TABLETS & CAPSULES
Solid Dose Digest
Insights, advice, and industry news about formulating, manufacturing, and packaging solid dosage forms brought to you by Tablets & Capsules *magazine*

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Ask an Expert

Granulation technologies for effervescent products

Q: What granulation technologies are best for manufacturing effervescent products?

A: Martin Koeberle, Hermes Pharma says:

Many people dislike swallowing conventional tablets and capsules, with over 50 percent of consumers reporting it to be difficult or uncomfortable. Developing more user-friendly dosage forms, such as effervescent tablets and instant drinks, is key to meeting patients' needs. However, since effervescent dosage forms are highly sensitive to moisture, their manufacture requires granulation technologies to improve their usability, stability, and overall quality.

Effervescent-tablet manufacturers have developed special granulation technologies that compensate for instability due to moisture, not only during production but also on the pharmacy's shelf and in the patient's home, prolonging the shelf life of the formulations and allowing them to perform optimally, even in high-moisture environments.

Manufacturers package instant drinks as sachets of loose powder or granules, whereas they form effervescent tablets via compression and package them in tablet tubes or foil strips. For both dosage forms, effervescence on exposure to water means the active pharmaceutical ingredient (API) swiftly releases into solution to produce a pleasant-tasting and easy-to-swallow drink.

Advantages of granulation

Granulation bonds primary powder particles together, improving their processability and allowing manufacturers to compress them rapidly and easily into effervescent tablets or manufacture them as instant drinks. In addition, granulation reduces the amount of dust within a powder, improving the overall flowability of a mixture for downstream processing, and ensures that the API is homogeneously distributed. Granulation can also alter the morphology of the powder particles to ensure an optimal particle size distribution and reduce the number of particles in the mixture with awkward shapes (such as needle-shaped), which are difficult to process.

This physical process of granulation reduces the accessible surface area of effervescent components in a powder, which is especially important for products that are highly moisture sensitive. Less surface area means that the overall product will be more stable because active ingredients cannot react readily via surface interactions. Similarly, altering the granule size and shape offers control over the bioavailability of the API, so it can be tuned according to requirements.

Two general types of granulation methods exist: wet and dry. Manufacturers can add a solvent to form larger, multiparticulate granules in a wet granulation process.

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Dry granulation

Dry granulation processes use physical compaction to bond the powder particles together. This method commonly calls for roller compaction, where a conveyor moves the powder into a compaction area between two oppositely rotating rollers. The rollers then compress the powder into a ribbon with a large amount of force. A size-reduction unit further processes this ribbon, milling it to the desired particle size.

If the effervescent components in the powder are stable enough, dry granulation offers cost advantages due to its high throughput and the ability to operate it continuously with minimal supervision. Also, dry granulation allows manufacturers to recycle any material that doesn't meet the required particle size, which reduces waste but can prolong the granulation process. The parameters of dry granulation are easy to control, and because it needs no water, it doesn't require an expensive drying step.

Wet granulation

In wet granulation, water or organic solvents, such as ethanol, partially dissolve the surface of the powder particles. A drying step removes the water or solvent, and the particles agglomerate to form granules, which manufacturers can further process into effervescent tablets and instant drinks.

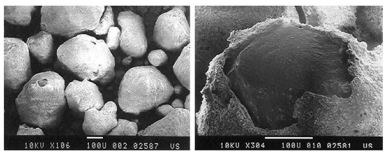
By continuously blending the material throughout the process as well as carefully controlling the parameters, wet granulation allows manufacturers to produce granulates with good batch-to-batch reproducibility. In addition, specialized wet granulation techniques enable manufacturers to produce highly moisture-stable products.

Specialized wet granulation techniques

Pharmaceutical manufacturers can use specialized wet-granulation techniques, such as TOPO vacuum granulation, to stabilize the moisture-sensitive components of effervescent dosage forms in air while maintaining their rapid reactivity in water.

Figure 1.

At left is a scanning-electron-microscope image of citric-acid particles coated with a layer of sodium citrate. At right is a magnified scanning-electron-microscope image of the sodium-citrate layer.



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Within all effervescent mixtures are acidic and alkaline components that are inactive when dry but that react vigorously in the presence of water to produce carbon dioxide gas and additional water. Typically, the acid used in effervescent products is citric acid, and the alkaline component is a carbonate. TOPO granulation can modify the surface of the reactive citric acid particles by a controlled reaction between the acid and the alkaline carbonate. This causes a layer of less reactive citrate to form on the surface of the acid particles to passivate them (Figure 1).

In addition to forming highly stable effervescent granules, this granulation method:

- Uses a vacuum, which prevents uncontrolled chain reactions and allows lower drying temperatures and shorter drying times, decreasing the likelihood of any thermal degradation of the effervescent components or APIs.
- Requires only a small amount of water, making it an environmentally friendly and sustainable technology.
- Accommodates the use of APIs that are sensitive to acidic or alkaline components through the passivation process.
- Allows adjustment of the particle size distribution of the granules for easy blending with additional excipients and ensures blend homogeneity.

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- Uses pure water, ensuring that no solvent residues are left in the finished product.
- Allows manufacturing to take place under atmospheric conditions of 30-percent humidity.
- Improves product effectiveness and stability in high-moisture climates, allowing production of medicines or dietary supplements for tropical and high-humidity regions.
- Minimizes or avoids the need for insoluble excipients, which can lead to unattractive foams or films when dissolved in water.
- Provides excellent compressibility characteristics, producing tablets with both high physical stability and rapid dissolvability.

A further development of TOPO technology, called continuous flow (CF) technology, uses an inclined drum, with the primary particle powder being fed in at one end and collected from the other. CF technology provides increased throughput compared to TOPO technology, allowing the processing of larger amounts of material in one batch.

Conclusions

Effervescent tablets and instant drinks are user-friendly alternatives to traditional solid oral dosage forms and help overcome the unpleasant effects that some patients experience when swallowing conventional tablets or capsules. When manufacturing effervescent tablets and instant drinks, granulation is important for turning fine pharmaceutical powders into free-flowing, dust-free granules, making further processing easier. Granulation also helps to ensure homogeneous API distribution and make unwieldy particle shapes more manageable to process.

The most suitable granulation process for your application depends on multiple factors, including the types of particles being processed, the API, the intended shelf life, and the objective of the final product. If the aim is simply to improve the processability and morphology of particles, then dry granulation may be sufficient. However, for products that contain one or more sensitive APIs, such as acetylsalicylic acid, dry granulation is often not a suitable approach, and a more specialized granulation process is required to create a stable product.

Martin Koeberle is head of analytical development and stability testing at Hermes Pharma.

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back to top

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