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eye on excipients

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In this edition of the column, Javier Belmar and Marc Ribé of Cafosa discuss the formulation and manufacture of direct-compression medicated chewing gum. Until recently, chewing gum required high-temperature extrusion. Today, formulators can use a combination of powder excipients to create chewing gums that run on standard tablet presses.

Medicated chewing gum (MCG) is an oral dosage form that releases an API or functional ingredient by the mechanical action of chewing. It has gained interest as an alternative and highly attractive delivery system for several categories of products, including prescription and over-the-counter pharmaceuticals and dietary-supplement products.

Until recently, MCG remained a niche pharmaceutical category best known for helping people quit smoking (nicotine replacement) and for treating motion sickness. Greater application of the dosage form was limited, however, due to its complex formulation and manufacture. The traditional process used in the confectionery industry uses hot mixing and extrusion that require technology and equipment unfamiliar to most pharmaceutical companies. The heat of the process alone made it unsuitable for many APIs.

Today, however, directly compressible excipients enable wider use of MCG production in pharmaceutical applications, and you can transform a mixture of dry powder excipients and the API into a quality chewing gum product using a standard tablet press.

The excipients open up the dosage form to pharmaceutical and dietary-supplement companies seeking a new delivery system that is more convenient and attractive than other dosage forms, such as standard chewables, orally disintegrating tablets, sachets and lozenges. Many consumers prefer a chewing gum format: It adds a pleasant sensation for consumers of medicinal or functional products. It also provides mild stress/anxiety relief, increases alertness and concentration, reduces food craving by its satiety sensation, and boosts oral health by promoting saliva flow and increasing pH that fights plaque acids.

MCG does not require water and there is no tablet to swallow. The simple action of chewing releases the API and allows fast absorption through the oral mucosa, implying quick onset of action. In addition, MCG prolongs the API's residence time in the buccal area, extending the local effect.

Direct compression versus traditional extrusion

Using powder excipients to directly compress chewing gum underscores its appeal to pharmaceutical manufacturers, many of whom see it as an innovative oral dosage form. The ability to continue using familiar processes and machinery is another benefit.

The standard (confectionery) process for making chewing gum begins with a heavy-duty, double-sigma mixer operating at about 50ºC (Figure 1). Next, the mass is extruded, shaped, and packaged. It usually takes more than a day to obtain the finished product because the extrudates must cool before they can be coated and packaged.

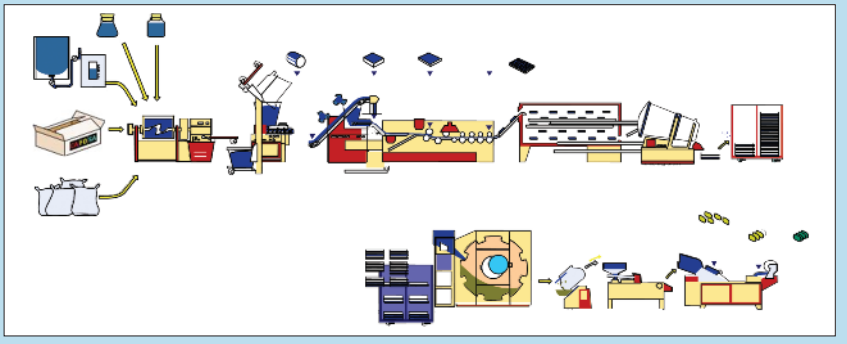
Directly compressing chewing gum—possible because of the powder excipients—has several advantages over traditional extrusion manufacturing:

- Identical to traditional tablet manufacture;
- Dry mixing of powders;
- Absence of heat;
- Content uniformity of APIs; and
- Low water activity.

Direct-compression chewing gum also has very good stability because the moisture content of the powder is very low, much lower than that of extruded chewing gum. Thus, APIs that are sensitive to heat or humidity are good candidates for use in chewing gum formulations.

FIGURE 1

Traditional method of manufacturing chewing gum



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Formulating MCGs

Our company offers a homogeneous, free-flowing powder that contains all the ingredients needed to produce chewing gum: Gum base, the essential ingredient that provides chewability; sweeteners (polyols such as sorbitol, isomalt, and xylitol); and softeners and anti-caking agents to enhance flowability and compressibility [1]. See Table 1. This combination of excipients readily accepts your API and runs on standard tablet presses just as any other direct-compression excipient or excipient combination.

TABLE 1

Typical ingredients in an 1,800-milligram tablet of medicated chewing gum

Ingredient	%	Weight (mg)
Active pharmaceutical ingredient	5.00	90
Health in Gum	89.70	1,614
Powder flavoring	2.00	36
Lubricant (magnesium stearate)	1.50	27
Glidant (silicon dioxide)	1.00	18
Liquid flavoring	0.60	11
Intensive sweetener(s)	0.20	4

Regulatory status. MCG is an accepted dosage form in the current pharmacopoeias, and the directly compressible excipients that our company offers comply with all regulations regarding gum base and other pharmaceutical monographs. A drug master file (type IV) is also available for some grades.

