
effervescent tablets

KEY FACTS ABOUT A UNIQUE,
EFFECTIVE DOSAGE FORM

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Effervescence has proved its utility as an oral delivery system in the pharmaceutical and dietary industries for decades. In Europe, effervescent dosage forms are widespread, and their use is growing in the US because they offer pharmaceutical and nutraceutical companies a way to extend their market share. This article summarizes the key facts about effervescent dosage forms, their formulation, and their manufacture.

Because few US companies have experience making effervescent tablets and powders, specialty contractors, such as the company I work for, do most of the work. This article describes what you should know about effervescent forms before hiring a manufacturer. You should understand what is possible and what is not.

Active ingredients

There are several categories of active ingredients:

Those that are difficult to digest or disruptive to the stomach. A classic example is calcium carbonate, the most widely used form of calcium. In a normal tablet or powder, the calcium carbonate dissolves in the stomach acid and is carried into the digestive system for absorption.

However, calcium carbonate releases carbon dioxide when it dissolves in the GI, which usually produces gas in the stomach. On the other hand, as people age, they have less acid in the stomach, and thus a calcium carbonate tablet may pass through the stomach without dissolving. That, in turn, may lead to constipation. However, if the calcium carbonate is taken in an effervescent formulation, the calcium dissolves in water, is readily available for the body to absorb, and there is no risk of excessive gas in the stomach or of constipation.

Those that are pH-sensitive, such as amino acids and antibiotics. The low pH in the stomach can cause active ingredients to become denatured, lose activity, or cause them to remain inactive. Effervescent ingredients, however, can buffer the water-active solution so that the stomach pH increases (becomes less acidic) and thus prevent the degradation or inactivation of the active ingredient. This buffering effect (via carbonation) induces the stomach to empty quickly—usually within 20 minutes—into the small intestine. The result is maximum absorption of the active ingredient [1].

Those requiring a large dose. A typical effervescent tablet (1 inch in diameter weighing 5 grams in total weight) can include more than 2,000 milligrams of water-soluble active ingredients in a single dose. If the required dose is larger than that, the sachet (powder form) is a common means of delivery.

Those that are susceptible to light, oxygen, or moisture. Many vitamins fall into this category. Typical effervescent formulations have less than 0.5 percent of free moisture. To maintain that level and prevent other damage from the ambient environment, the formulation's package should be 0.001-inch-thick aluminum that completely blocks light, oxygen, and moisture.

Formulation

Effervescence is the reaction (in water) of acids and bases producing carbon dioxide. Typical acids used in this reaction are citric, malic, tartaric, adipic, and fumaric. Citric acid is the most commonly used, and it imparts a citrus-like taste to the product. Malic acid can be used in effervescent formulas for a smoother after-taste, but the price of malic acid is higher than that of citric acid. Tartaric, adipic, and fumaric acids are used sparingly because of their low water solubilities.

Typical bases used in the effervescent reaction are sodium bicarbonate, potassium bicarbonate, sodium carbonate, and potassium carbonate. Sodium bicarbonate is very common in effervescent formulas and produces a

clear solution after tablet disintegration. When sodium levels are a concern, potassium bicarbonate is used. Both types of carbonates are used mainly as desiccants.

Binders are normally necessary in effervescent tablets to bring the tablet hardness to a point where handling is possible. These binders should be water-soluble and include dextrose, sorbitol, xytilol, and lactose. A binder should be used very cautiously because binders can carry free moisture into the tablet, which is undesirable and can increase disintegration times when used in large quantities. The ideal amount of binder is one that makes the tablet hard enough to handle, but soft enough to disintegrate (the harder the tablet, the slower the disintegration) and dry enough to be stable.

FIGURE 1

Effervescent tablets coming off a tablet press. Most steps in the manufacture of effervescent tablets are identical to those used for making conventional tablets.



Lubrication of effervescent tablets has historically been the main stumbling block to an acceptable, marketable product. Typical lubricants such as magnesium stearate are not useful due to their insolubility in water. Most formulators have to use water-soluble lubricants such as sodium benzoate, polyethylene glycol, and adipic acid. These are minimally effective, and depend heavily on the type of granulation they are used in. There are tablet presses that use lubrication spray on the punches so that the formula does not require lubrication.

Depending on the product, formulators can use color (artificial or natural), sweeteners (acesulfame potassium, sodium saccharin, aspartame, and surcalose), and flavors (artificial or natural) to enhance a product or to mask off-notes derived from the active ingredients.

Production

Effervescent tablets and powders are produced in much the same manner as conventional tablets and powders, but production must occur in very low humidity areas. Effervescent granulations can be mixed in conventional blending equipment, such as ribbon, twin-cone, and V-type blenders. All equipment should be well grounded and should allow you to make it completely and absolutely dry after wash-down. Any traces of moisture in the equipment will give erratic granulation results and most likely result in lost batches of product. Figure 1 shows a tablet press making an effervescent dosage.

Wet granulation of the effervescent base can be performed by carefully adding 0.1 to 1.0 percent water (weight-to-weight basis) to the chosen blending equipment. The granulation steps must be precisely timed and the ingredients mixed thoroughly to distribute the solvent or binder solution evenly in the blend. The mix is then quickly discharged to drying ovens. You must constantly monitor the operational parameters of all equipment, especially drying equipment, as variations in drying times and temperatures can affect the finished product. While stable granulations will ultimately be made, vast differences in tablet hardness and disintegration times can result from over- or under-reacting the granulation. After drying, the granulation is sized, and a final mix is performed.

