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Choosing Capsules: A Primer

Capsules offer certain benefits over tablets for oral-solid dosage drugs, and several types of capsules are available.

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Oral-solid dosage (OSD) drugs can be formulated in tablet or capsule form. Some drugs are available only as capsules or tablets, and some are available as both. Various types of capsules, with shells made of different materials, are available. When choosing a capsule type, formulators should consider factors such as the shell's barrier to water and oxygen, reactivity, and the material it is made of.

Selecting a capsule type

The most widely used capsules can be classified as shown in **Figure 1** and discussed in the following sections. Dry-filled capsules include mainly hard gelatin and hard hydroxypropyl methylcellulose or hypromellose (HPMC) capsules. Liquid-filled capsules include hard capsules (gelatin or HPMC) and softgel gelatin capsules.

The larges size (000) is mainly used in veterinary practice. Fill weights increase with the size of the capsule as well as with the bulk density of the filled material, which can range from 0.3–1.5 g/cc. Fill weights in the smallest capsules might be 39 mg, for example; the largest may weigh 1425 mg.

The shell of hard gelatin capsules contain 13–16% water. Storage of hard-gelatin capsules at very low humidity can cause them to turn brittle. Gelatin capsules do not protect hygroscopic materials from atmospheric water vapor because moisture can diffuse through the gelatin wall. If stored at high humidity, the capsules become flaccid. In such cases, primary packaging material such as aluminum strip packing, moisture barrier blister foil (e.g., Aclar), or bottle packs should be used.

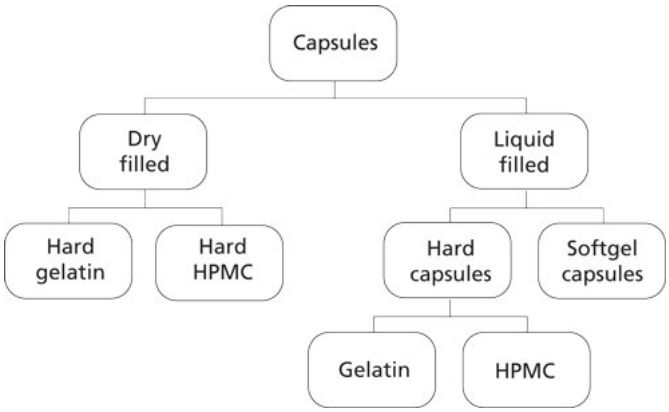

Figure 1: Classification of major capsule types. Figure is courtesy of the author.

Hard gelatin capsules. The gelatin used in the manufacture of most common capsules is obtained from collagenous material by hydrolysis. Gelatin is a natural, safe, non-allergenic, clean, and economical ingredient. The two-piece hard gelatin capsule is available in a range of sizes; from largest to smallest, these sizes are 000, 00el, 00, 0xel, 0el+, 0el, 0, 1el, 1, 2, 3, 4, 5.

HPMC capsules. HPMC capsules are stable at low humidity levels, have low moisture content (3–8%), and low static charge. These natural capsules are available from size 00 to 4. HPMC capsules are suitable for highly reactive molecules (because they have no cross-linking reactions). Compared to hard gelatin, HPMC is more suitable for moisture-sensitive products, hygroscopic products, and for low relative-humidity applications. HPMC is not of animal origin and does not pose a risk of contamination with organisms that cause bovine spongiform encephalopathy (BSE) or transmissible spongiform encephalopathy (TSE). HPMC capsules are used in a wide range of OSD pharmaceuticals as well as nutraceuticals, dietary supplements, and herbal products, due to the vegetarian nature of HPMC.

Fish gelatin capsules. Marinecaps are made from fish gelatin and do not pose risk of BSE or TSE. They are preferred for filling marine supplements such as EPA [eicosapentaenoic acid]-rich fish oil.

Starch capsules. Starch capsules are made from potato starch. Their dissolution is pH independent, and they are suitable for enteric coating. The moisture content of starch capsules ranges between 12–14% w/w, with more than 30% being tightly bound (1).