The key to formulating an MCG is adding a sufficient amount of the gum base-excipient powder to achieve good chewing consistency. An amount that comprises 85 to 90 percent of the sum of all ingredients is typical, regardless of the API dose the formula requires. That means that the API dose must increase as the size of the chewing gum tablet increases in order to maintain the correct proportions.

In the confectionery industry, chewing gum pieces weigh between 1 and 2 grams, enough for a convenient cud (volume of remaining gum base) after the soluble ingredients—sweeteners and the released portion of the API—are swallowed. Smaller or bigger cuds are difficult to chew, and consumers will not readily accept them.

Flavors. The flavor of chewing gum is key. Flavors provide not only taste, they can plasticize the chewing gum, and thus the desired properties of the product will be highly dependent on the flavor balance. Most flavor technologies on the market are suitable for medicated chewing gum and come in powder, liquid, and encapsulated form. Figure 2 illustrates the release of flavors as a function of chewing time.

We recommend adding lipophilic liquid flavoring to extend the gum's taste, but it should comprise less than 1 percent of the total. If too much is added, the gum may become sticky due to over-plastification of the mix during production. Powder flavors can be added without limitation, bearing in mind the maximum dilution percentage cited above.

Most APIs have an unpleasant taste, and flavoring plays a key role in masking it. In the case of APIs delivered with chewing gum, taste masking is of great concern because the residence time in the mouth is much longer (average of 20 to 30 minutes) than it is for other dosage forms.

Keep in mind: The flavor technologies you select will depend on the release profile of the API, and a range of flavor strategies is available. One approach is to combine different flavor technologies with different combinations of intensive sweeteners. Another is to use complexing agents (e.g., cyclodextrin or ion-exchange resins).

Intensive sweeteners. Sweeteners enhance the taste and mask off-tastes; they also compensate for the lack of sweetness in sugar-free chewing gums. Intensive sweeteners are 200 to 6,000 times sweeter than sugar, and their levels of use are limited by regulation. The most commonly used intensive sweeteners in chewing gum are aspartame, acesulfame-potassium, and sucralose. Other intensive sweeteners include thaumatin and neohesperidine dihydrochalcone. Stevia is also starting to be used, although the gum formulation would need to be modified to account for the ingredient's own taste.

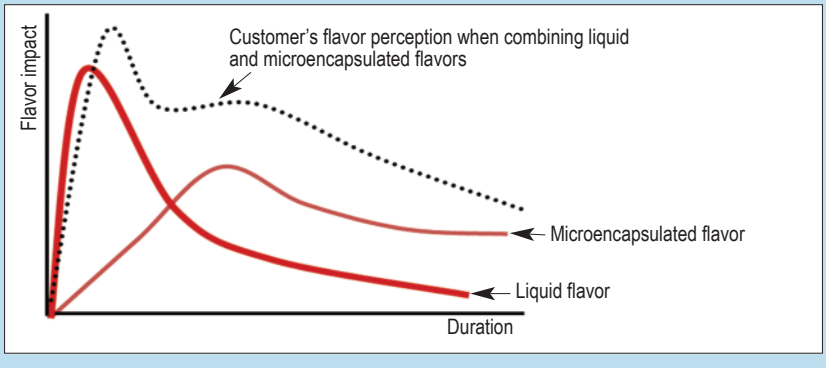
Production of MCG

Mixing. Using a combination of powder excipients, such as the one our company supplies, means that the ingredients must first be combined in standard solid blenders (ribbon mixers, ploughshare mixers, or mixer-granulators). We recommend using these horizontal mixers instead of vertical mixers to minimize lump formation due to the pressure of the powder column (photo).

Vertical mixer-granulators are suitable for traditional chewing gums, but not for mixing powder excipients.

FIGURE 2

Release of flavors as a function of chewing time



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If a liquid flavor is to be added and the mixer has no spraying system, premixing the liquid with silicon dioxide will promote homogeneous blending as the other ingredients are added.

As in most compression processes, lubrication is required to prevent the mixture from sticking and to promote steady production. Stearates and/or talc are commonly added, usually in the last steps of blending. Because the chewing gum is likely stickier than other excipients, lubricant levels may be higher than in standard tablets, in the range of 1.5 percent. Systems that supply external lubrication to the tablet press are also available and usually add great value because they increase production speed and consume less lubricant.

