

Letters to the Editor

Safety Concerns Regarding the Transportation of Organic Powders on Dry Ice: How CO₂ Adsorption Can Lead to Powder Spills

To the Editor:

Introduction

In the development of a new drug, samples of the active pharmaceutical ingredient (API) and of some intermediates needed to be shipped between laboratories in different countries. Since the stability of the API is limited at room temperature, these shipments were performed on dry ice. The product is not only thermally instable but also prone to hydrolysis and should therefore be kept away from humidity as much as possible. For this reason, it is standard procedure to open the sample bottles only when they are at room temperature, in order to prevent condensation of atmospheric moisture on the cold bottle or product.

On several occasions, it was noted that pressure build-up occurred in the bottles when they had reached room temperature. In at least one case, the pressure build-up was so high that the lid was blown off the sample bottle, leading to a serious powder spill. Fortunately enough nobody was near the bottle at that time, so nobody was exposed to the powder. Obviously, the root causes of this pressure build-up needed to be known, so a detailed study was started.

Testing of the Materials

Pressure build-up after shipment on dry ice was first observed in the API samples. As mentioned above, this product is thermally not very stable, which is the reason why it is shipped on dry ice. The observed pressure build-up in the sample bottles could not originate from thermal decomposition, however. Decomposition tests in closed circumstances (Thermal Screening Unit, HEL UK) showed no measurable pressure increase when the sample was heated to 70 °C. This ruled out the possibility of relevant thermal decomposition, since the samples had not been at temperatures above ambient. Another possible explanation could be the thermal expansion of the air present in the sample bottles. A quick calculation showed, however, that this could only lead to a maximum overpressure of 0.5 bar, which is considered to be too low to explain the observed violent powder spill.

Other explanations were needed, and the possibility of CO₂ adsorption by the product was considered. If the sample could adsorb CO₂ at lower temperatures and if this would be desorbed when bringing the sample back to room temperature, a pressure increase like the one observed could be expected. This hypothesis was experimentally tested by means of subambient thermogravimetry. A sample of the product was placed in a TGA at room temperature under nitrogen atmosphere. The purge gas was switched to pure CO₂, after which the sample was cooled to -70 °C at 1 °C/min. It was then kept isothermally at -70 °C for 30 min, after which it was heated back to room

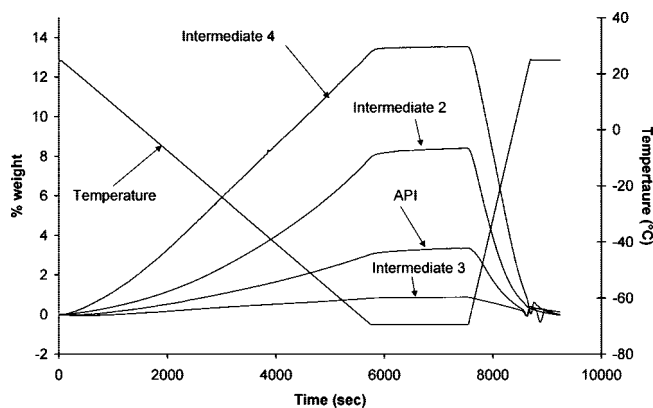


Figure 1. Cryo-TG data of the samples tested. A clear weight increase at lower temperatures in a CO₂ atmosphere is observed upon cooling. When the samples are heated back to room temperature, this adsorbed CO₂ is released.

Table 1. Overview of CO₂ adsorption by the various samples and the worst-case overpressure that could be reached in the sample containers

compound	weight increase (%)	molar adsorption (mol/mol)	final overpressure worst-case (bar)
intermediate 1	0.04	0.002	0.6
intermediate 2	8.32	1.5	136
intermediate 3	0.88	0.1	14
intermediate 4	13.54	3.2	220
API	3.37	0.5	55