Fluid-bed dryers have been used for many years to make effervescent granulations. Basically, the water or binder solution is sprayed onto the effervescent mixture while it is suspended in a stream of hot, dry air. The humidity and temperature of the air serve to stop the effervescent reaction quickly and uniformly. To ensure that you produce a free-flowing granulation, chose the particle sizes carefully and monitor all systems closely.

Vacuum granulators have also been used to make effervescent granulations. This equipment gives you a very controlled granulation of the product and allows a dust-free environment. The equipment also generally requires less power and less operating space than other types of granulators. In operation, the water or binder solution is sprayed onto the effervescent mixture during blending. Drying occurs by placing the granulation under vacuum and heating it via a thermal jacket.

Effervescent products normally require tablet presses that can deliver high compression forces. If the tablets are to be wrapped in foil or placed into a tube, give careful attention to the tablet parameters during compression. Monitor the tablet thickness to ensure the wrapping or packaging equipment can handle the tablets.

Strict control of temperature and humidity in all areas is a must (65 to 75°F, relative humidity of 10 percent), or the formulation will begin a chemical reaction after it's packaged. In essence, the tablet will self-destruct because the byproducts of an effervescent reaction are water and carbon dioxide.

The best way to stabilize an effervescent product is to

FIGURE 2

Packaging must completely protect the effervescent tablets from water vapor or they may self-destruct.



produce it in an environment where humidity is under strict control and to package it in a suitable moisture barrier. All ingredients in the formulation must be anhydrous. Your contractor should test for free moisture before packaging.

Packaging materials

Many effervescent product failures occur each year due to inadequate packaging materials. Many times the choice of packaging material is made based on pricing, rather than considering stability issues.

The most common types of packaging are foil packets and tubes. Pinholes are a common problem in foil packets. By going to a heavier-gauge foil (usually more expensive), you will greatly reduce the number of pinholes. The area within the packet should be large enough to hold the tablets without creating stress on the foil. Yet, it should also be as small as possible to minimize the amount of "room-air" that it can trap inside with the tablets. Given the very low humidity of effervescent tableting operations, the tablets are so dry that a relative humidity of even 10 percent is fairly high when it's trapped in close contact with tablets. Tubes are made of plastic, glass, or extruded aluminum with fitted caps containing desiccants. Desiccants are used to "bind-up" any free moisture in the tablet or in the air to prevent the effervescent reaction from starting prematurely. Be sure to conduct well-performed stability studies on tubes and any

other packaging you are considering. Figure 2 shows a packaging machine wrapping effervescent tablets.

After packaging, effervescent products should be placed in a test chamber set at 40°C and 75 percent relative humidity for at least 3 months to determine whether they will be stable. At the end of the third month, you should perform physical tests (package leak test, tablet appearance, disintegration time, tablet hardness, and sensory evaluation of the product) to determine whether any off-notes developed during testing. You should also perform chemical assays (HPLC/MS) to test the actives in the tablet. Has there been any product degradation? If so, why?

The common reasons for degradation of an effervescent product are

- **The packaging material does not have a moisture vapor transmission rate of 0.** Moisture vapor can enter the package.
- **The seal of the foil pouch is compromised.** This can happen when there is too much dust in the packaging area or when a machine malfunctions during wrapping of the product.
- **There are ingredients in the formula that are not compatible with each other or with the effervescent components chosen for the product.** Here, the pharmaceutical or nutraceutical company should ensure that its R&D department collaborates closely with the contract manufacturer. Each staff member must learn which raw materials are suitable for a successful effervescent product and which are not.

Advantages of effervescent formulations

Incorporation of large amounts of active ingredients.

In many cases, one effervescent tablet will equal three to ten conventional tablets in active dose amounts.

No need to swallow tablets. The number of people who cannot swallow tablets or who dislike swallowing tablets and capsules is growing. And many products require the patient or customer to swallow several tablets at a time. The elderly, in particular, have difficulty swallowing tablets. With an effervescent dosage form, one dose can usually be delivered in just 3 or 4 ounces of water. That's about the amount used when someone swallows a conventional tablet or capsule.

The product is typically self-mixing and flavorful. Many times effervescent tablets can include flavorings so they taste much better than a mixture of a non-effervescent powder in water.

Better dosing. Many studies have demonstrated that effervescent tablets and powders enhance absorption of a number of active ingredients (e.g. disulfiram and caffeine), compared to conventional formulations [2, 3, 4]. That's because the carbon dioxide created by the effervescent reaction can induce enhanced active-ingredient permeability due to an alteration of the paracellular pathway [5]. The paracellular pathway is the primary route of absorption for hydrophilic active ingredients in which

solutes diffuse into the intercellular space between epithelial cells. It is theorized that the carbon dioxide alters (widens) the intercellular space between cells, which leads to greater absorption of active ingredients (both hydrophobic and hydrophilic) [6]. The increased absorption of hydrophobic active ingredients could be due to the non-polar carbon dioxide gas molecules partition into the cell membrane, thus creating an increased hydrophobic environment, which would allow the hydrophobic active ingredients to be absorbed [6].

Possible drawbacks

Off-notes of some active ingredients. Some active ingredients have off-notes that cannot be masked by flavors and sweeteners. This will lead to an unacceptable product.

Disintegration time. In a tablet form, disintegration can take up to 5 minutes. This depends mainly on the temperature of the water and the active ingredients present.

Conclusion

Effervescent technology provides a novel dosage form for nutritional supplements and pharmaceuticals. The ability to incorporate large dosages of a wide variety of active ingredients in an easy-to-swallow liquid, plus increased absorption of the active ingredient, offers advantages over conventional tablets. T&C

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