Effervesence is an underused formulation approach that offers functional and consumer advantages over conventional products in the pharmaceutical, dietary supplement, and other market segments. While the basic chemistry and process technology used to make effervescent products is not new, their complexity requires special formulation and manufacturing techniques. This article discusses the important factors to consider.

Is there anyone over 40 who doesn’t recognize “Plop, plop, fizz, fizz. Oh, what a relief it is”? That jingle—used in Alka-Seltzer commercials in the 1970s—is not only recognized as one of the most memorable advertising lines ever, but it also neatly conveys the essence of effervesence. Drop two tablets into water. Watch them fizz as they disperse the active ingredients. Get quick relief.

Likewise, many of today’s marketers realize that the aesthetic and functional benefits of effervescent tablets

Effervescent technology for today’s pharmaceuticals and dietary supplements

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can be promoted as improving the consumer’s experience. Just look at the evidence: A surge of effervescent products is showing up on store shelves, online, and through direct marketers. The new products run the gamut: pharmaceuticals, dietary supplements, foods, and cleansers.

Why use effervescent technology?

For consumers, effervescent products provide a multisensory in-use experience. They watch the fizzing action, hear the bubbling, and receive a drug product or dietary supplement that tastes good. Experienced formulators know that the more senses a product stimulates, the more likely it is to delight consumers.

Since effervescent products are almost always dissolved before they’re ingested, they allow active ingredients to be solubilized or dispersed before they reach the gut. That can speed adsorption and bioavailability. Pre-dissolution also benefits patients who have trouble swallowing conventional tablets or capsules. In addition, effervescent bases provide an excellent environment for moisture-sensitive active ingredients. That’s because the bases are anhydrous, which practically eliminates the risk of hydrolysis, a common cause of degradation. This is discussed in more detail below.

Product forms

Most effervescent products are tablets, and many of them sell under well-known brands, including Alka-Seltzer, Airborne, Nuun, Berocca, Blowfish, Liftoff, Best Defense, Polident, and Efferdent. Most are packaged in foil or in tubes. If they’re powders or granules, the products are packaged in stick packs and sachets. Examples of these include Emergen-C, Efferdent Crystals, and Fresh Guard.

Effervescent chemistry

The chemistry that underlies the appeal of effervescent products is quite simple (Figure 1). An acid is used to neutralize a carbonate salt. That causes a reaction that produces carbon dioxide (CO₂) gas, the salt of the acid, and water. It’s the CO₂ gas—the fizzing—that makes effervescent products appeal to our senses.

Figure 1

<table>
<thead>
<tr>
<th>Effervescent reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid + carbonate salt → CO₂↑ + Acid salt + H₂O</td>
</tr>
</tbody>
</table>

Example

Citric acid + 3NaHCO₃ → 3CO₂↑ + Na₂Citrate + 3H₂O

A few important points about the reaction may not be obvious. First, water is needed. Without water, neither the acid nor the carbonate can dissociate, and without dissociation, no effervescent reaction can occur. Once the reaction does start, the stoichiometry dictates that it generates more water. In other words, once started, the acid and carbonate will continue to dissociate and the effervescent reaction will self-propagate. This means that effervescent products are inherently unstable and must be carefully formulated, manufactured, and packaged.

Doing this entails keeping the raw materials virtually anhydrous and warehoused so they remain dry. Likewise, the manufacturing environment must be highly dehumidified to prevent the products from picking up unwanted moisture. And the packaging must include a moisture-barrier film, usually with an aluminum foil layer. The other option is to place the product in a tube that contains a desiccant to protect it from ambient humidity during shipping, storage, and use. Any lapse that allows moisture infiltration can cause the product to give off CO₂ and water before it reaches the consumer. If that happens, the product will become mushy and the foil package will look like a puffy pillow.

Flexible foil and aluminum or plastic tubes are the two most common packages for effervescent tablets because of the moisture barrier they provide.
Raw materials: Acids, salts, and other excipients

Carbonate salt is a key material in effervescent formulas because it’s the source of CO₂. The most commonly used carbonate salts are sodium carbonate (soda ash) and sodium bicarbonate (baking soda). See Table 1.

Sodium carbonate has a lower percentage of CO₂ than sodium bicarbonate, and since it requires 2 moles of acid per mole of the salt, it’s slightly more difficult to neutralize. That makes products formulated with sodium carbonate a bit more stable than those containing only sodium bicarbonate. Even so, ingestible products typically don’t use sodium carbonate because the appropriate grades (USP, NF, and FCC) are not easy to find and can be expensive. Non-ingestible products, however, such as cleansers, often include it.