Tabletting. Compressed MCG can be made with good results using a range of equipment. Whatever equipment is used, the powders must be fine and free-flowing so that they feed reliably and accurately. When compression begins, we recommend that you operate the press very slowly to ensure that it operates properly and that all parameters are in balance. Using a pre-compression station will reduce the risk of capping.

The suggested initial main parameters for a 1,100-milligram square tablet are listed in Table 2, although the parameters will vary depending on the tablet press.

TABLE 2

Tablet press settings for manufacturing an 1,100-milligram square tablet of medicated chewing gum

Parameter	Setting
Pre-compression (kN)	3.3
Main compression (kN)	8.0
Fill depth (mm)	8.5
Tablet cylinder height (pre-compression, mm)	5.1
Tablet cylinder height (main compression, mm)	4.6

Room conditions. The sticky nature of chewing gum makes it critical to maintain a low temperature and humidity during manufacture, similar to what effervescent tablets require. Ideally, the manufacturing suite will remain at 20°C and at less than 35 percent relative humidity (RH). As a rule of thumb, the temperature should not exceed 27°C and RH should not exceed 50 percent. A common means of reducing stickiness is to cool the mass before compression.

Speed. The tabletting speed you can obtain depends on the equipment used, and the heat it generates. (Chewing gum sticks when exposed to heat.) If high speed is required, external lubrication of the tablet press is recommended. Standard output of chewing gum is about 90,000 pieces per hour when manufactured under the recommended conditions.

Coating. Coated chewing gums have broad acceptance, and consumers worldwide prefer them. Adding a film coating—be it sugar-free or flavored—to compressed chewing gum improves mouth-feel, (crunchy effect), intensifies the flavor sensation, and protects the product.

Sugar-free coatings are made with water-based syrups. In some cases, a gumming process (using a hydrocolloid) is used to protect water-sensitive cores. Table 3 lists the ingredients typical of an isomalt-based coating syrup. Film coating, the standard process for most tablets, can also be used with chewing gums to protect their centers, improve their shine, and add color.

TABLE 3

Example of ingredients in an isomalt syrup for coating tabletted chewing gum

Ingredient	%
Isomalt	61.70
Water	33.40
Gum arabic solution (50%, w/w)	4.60
Color (if required)	0.30

Production issues. Two of the most common problems in tabletting MCG are formulations that stick to punches and tablets that crumble easily. As noted above, proper lubrication and/or lower temperature and RH in the manufacturing suite often overcome sticking issues. The remedy for tablets that crumble easily is to use no less than the minimum recommended amount of excipients. It's also important that you maintain the pressure at 7 to 9 kilonewtons. Higher pressures will yield very hard and crumbly tablets. Lower pressures will cause poor cohesion, causing the tablet to break into pieces and making it difficult to chew. Other common issues with tablets, such as capping and picking, can also occur and those are handled as you would when making conventional tablets.

Quality control, stability, and packaging

The quality of compressed MCGs is evaluated just as standard tablets are, including measuring weight uniformity, content uniformity, and friability (hardness or crumbliness). The first two parameters are measured the same as standard tablets. But the last parameter is best assessed using a sensorial analysis to replicate the chewing action in the mouth.

In stability tests, the properties of uncoated chewing gum may change due to the hygroscopicity of the polyols used. (Sorbitol and xylitol are hygroscopic.) Coating, as mentioned before, improves the MCG's shelf-life, especially if the product is marketed in areas where humidity is high. A minimum shelf-life of 2 years can be achieved by using proper packaging materials to protect the MCG pieces from exposure to light and moisture, two parameters that must be minimized to prevent stress and oxidation of the gum base and other ingredients in the formula.

Which packaging format you select depends on the needs of the formulation and the market. In the USA plastic bottles are common, and thus a small desiccant bag to absorb internal humidity may be required. In other areas, such as Europe, blister packaging is preferred, and plastic-aluminum films are more common.

Dissolution testing

Although it is not mandatory that you analyze the release of the API, nowadays such analysis is a common quality control procedure. In gums that offer nicotine-replacement therapy, for example, a chewing apparatus is used for in vitro tests. In fact, two such machines are now part of the European Pharmacopeia (method 2.9.25), and one is commercially avail-

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able. Using that apparatus, the final product is chewed in artificial saliva for a time at a set speed. Standard techniques are then used to determine how much API is dissolved in the saliva.

The release of different APIs depends on different factors, but water solubility is a key point in most cases, and solubility can influence the dissolution rate from an MCG matrix. We know that APIs that are highly water/saliva soluble release completely and more quickly than slightly or poorly soluble ones, which require more chewing time; even then, sometimes only a fraction of the total API content is made available because the rest remains trapped in the gum base. Adding solubility enhancers can be a good strategy to promote better oral dissolution of poorly soluble APIs. Placing some portion of the API in a sugar-free coating may also help. *T&C*

Reference

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