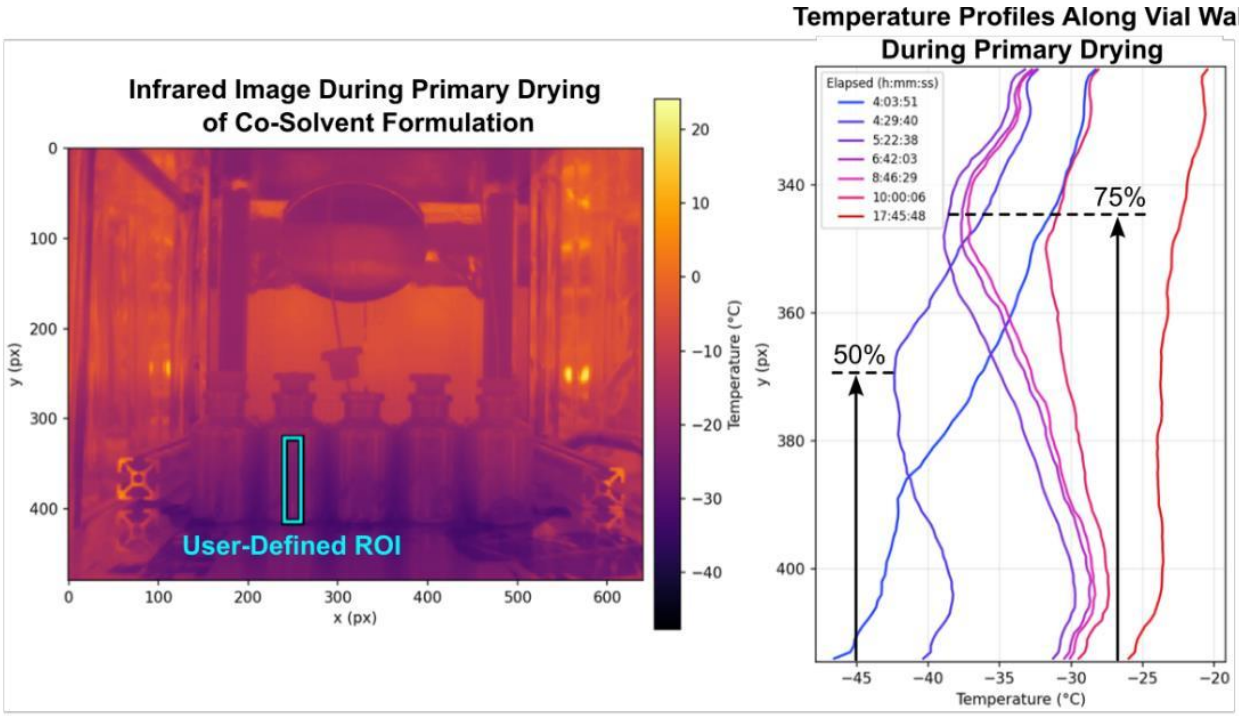


*Figure 2. Left: infrared image of the edge vials during primary drying, with the region of interest on one vial wall. Right: temperature profiles along that vial wall from about 4 to 18 hours elapsed, with the 50% and 75% heights marked.*

## What it means for process development and manufacturing teams

Cake lifting is visible in real time from outside the vial.

- **Detection during the run.** The wall temperature profile shows when and how far the cake lifts, without opening the chamber or touching the product.
- **Cycle limits from data.** Knowing the conditions under which lifting starts lets developers set cycle limits to prevent it, without defaulting to an overly conservative cycle.
- **Several vials at once.** Edge vials are the warmest in the batch and the most likely to lift. Monitoring several of them in one run, across several cycles, builds the statistical picture needed for a robust, efficient process.

## Limits

- **One formulation.** This note reports one formulation, 10% v/v ethanol with 3% w/v sucrose, in 20 mL vials with a 5 mL fill.
- **Detection, not a fix.** We show lifting being detected. We have not shown a cycle redesigned to prevent it here.
- **Edge vials only.** The camera sees the vials facing it. Center vials may behave differently.
- **Inferred position.** Cake position is inferred from the wall temperature profile, not observed directly.
- **Single run.** We report one cycle, so these results do not show run-to-run variability.
- **Scale.** The example ran on a laboratory freeze-dryer with a single shelf. This note makes no claim about production equipment.

NEXT STEP

## Talk with us about your cosolvent cycle

If your formulation needs a cosolvent and lifting is a risk, tell us about your product, containers, and equipment, and we will follow up. LyoVision™ mounts to a standard 3- or 4-inch sanitary port on existing freeze-dryers.

**Contact us at lyowave.com/contact**

## Source

**Source.** LyoWave, Inc. laboratory data, August 7, 2026.

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