Because sodium bicarbonate has a higher proportion of CO₂ than sodium carbonate and can easily break down and release water, products formulated with it tend to react/dissolve more quickly and be less stable than products that use sodium carbonate. Some manufacturers have developed proprietary processes that improve the stability of products that use sodium bicarbonate. Potassium, magnesium, and calcium carbonate salts can also be used.

The other key component in effervescent compositions is the acid (Table 2). Citric acid is the most commonly used. It’s inexpensive, easily available, and highly soluble and it has good neutralizing power. It’s available in several grades, which differ by particle size distribution. The choice of grade hinges on compression and product-uniformity considerations.

Fruit acids such as malic acid and tartaric acid are also suitable. They are more expensive than citric acid, but they often moderate citric acid’s sharp flavor. Fumaric acid is used occasionally and, even though it’s only divalent, it’s actually a more efficient neutralizer than citric acid on a weight-to-weight basis. Fumaric acid, however, is much less soluble than citric acid and thus reacts more slowly. That’s likely why products containing fumaric acid tend to be more stable than those that use citric acid.

As with the carbonate salts, the acid you choose depends on how you want the product to perform and how you plan to manufacture it. The ratio of acid-to-carbonate will also have an impact on the product. In general, the higher the acid-to-carbonate ratio, the faster the reaction. A higher proportion of acid will also ensure that the carbonate is completely reacted. At minimum, the acid must stoichiometrically balance the carbonate. Otherwise, some of it will remain unreacted and settle at the bottom of the dissolving vessel. A 1-to-1 ratio of acid to total carbonate (by weight) is common. However, highly reactive, highly soluble combinations may have ratios as high as 10-to-1.

When formulating ingestible products, flavor must also be considered. If there is a high proportion of acid, the product could become too tart. Conversely, too much carbonate could make it too salty. The goal is to balance the ratio in combination with the flavoring and sweetening ingredients to make the product appeal to consumers.

If the product is a tablet, the acid-to-carbonate ratio affects how fast it dissolves. As the acid level increases, dissolution time generally decreases due to increased reactivity. The drawback to faster dissolution is a decrease in stability, so you’ll need to strike a balance.

Like all tablets, effervescent tablets require lubricants so they eject smoothly from the press. The most common tablet lubricants, however—magnesium stearate and stearic acid—are of limited use. That’s because virtually all effervescent tablets are dissolved in water before consumption and stearates are insoluble in water. Thus, they tend to float on the surface, creating an unattractive “oil slick.” Sometimes this can be countered using emulsifiers, such as lecithin or dioctyl sodium sulfosuccinate. An

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**Table 1**

<table>
<thead>
<tr>
<th>Two common carbonate salts</th>
<th>Na₂CO₃</th>
<th>NaHCO₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>106</td>
<td>84</td>
</tr>
<tr>
<td>Equivalent of acid</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>CO₂ (%)</td>
<td>41.5</td>
<td>52.4</td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Citric</th>
<th>Fumaric</th>
<th>Malic</th>
<th>Tartaric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>192.1</td>
<td>116.1</td>
<td>134.1</td>
</tr>
<tr>
<td>Moles of acidity</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Equivalent weight</td>
<td>64.05</td>
<td>58.05</td>
<td>67.05</td>
</tr>
<tr>
<td>Solubility (%)</td>
<td>68.6</td>
<td>1.1</td>
<td>55.8</td>
</tr>
</tbody>
</table>

Effervescent products must be manufactured in a highly dehumidified environment to prevent them from picking up unwanted moisture.
alternative to adding stearate lubricants to the blend is to add them externally. Typically, that entails spraying a small amount of stearate into the tablet dies just before they’re filled. This technique allows the tablets to eject easily and minimizes the amount of lubricant they contain. More often, formulators choose water-soluble lubricants, such as polyethylene glycol, sodium benzoate and, sometimes, leucine.

Binders are almost always needed to make good, solid effervescent tablets. Soluble materials such as sorbitol, lactose, and maltodextrin are usually used at levels of 10 to 20 percent. If the product need not dissolve into a clear solution, it could include insoluble binders such as dicalcium phosphate or microcrystalline cellulose. Which binder you use and how much obviously affects tablet hardness. As hardness increases, dissolution time usually does, too. Finding the proper balance between tablet hardness and dissolution time will require some experimentation.

