dosage forms

Selecting the final SODF: A comparison of capsules and tablets

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Many variables come into play when selecting a final solid oral dosage form (SODF) for a drug product. Among them are the formulation, the manufacturing process, scalability, validation requirements, quality control, overall cost, and patient perception and preference. This article briefly analyzes several of these variables, mainly by comparing hard capsules to tablets.

Hard capsules, also known as two-piece capsules, offer an extremely versatile drug delivery method. Most are dry-filled with powders, granules, pellets, tablets, or mini-tablets. But hard capsules also accommodate semi-solids—non-aqueous solutions and suspensions—and other liquid fills, which enable formulators to create sophisticated combined formulations, such as pellets in a liquid and a softgel or hard capsule within a larger capsule. Hard capsules even go beyond oral delivery: Many products are delivered to the lungs using a capsule-based dry powder inhaler.

From the beginning

The benefits of hard capsules start in R&D, where they enable manufacturers to reduce a drug product's time-to-market. During product development, capsules are simple to handle on a small scale and can be filled manually or with semi-automatic equipment that is comparable to industrial-scale capsule fillers in terms of compression force. The filled capsules also perform comparably in dissolution testing. Furthermore, they are more suitable for use when the API is in short supply because they conserve costly material. Hard capsules also facilitate proof-of-concept exercises, possibly eliminating the need to formulate because neat API can be dosed to the capsule. This absence of formulation involves minimal risk of incompatibility regarding API stability because the only possible interaction would be with the capsule shell.

As an investigational drug product moves toward pre-clinical and toxicity testing, tiny hard capsules enable researchers to deliver the correct dose to the stomach of conscious animals without stressing them. When advancing to clinical testing with humans, the usual choices include chemical-in-capsule, formulated capsules (including binary blends), and chemical-in-capsule-in-bottle. Which to use depends on whether an exploratory or commercial approach is selected.

Exploratory formulation approach. This option calls for the simplest possible formulation applicable to clinical testing (such as neat API-in-capsule). The goal is to achieve early-phase safety and proof-of-concept data.

Commercial approach. Here the objective is to produce a formulation that resembles the commercial formulation, usually involving second-generation compounds. This approach can reduce the need for bioequivalence studies in later stages of clinical testing.

Whatever the strategy, hard capsules offer a high degree of flexibility in Phase I formulations because they enable you to cover a wide range of doses in the trial, such as 1, 10, and 100 milligrams. In addition, the variety of colors and sizes of capsules makes them well suited for preliminary drug studies and blinded clinical trials.

Clinical trials

In the past, clinical trials typically used hard capsules for preliminary development, followed by a tablet formulation when the scale of the trials increased. Although this generally was considered an easy conversion, the regulatory requirements have changed in the last 25 years. Changing the dosage form requires robust evidence, including stability studies (ICH Q1), in vitro bioequivalence studies for drug products of all BCS classes, and possibly in vivo testing (particularly for BCS classes II and IV), which is quite expensive. Switching from a capsule to a tablet at the end of Phase II clinical trials, however, is still common because many pharmaceutical production sites have tablet presses that are qualified and ready to use. Another point to consider is that the sites have staff skilled in tabletting and the GMP certifications, validations, and documentation required to make tabletted drug products.

Manufacturing advantages

However, in the realm of SODFs drug products, capsules retain several advantages over tablets:

Capsules often require fewer excipients than tablets. In addition to the active(s), both dosage forms typically include diluent(s) and a lubricant. Capsule formulations, however, may only require adding a glidant, while tablets require, at minimum, a disintegrant and a binder if they are dry- or wet-granulated. Coated tablets incorporate even more excipients. See Table 1.

Capsules require less compression force than tablets. The force applied to form a powder plug to fill the capsule ranges between 0.01 and 0.1 kilonewtons, while tablets are compressed at 10 to 100 kilonewtons.

