

▶ Altering the calcium landscape

Changes in calcium carbonate production methods are making everything old, new again.

BY MICHAEL TARQUINI

Calcium carbonate is a key active ingredient in antacids, nutritional supplements, and other pharmaceutical preparations. In 1997, however, the sourcing market for calcium carbonate—valued at \$50 million per year—was significantly altered by the California Proposition 65 class-action lawsuit (www.oehha.org/prop65.html). Proposition 65 effectively drove the lead out of pharmaceutical products and their USP ingredients, stipulating that there must be <0.5 µg of lead/day based on the maximum daily recommended dosage.

At the time, the major source of calcium was ground calcium carbonate (GCC), which miners harvest directly from the ground using traditional mining techniques. Because GCC is drawn from numerous locations, its purity—and particularly lead levels—varies from source to source (1). Unfortunately, using this method, manufacturers of GCC had trouble complying with the new lead standards from the known natural sources at the time. In contrast to GCC, chemists manufacture precipitated calcium carbonate (PCC) by reacting calcium hydroxide with carbon dioxide. The calcium hydroxide is commonly obtained by slaking lime (calcium oxide).

Seeing an opportunity to sell a more expensive ingredient, manufacturers of PCC promoted their <125-ppb lead levels as one more “purity cushion” to the pharmaceutical industry. Their plan worked. Pharmaceutical formulators gravitated from natural GCC to the more expensive synthetic PCC, which typically contained <50 ppb lead. “After all,” the thinking went, “what can be purer than a precipitated compound?”

For antacid and nutritional supplement manufacturers and their raw material suppliers, the stakes are high. These products typically contain 96–98% calcium carbonate, and the cost differential between mainstream PCC and GCC can be as high as 50%

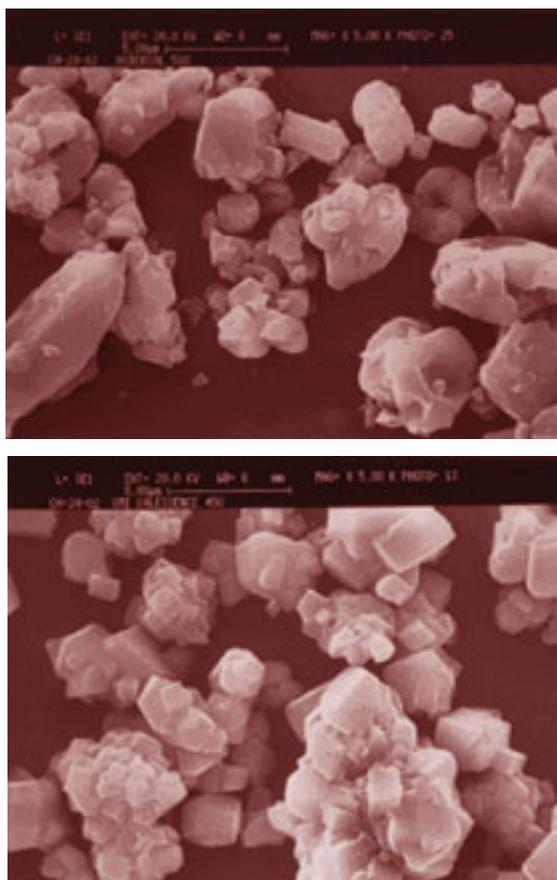


Figure 1. Picture perfect. Photomicrographs of 6-µm GCC particles (top) and 4.5-µm PCC particles (bottom). Sharp edges on particles abrade mixers and tableting dies, contaminating product in the process. (Courtesy of J. M. Huber Corp.)

(although 20–30% is standard). Also at stake is the opportunity to again advertise



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a product as “all natural” and “organic”, because GCC is a natural product.

In response, J. M. Huber (www.huber.com) discovered and developed GCC sources that were intrinsically purer and freer of lead. This development appears to be changing the landscape back to its former status.

Getting the lead out

Recent independent data show that some GCCs commercialized since the passage of Proposition 65 are actually purer than the leading PCCs and contain lead levels well below the industry-accepted 125-ppb threshold. This new level of purity is achieved because miners excavate the material from calcium carbonate deposits that have particularly low lead levels. So, many antacid and calcium supplement manufacturers are now returning to GCC in the new high-purity form. About a dozen such manufacturers have standardized on the high-purity GCC, and most granulators supplying the market now use it as well. Moreover, most larger antacid manufacturers are currently in various stages of qualifying the high-purity GCC for use.

For example, Huber had technicians at West Coast Analytical Service (www.wcas.com) determine lead levels in various PCC and GCC samples (including Huber samples). Following the California Proposition 65 protocol, the technicians measured the lead using inductively coupled plasma–mass spectrometry (see box, “Pushing the detection limits”). The other chemical assay testing was performed using the standard USP testing protocol involving a colorimetric test (www.usp.org/standards/summary/1999/1999_12a.htm).

Using the assays, the technicians determined that the new GCC was the purest of all samples tested (99.9%) and con-

Pushing the detection limits

Flame atomic absorption (FAA) spectroscopy is predominantly a single-element technique that uses a flame to generate ground-state atoms. When light is passed through this atom cloud, specific wavelengths of light are absorbed that are characteristic of the presence of the metal of interest. The amount of light absorbed indicates the amount of analyte present. FAA spectroscopy is capable of part-per-million detection limits.

Graphite furnace atomic absorption (GFAA) spectroscopy is also a single-element technique, although some multielement instrumentation is now available. GFAA works on the same principle as FAA, except that a small heated graphite tube generates the atoms instead of a flame. Because the ground-state atoms are concentrated in a smaller area than with a flame, more light absorption takes place, resulting in detection limits about 100 times lower than those of FAA.