Excipients that help powders flow more efficiently and prevent clumping in the production equipment are called processing aids or glidants. The most frequently used include fumed silica, calcium silicate, corn starch and, sometimes, talc. In general, these glidants work well at just a few tenths of 1 percent.

Virtually all effervescent products are based around an active or functional ingredient. That is, after all, what provides the benefit to consumers. It could be a pharmaceutical active, a dietary supplement, a cleaning chemical, or some other substance. From a formulator’s perspective, it’s important to choose a functional ingredient that is anhydrous and compressible and whose particle size distribution facilitates uniform distribution in the finished product.

Production methods

For tablets, direct compression is the most common manufacturing method because it’s the simplest and most cost effective. With this method, blends of dry ingredients go straight to the tablet press or other compression machinery without a granulation step. It works well when the ingredients are inherently compressible and their particle size distributions are closely matched. If that’s not the case, the ingredients must be granulated using a dry or wet process.

The dry granulation process uses a roll compactor to compress the powder blend into ribbons that pass through a mill and screen, which sorts the granules by size. A roll-compacted blend may or may not be effervescent. If it does, in fact, contain the acid-carbonate combination, then it must be handled and stored in appropriate environmental conditions to prevent the reaction from occurring. If, however, only the acid or carbonate is granulated (usually with other ingredients), then the packaging and storage conditions can be less stringent. If a roll compactor isn’t available, you can use a tablet press to compress the powder into slugs and then mill and screen them to size.

With wet granulation, a small amount of liquid, typically water or alcohol, is added to some or all of the for-

What to ask contract manufacturers about making effervescent products

Formulating and manufacturing effervescent products requires specialized knowledge and equipment, and only a few companies offer both. These questions should help you vet the candidates bidding for the job.

• What is the environmental infrastructure? Does the company have sufficient equipment to control the temperature and humidity of the production areas to ensure the stability of the finished products?
• What proprietary or public technology does the company offer to improve product stability?
• Are pilot facilities available to support product development? Can the company rapidly assess the stability of prototype formulations?
• How much experience does the company have packaging products that require moisture-proof seals? Can it package into foil strips and/or tubes? How does the company plan to test the adequacy of the seal or closure system?
• Has the company developed a range of products, including pharmaceuticals, supplements, cosmetics, beverages, and/or cleansers?
• Does the company have patents or proprietary knowledge to support the product you want to develop?
• If the product is a pharmaceutical, dietary supplement, or device, does the company offer GMP-compliant facilities?
• Does the company have the analytical resources to assess incoming materials and finished products?

—A.H.R.
mula’s components. The liquid causes the powders to agglomerate into granules that are easier to handle and compress. In cases where the starting blend includes both the acid and carbonate, adding solvent will initiate the effervescent reaction. Therefore, the addition must be made under controlled conditions and the solvent must be removed completely from the granules. That usually means drying them in an oven dryer or subjecting them to vacuum treatment. Fluid-bed processors can also be used to form and dry granules. When the effervescent granules are the finished product, they’re typically packaged in stick packs or sachets.

**Today’s effervescent products**

Today, dietary supplements are the major source of growth for effervescent products. In Europe, vitamins have been delivered via effervescence for years, and that idea is now taking hold in the USA. Vitamin C-based supplements, such as Reckitt Benckiser’s Airborne and Alacer’s (Pfizer’s) Emergen-C have captured significant market share. Bayer’s Berocca and Herbalife’s Liftoff deliver caffeine and vitamins, capitalizing on the demand for energy/alertness products. Nuun has established a large line of products devoted to the hydration benefits of electrolytes.

Among over-the-counter (OTC) products, Alka-Seltzer remains the most recognizable effervescent. Its manufacturer, Bayer, offers a line of aspirin-based analgesics, antacids, and cough-cold products under the Alka-Seltzer brand. Also found in the OTC aisle is hangover remedy Blowfish, a product from Rally Labs that combines aspirin and caffeine in an effervescent base.

A number of effervescent prescription drug products are also available, including potassium supplements based on potassium bicarbonate and/or potassium chloride. GlaxoSmithKline offers an effervescent version of Zantac for pediatric use, and Mission Pharmacal markets Binosto effervescent alendronate sodium.

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