Manufacturing speed facilitates scale-up. An average tablet press operates faster than most capsule fillers, but the speed of plug formation in capsule filling is the same for both low- and high-speed capsule fillers. This is not true of tablet presses, and a tablet formulation designed using a low-speed press may not perform the same when it moves to a high-speed machine.

Table 1

Number of excipients included in tablet and capsule formulations

Number of excipients	Tablet product	Coated tablet product	Capsule product
1 to 2			• Metamizol • Ultibro Breezhaler (indacaterol and gylcopyrronium bromide) • Tranxilium (dipotassium clorazepate) • Clamoxyl (amoxicilin)
3 to 5	• Aciclostad (aciclovir) • Acentensil (enalapril) • Eutirox (levotiroxina) • Primperan (metoclopramide) • Clamoxyl (amoxicilin)		• Lyrica (pregabalin) • Celebrex (celecoxib) • Enantyum (dexketoprofen) • Fluconazol • Tacrolimus
6 to 9	• Paracetamol • Acfol (folic acid) • Dilitiazem	• Losartan • Crestor (rosuvastatina) • Zomig (zolmitriptan) • Enantyum (dexketoprofen) • Ebastel (ebastin) • Brainal (nimodipin) • Sertralina	
More than 9	• Tryptizol (amitriptyline)	• Aldomet (methyldopa) • Atripla (efavirenz, emtricitabina, and tenofovir disoproxil) • Levonorgestreland ethinyl estradiol	• Omeprazol

Additionally, there are fewer steps in manufacturing capsules compared to tablets, with the exception of tablets that are made without using a granulation step. These products, however—known as direct-compression or direct-to-press tablets—account for the smallest number of tablet formulations produced commercially due to the difficulty in obtaining powder blends that flow and/or compress well without modification [1]. Wet granulation, the most complex preparation method, is used about 75 percent of the time in tablet making, followed by dry granulation. Both methods require more than twice the number of steps to produce a final drug product compared to manufacturing a hard capsule product. See Figure 1.

Using liquid fills facilitates accurate blending, homogenization, and dispensing. Liquids are also advantageous for processing highly potent and/or low-dose actives.

Other benefits of manufacturing drug products in capsules include spending less time and money on inventory, less handling, fewer supplier qualifications, and faster quality control and release of excipients. Coupled with their simpler production process, capsules require less time per unit compared to tablets, even though tablet presses operate at higher speeds.

Liquids

One of the simplest capsule drug products to formulate is the liquid-filled capsule. Today, more than 70 percent of new chemical entities are poorly water-soluble compounds that are difficult to formulate. One way to succeed with these challenging substances is to use lipid-based formulations of liquid-filled capsules. Liquids facilitate accurate blending, homogenization, and dispensing. Liquid-filled hard capsules are also advantageous when the active is highly potent and/or used in low doses, such as cytotoxic agents, hormones, and others. They are also suitable for use with drug substances that have a low melting point or that are unstable. A hard capsule shell can prevent oxidation of vitamins in oil, for example.

Patient preference and adherence

It is also important to mention that liquid-filled hard capsules are among the solid oral dosage forms most associated with perceived efficacy. That is, patients and consumers think that the dosage form itself allows the active ingredient to take effect more quickly and preserves the strength and/or potency of the medication [2]. Branded capsules, which also rank high in terms of patients' perception of efficacy, enable formulators and/or marketers to create unique means of identifying and differentiating their products. Options include a wide range of opaque and transparent colors for the cap and body and diverse printing schemes. These provide significant advantages to patients and healthcare providers by:

- Deterring counterfeiters due to the high complexity of features, making them difficult to copy;
- Increasing drug safety, especially for elderly patients, and helping medical staff to distribute the correct medications thanks to clear product identification; and
- Improving adherence because the product is easy to recognize.

In fact, adherence—taking the medication as prescribed—among patients with chronic diseases or among those who take multiple medications daily, is a major problem. It concerns not only the pharmaceutical industry, but the healthcare community as a whole. Certainly, offering drug products that are easy to identify and self-administer—and that patients prefer—can only help improve adherence.