Inductively coupled plasma–optical emission spectroscopy (ICP-OES) is a multielement technique that uses an extremely hot plasma source to excite atoms to the point that they emit wavelength-specific photons of light characteristic of a particular element. The number of photons produced is directly related to the concentration of that element in the sample. ICP-OES instruments come in two configurations, radial and axial, which cover the range of part-per-million to part-per-billion detection limits.

ICP-MS also uses a plasma source, but unlike ICP-OES, the plasma is used to generate trace metal ions. The ions produced in the plasma are transported and separated by their atomic mass-to-charge ratio in the mass spectrometer. The generation of such large numbers of positively charged ions allows ICP-MS to achieve detection limits at the part-per-trillion level.

(Adapted with permission from Thomas, R. L. *Today's Chemist at Work* **1999**, 8 (10), 42–48; available at <http://pubs.acs.org/hotartcl/tcaw/99/oct/element.html>.)

tained only 88 ppb lead (Table 1). It was also lowest in acid insolubles (<0.01%). These values exceed U.S., European, and Japanese Pharmacopeia purity standards.

But lead is not the only trace metal that pharmaceutical makers want to avoid in their preparations. Performing the USP protocol testing for iron, the technicians

dict the abrasivity of their dental silicas.

The technicians tested two different grades of Huber GCC, differing mainly in particle size (4.5 and 15 μm), and two comparable grades of the leading PCC products. They found that the two GCC samples exhibited less than half the abrasiveness of the leading PCC products of

Table 1

Comparative analysis of calcium carbonate samples

	Leading GCC	Leading PCC	Huber GCC	Standard	Specification
Identification	Pass	Pass	Pass	Pass	Pass/fail
Acid insolubles (%)	0.09	0.09	<0.01	0.05	0.2
Mg and alkali salts (%)	0.51	0.47	0.31	0.91	1.0
Lead (ppb)	159	40	88	278	—
Purity (%)	99.4	97.2	99.9	99.1	98.0–100.5

found that iron levels were substantially lower in the high-purity GCC than in either the leading PCC or standard GCC. Similarly, aluminum levels were much lower than in the PCC and comparable to that of the GCC. High aluminum levels in the PCC likely come from the lime used in the precipitation process.

Sample processability

The abrasiveness of any dry bulk material has an enormous affect on the useful life and service interval of all processing equipment that it contacts. Tableting dies are especially expensive, and shutting down the line is required to change out a set. Moreover, every particle of metal abraded off the equipment winds up in the product as a contaminant. So abrasivity affects purity. The key is to use ingredients that are as nonabrasive as possible.

To test sample abrasivity, Huber technicians used the Einleher Method (Huber Standard Evaluation Method 2.122), an accepted procedure for predicting abrasion in processing equipment, at least in a relative sense. Using this method, the technician exposes a Fourdrinier wire screen (a phosphor bronze P.M. wire disk) to an abrasive suspension for 100,000 revolutions over approximately 49 min. The researcher then determines the weight loss of the screen. Huber technicians have used the Einleher Method for years to pre-

comparable size.

This difference in abrasivity can best be explained by taking a closer look at the particle morphology. Figure 1 shows the two particles under a scanning electron microscope. The precipitated product at the bottom has sharp, jagged edges, whereas the ground product at the top has more-rounded edges. All things being equal, the rounder edges mean there is less scraping during processing.

Of course, hardness also makes a difference. Particle shape being similar, the harder the material, the more abrasion it causes. The material doing the damage must be harder than the material being damaged, which is certainly the case for PCC and GCC compared with stainless steel in a mixer. No formal hardness studies have been done on PCC and GCC particles, but subjective crushing and rubbing of the two forms have indicated that the GCC form is much softer.

Sensory testing

Because consumers take antacid and calcium supplements principally by mouth in tablet form, mouthfeel and grittiness of the calcium carbonate are important considerations for determining what calcium carbonate to use as a formulation source. Thus, technicians at 21st Sensory, Inc. (www.21st Sensory.com), performed texture analysis using the methods described by

A question of bioavailability

Even though several other sources of calcium are available, calcium carbonate delivers the most calcium at the lowest cost, and its bioavailability is at least equivalent to that of other calcium sources. Published research states that calcium carbonate has essentially the same absorption as milk, superior bioavailability to tricalcium phosphate, and equivalent bioavailability to calcium citrate, lactate, and sulfate.

Several research groups have determined bioavailability using various techniques. The literature commonly reports calcium bioavailability studies in which changes in calcium levels in urine and blood serum are measured after a controlled dosage of calcium supplementation (2, 3). In other studies, researchers have fed animals diets rich in various calcium supplements and measured changes in bone density (4).

the American Society for Testing and Materials (www.astm.org) as “Sensory Testing Methods” and “Descriptive Analysis Testing for Sensory Evaluation”.

The technicians had trained panelists evaluate blinded samples repeatedly over a two-day period, comparing the mouthfeel of the samples with those of custom-developed references chosen from some familiar food items. Actual chewing is defined as “chewdown”, or 10–12 chews before recording their rating. With respect to grittiness, less grit means a better mouthfeel. The panelists decided that the GCC sample had a less gritty mouthfeel and left less residual grit in the mouth than the PCC sample, which are two of the factors that consumers consider most important.

New landscape

Historically, the formulator’s choice was between natural GCC for its cost/benefit advantages and PCC for its purity, but this new data changes the calcium carbonate landscape. It shows for the first time



that the formulator can choose a natural product and actually improve purity while gaining cost and processing advantages. And today, high-purity GCCs are the new materials of choice for many solid-form applications.

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Michael Tarquini is a leader of new product development, Food and Nutrition, for J. M. Huber Corp. (www.huber.com). Send your comments or questions about this article to mdd@acs.org or to the Editorial Office address on page 3. ■