temperature at 5 °C/min. During the entire experiment, the mass of the sample was recorded accurately. The API and some of the intermediates were tested using this procedure, and the results are shown in Figure 1. It can be clearly seen that all products tested, except intermediate 1, adsorb considerable amounts of CO₂ during the cooling phase. This mass increase continues during the isothermal stage, albeit at a slower rate. When heating the samples back to room temperature, the weight of the sample falls back to its original value. This is unambiguous proof of the fact that these products do adsorb CO₂ at lower temperatures when exposed to a CO₂ atmosphere. The extent of the mass increase differs from the one product the other; an overview is given in Table 1. Although the weight increase might seem rather limited, the pressure increase that can result is dramatic. This was calculated for a worst-case scenario, where we considered a glass sample bottle with 75 g of product and a free headspace of 25 mL. We assumed that the product would adsorb CO₂ to the same extent as in the TGA measurements, that all of this CO₂ would be set free during thawing, and that no leaks were present at that stage, leading to a maximum pressure increase. As can be seen in the table, this could lead to a final pressure of 220 bar in the case of intermediate 4. This would obviously be sufficient to blow off the lid of the container or could even lead to rupture of the entire bottle.

A satisfying answer to the questions of why these components adsorb CO₂ and why they do so to a different extent has

not been found yet. We believe that the presence of several carbonyl groups in the molecule can be part of the answer, but this does not explain the different adsorption behaviour of the API and the intermediates, however. The extent to which the CO₂ is adsorbed might be dependent on the morphology of the samples. We know that the API is at least partially amorphous, and we believe that a difference in surface area and surface morphology can determine the amount of CO₂ that can be adsorbed.

Influence of the Sample Container

The possibility for CO₂ to enter into the sample bottle was briefly tested as well. To achieve this, colouration crystals (Draeger) were used. This is a type of material that is colourless in its pristine state but turns pink when it comes in contact with CO₂. Some of these crystals were put in a typical sample bottle, all the time working in a glovebox under nitrogen atmosphere. The sample bottle was then closed and taken out of the glovebox. At that time, the crystals were still colourless. The bottle was then placed in a box with solid CO₂ and allowed to cool down. After a couple of hours, the bottle was removed from the box and transferred back to the glovebox. After it had reached room temperature, the bottle was opened, and the crystals inside were clearly pink, confirming our assumption that CO₂ could enter the bottles at lower temperatures.

Finally, an explanation is needed for the observed pressure increase in the bottles, bearing in mind the fact that they are not airtight at lower temperatures. At first thought, one would believe that any overpressure being generated would leave the system, the same way as the CO₂ entered it. There are two possible explanations for this. First, it is not very uncommon for sample containers to be leaky towards underpressure and airtight towards overpressure, or vice versa. Second, the different heat capacities and expansion coefficients of the lid, the glass bottle, and the sample could result in different behaviour when the bottles are cooled and heated back to room temperature. This different behaviour can result in a sample container that is airtight at one temperature but not at another temperature.

Whatever the explanation for this behaviour is, the most obvious preventive measure to avoid the observed pressure

build-up is to prevent any contact between the sample and the CO₂ atmosphere. This can be done by using specially built (and tested) sample containers that are proven to remain airtight at subambient temperatures or, more conveniently, by using a secondary containment. We opted for the use of laminated aluminium bags, in which the ordinary sample bottles were placed, and these bags were then hermetically sealed by means of thermal sealing.

Experimental Section

All TG experiments were performed at the facilities of Setaram (Lyon, France). The instrument used was a Sensys TGDSC from Setaram. The testing procedure has been described in the text above. Mr. Luc Benoist is kindly acknowledged for his assistance in setting up the testing rationale.

Summary

Samples of an API that had been shipped in boxes with dry ice experienced powder spills when they were brought back to room temperature. During this thawing process, there was a pressure build-up in some of the glass bottles, resulting in the lid and part of the powder being blown away. Testing of the material in various conditions revealed that it can adsorb substantial amounts of carbon dioxide at low temperatures, which is then released when the product is heated back to room temperature. This desorption of CO₂ can lead to pressurisation of the container and the observed powder spills. The only possible way to prevent this adsorption is to use sample containers that remain airtight throughout the entire temperature range, so that contact of the sample with the CO₂ atmosphere is no longer possible.

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