Another key factor in patient preference and adherence is ease of swallowing. A study of 2,000 consumers in Germany and the USA conducted by Hermes Pharma shows that 32 percent of respondents have broken up a tablet before ingesting it. Another 17 percent have crushed a tablet and dissolved it in water before swallowing. Only 6 percent have emptied a capsule to take its contents [3]. The study shows that consumers often undertake these behaviors because they perceive the dosage form as difficult or uncomfortable to swallow when self-administered. This can lead them to alter the dosage form in a way that reduces or interferes with dosing frequency, efficacy, API release, and bioavailability, which ultimately leads to incorrect treatment.

The other benefits of capsules, which patients acknowledge, include the possibility of combining drug products to reduce the number of pills they must take. Capsules are also less prone to breakage by accidental mishandling, and they block unpleasant odors and tastes better than uncoated tablets.

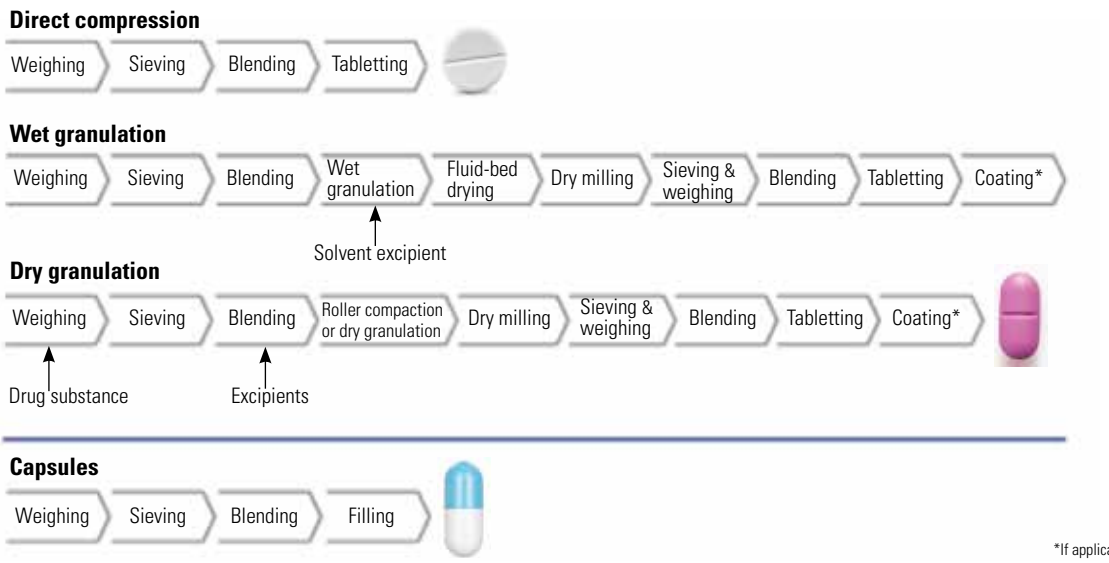
In summary

Hard capsules offer advantages throughout the lifecycle of drug products because of their versatility in accepting different formats, from dry and liquid formulations to combinations thereof. Working with capsules in R&D can shorten a drug product's time-to-market because capsules enable a rapid demonstration of a therapeutic approach's proof-of-concept.

Formulating with capsules instead of tablets also reduces the cost and time needed to develop and validate the process and the analytical methods throughout the development phase. Scaling up the process is also easier. As for manufacturing costs, although most capsule filling machines operate more slowly than tablet presses, hard capsules can provide a higher output in time per unit while minimizing the need for excipients. Finally, capsules endow the final product with an intangible value in terms of product identification and perceived ease of swallowing and efficacy, which improves adherence. *T&C*

FIGURE 1

Process steps required to manufacture tablets versus capsules



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