Pullulan capsules. These vegetarian capsules are made from tapioca, which is

naturally fermented into pullulan. They provide a high barrier to oxygen.

Polyvinl acetate (PVA) capsules. Capsules made from PVA can be used for filling insoluble drugs dissolved in polyethylene glycol (PEG) 400. PEG 400 when used as single vehicle is not compatible with other hard capsules. The oxygen permeability of PVA is low, resulting in a high barrier to oxygen.

Liquid-filled hard capsules (LFHC). Two-piece hard capsules made of either gelatin or HPMC can be used for filling and band sealing non-aqueous liquid, paste, suspension, hot melts, and other vehicles that melt up to 70 °C and flow easily. LFHC can also be filled with tablets, pellets, or other capsules as combination fill. LFHC can be used for moisture-sensitive drugs. These can be a cost-effective alternative to some soft gelatin capsule products and can also enhance bioavailability and improve product stability. Liquid encapsulation technology helps overcome many problems associated with the use of softgel capsules including high cost, waste, cross-contamination, migration of the drug into the capsule shell, and issues with low bioavailability. Liquid-filled and semi-solid capsules by their nature are resistant to crushing and powdering and therefore provide a good basis for developing an abuse-resistant formulation. These capsules can also be enteric coated. HPMC hard capsules do not become brittle when they lose water (2).

Soft gelatin capsules (SGC). SGC have soft, globular, gelatin shells somewhat thicker than that of hard gelatin capsules. The gelation is plasticized by the addition of glycerin, sorbitol, or a similar polyol. It may contain preservative to prevent the fungal growth. Large-scale production methods are generally required for the preparation of SGC.

Benefits of capsules as a dosage form

Consumer preference. The growing interest in capsules as a formulation is consumer driven. Consumers prefer capsules because they are tasteless, odorless, and easier to swallow. Capsules are also considered to work faster and better. In a study conducted by Burke Marketing Research, 1000 patients were asked about the form of drug administration they preferred, and more than half (54%) chose capsules (3). Another study, conducted with several hundred patients in two hospitals in Copenhagen and published in 2001, found that 66% preferred capsules (3). This preference has prompted pharmaceutical manufacturers to market products in capsule form even if the product already has been produced in tablet form.

Rapid dissolution. Most filled capsules disintegrate in 5–10 minutes. Some of the immediate release tablets may have much lower disintegration time. Once a capsule disintegrates, however, dissolution may be faster and dissolution levels achieved may be similar to tablets at 15 minutes. HPMC capsule shells can lead to rapid dissolution. However, these differences will not necessarily produce considerable alterations in the pharmacokinetic profiles of the drug product because the f2 value used to determine dissolution differences is often too discriminating, particularly when the dissolution is very fast relative to permeation and/or absorption is very fast relative to disposition (4).

Formulation development. Capsules are easier and faster to develop and manufacture in comparison to other OSD forms because the capsule manufacturing process involves fewer steps and a lower number and quantity of excipients. For example, as per studies conducted by Aspire Advisors, Acetazolamide 250 mg tablet weight is 516 mg but Acetazolamide ER 250 mg capsule fill weight is only 328 mg. Some coarse, free-flowing, Biopharmaceutical Classification System Class I drugs can be filled directly into capsules. Capsules can also be used for poorly compressible drugs.

Capsules provide relatively better stability than other OSD forms. Encapsulation does not create high heat and pressure, thus heat-sensitive drugs can be more readily formulated as capsules. Capsule walls can be made opaque, providing protection for light-sensitive compounds. Sealed hard gelatin caps can be good oxygen barriers. As capsules generally require fewer excipients, drugs that are sensitive to or highly reactive with other chemicals may be more readily formulated as capsules.

Further, due to fewer processing steps, capsules can minimize human exposure to potent drugs. Capsules reduce airborne dust levels, lowering the risk of cross-contamination and offer improved content uniformity particularly at low dosage levels and for potent drugs. Overall, they reduce the capital requirements for dedicated facilities, air-handling, and process equipment.

Formulation flexibility. Encapsulation technology has made progress in recent years. For example, soft gelatin capsules and LFHC are increasingly being used for filling and/or sealing (band sealing in case of LFHC) of liquid and pastes. Furthermore, a single capsule can now encapsulate not only powders or granules, but also one or more ingredients that are in liquid, pellet, tablet, or another capsule form. Incompatible ingredients can thus be combined into a single capsule, which helps to develop combination products.

Enteric coating of hard capsules or use of enteric hard capsules further expands the scope of capsules usage (5). In addition, capsules can be used for active ingredients that need modified release. Modified-release capsules can now be developed that disperse freely in the gastrointestinal tract, providing more uniform distribution of drug into the bloodstream. These capsules help to maximize absorption and minimize side effects. They also reduce inter- and intra-patient variability. Calcifediol and oxycodone extended release (ER) capsules are two examples of ER capsules approved in 2016 as new drug applications.

Dissolving the active ingredient in a mixture of liquids, semi-solids, or hot-melts can result in better solubility and higher absorption. For example, isotretinoin solubilized in sorbitanmonooleate, soybean oil, and stearoylpolyoxylglycerides filled in hard capsules (marketed as Absorica in the United States) gave higher absorption in fasted state than the original softgel product Roccutane/Accutane (6). Those drugs that cannot be solubilized in this manner may be formulated as a self-emulsifying drug delivery system.

Capsules are also useful for clinical trials. Specialized capsules for clinical trials are unique two-piece gelatin capsules that are specially designed to carry out double-blind studies during clinical trials. After closure (locking), the elongated cap closes tightly on the body. Once locked, only the dome of the body is visible, making it almost impossible to open the capsule.

Capsules can be developed faster than tablets for new chemical entities. Because Phase I and II clinical trials are mostly carried out using capsules, additional bioequivalence/bioavailability studies are needed when converting from capsules to tablets. Moving a product to market one year faster can give one year more effective patent life. Similarly, other types of innovations and FDA applications, such as abbreviated new drug applications, can be marketed faster.

Anticounterfeiting. Capsule manufacturing companies have developed a unique technology that enables capsules to be printed in multiple colors, which creates brand differentiation and serves as an effective anticounterfeit measure. Further, it is now possible to imprint brand logo, brand name, and graphics on the capsule, providing further brand identity (7).

Conclusion

In summary, capsules are an attractive OSD form that enjoys patient preference, improved pharmacokinetic profile, faster development, and formulation flexibility. In addition, capsule formulations offer brand recognition in a crowded pharmaceutical market. Switching to capsules from other OSD forms also gives manufacturers an excellent opportunity to get out of the competitive environment of generics while still enjoying a development process that eliminates most preclinical studies as well as extensive safety and efficacy tests.

References

1. S. Arora, et al., “Capsules” in *Theory and Practice of Industrial Pharmacy* by Lachmann and Lieberman, R.K. Khar, S. P. Vyas, F.J. Ahmad, and G.K. Jain, Eds. (CBS Publishers & Distributors, 4th ed., 2013), pp. 546-578.
2. G. Rowley, “Filling of Liquids and Semi-solids into Two Piece Hard Capsules” in *Pharmaceutical Capsules*, F. Podczeck, B.E. Jones, Eds. (Pharmaceutical Press, 2nd ed. 2004), pp. 169-194.
3. A.B.A. Overgaard, et al., *Pharmacy World & Science* 23 (5) 185-188 (2001).
4. J. Al-Gousous, et al., AAPS Annual Meeting and Exposition Poster Number M3293 (2016).
5. H. Schaub, C. Scialdone, and J.V. Carey, *ONdrugdelivery* 34, 4-8 (2012).
6. G.F. Webster, et al., *J Am. Academy of Dermatology* 69, 762-767 (2013).

7. ACG World, “Drug Anticounterfeiting Solutions,” www.acg-world.com/resources/drug-anti-counterfeiting-solutions.php [2], accessed Aug. 25, 2017.

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