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Recent Options for Phase 1 Formulation Development and Clinical Trial Material Supply

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Pharmaceutical companies are challenged with choosing a dosage form that will reach clinical studies quickly and that can be made using a cost-effective process. To meet the demands of early-stage development, contract research organizations can evaluate various dosage-form options. The author examines various methods of capsule filling, including binary blends.

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Large and small pharmaceutical companies as well as emerging companies that may operate as virtual companies strive to shorten drug-development times. The ability to hasten drug development is particularly important for virtual pharmaceutical companies, which focus on drug discovery and development but rely heavily on outsourced services to perform the functions necessary to move a drug through development to commercial manufacture. The ability of these companies to stay competitive depends on transforming new chemical entities into clinical products. The increase in the number of virtual companies has resulted in enormous investments in investigational new drugs. The active pharmaceutical ingredients (APIs) coming out of synthesis are challenging formulators' abilities to develop dosage forms.

Scientists have developed various methods to improve preformulation properties. The situation remains challenging: About 60% of compounds in development are poorly soluble. The literature reports that one-tenth of marketed drugs have solubility problems, more than one-third of drugs in the pipeline are poorly soluble, and nearly two-thirds of drugs coming directly from synthesis have low solubility (<0.1 mg/mL) (1). Poor solubility contributes to dissolution problems. Another challenge has been APIs with poor flow characteristics. All these aspects of the traditional dosage formulation-development process present challenges and increase the amount of time it requires.

Outsourcing early formulation development and clinical trial material manufacturing is an important strategy for virtual pharmaceutical companies and for larger pharmaceutical companies that seek to reduce cost and time in early drug development. Several options for dosage forms may be used in early-stage formulation development, including API in a capsule, drug in a bottle, liquid in capsule, and binary blends.

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API in a capsule

Filling an API directly into a capsule is probably the quickest and best option for entering clinical trials. This method offers the advantage of having little or no need for excipients, thereby potentially saving as much as six months of formulation-development and stability-testing time. At the early clinical phase, the API manufacturing process is often altered, and lot-to-lot variation in the physical characteristics of the API is common.

Filling API into capsules is quick for noncohesive APIs with good flow characteristics. These APIs do not need a flow-aiding excipient or a physical processing step. Interestingly, it takes less time to implement a processing step for high-dose APIs than for low-dose APIs, which require a manufacturing process that enables them to meet content-uniformity criteria. Excipients are included only to improve the physical characteristics of the API but not to modify the chemical characteristics with antioxidants, buffers, chelators, or moisture scavengers. If an excipient is needed to influence chemical characteristics, then the project path can lead toward a routine formulation-development process, which can help overcome dissolution and content-uniformity challenges.

However, the API in a capsule approach does not involve developing a dissolution method or conducting content-uniformity testing. Thus the approach saves time that would have been spent on analytical methods and formulation. Of course, if the approach is successful, then additional time is saved in ordering, receiving, testing, and releasing the excipients as well as writing and approving specifications. The approach is suitable for both gelatin and hydroxypropyl methylcellulose capsules. It is a matter of getting one capsule type and API lot released for clinical use and creating an approved batch record.

One type of filling equipment is the “Xcelodose 600 S” (Capsugel, Peapack, NJ, see Figure 1) microdosing system, which can fill amounts as low as 100 μg at speeds of more than 600 capsules/h at lower than 2% RSD weight range (2). In general, the equipment is approximately 10 \times faster than filling by hand and provides 50% greater throughput than the earlier “Xcelodose 120 S” system (Capsugel). The tapping, dispensing head, movement of the dial plate, and the turret system provide accurate dispensing into a capsule shell. A microbalance makes the filling process suitable for dispensing precise microquantities. The Xcelodose 600 S model fills into vials, tubes, blisters, and cassettes and can fill granules or beads in a capsule.

An important feature of the Xcelodose manufacturing equipment is that they check every capsule’s weight for acceptance or rejection. The microbalance not only supports the accuracy and sensitivity of the device, it also allows for setting acceptance and rejection parameters. The need for a weight-sorting step in the manufacturing process is thus eliminated. The weight-checking



Figure 1: The “Xcelodose 600 S” capsule-filling system.

traceability, with a printability option, of each capsule manufactured simplifies the capsule count required at the end of the batch for yield-check calculations.

In addition, the Xcelodose process for filling API into capsules reduces analytical-method development time because the capsules are tested for moisture content, assay, and impurities. The necessity of testing for content uniformity of the capsules is a regulatory concern because each capsule is zeroed before the API is dispensed, and the system automatically rejects filled capsules that are outside the set weight-variation range. The time needed to qualify an assay and impurities method is short because of the absence of excipients. Even the API assay method

can be qualified for product release, provided the amount of API in the capsules is not low. A low amount of API might require dissolving the capsule to obtain the complete amount of API in the flask. All these aspects reduce the time needed for chromatographic analysis. A quick disintegration test may be sufficient for dissolution testing, rather than a complete dissolution method. Lastly, if the amount of API in a capsule is low, then moisture-content testing will require a large number of capsules.

The capsule filler’s software is designed to meet 21 *CFR* Part 11 audit-trail and password-protection requirements. Because a specified amount of API is weighed into each capsule, the process produces minimal wastage compared with tablet presses or encapsulators. Little API remains in the hopper, which minimizes loss.

Drug in a bottle

Often an API is poorly water soluble and has poor dispersibility characteristics, which makes reconstitutable suspension an option. If the API is soluble in one of the readily marketed oral syrup vehicles such as “Ora-Sweet” (a combination of sucrose, glycerin, and sorbitol, Paddock Laboratories, Minneapolis, MN), then the filling of the dispensing bottles with an API may be an option to consider. The technique does not involve formulation work, and because the dispensing bottles are only filled with the API at the contract research organization’s (CRO’s) site, it saves time and cost. A pharmacist or clinician administering the dose can dilute filled bottles with Ora-Sweet or a polymer dispersion containing methylcellulose, sodium carboxymethylcellulose, or mineral oil. Another advantage of the dispensing-bottle option is that multiple doses can be dispensed in the clinic and taken home by patients, if required. Reconstituting multiple doses at the clinic means less frequent visits of the clinical subjects to the clinic site.

One option for evaluating taste is using an electronic tongue (e.g., “Astree Electronic Tongue,” Alpha M.O.S., Toulouse, France). The electronic-tongue taste evaluation quantifies the



Figure 2: The “CFS 1200” unit for filling and sealing liquids or semisolids into capsules.

bitterness of the API, helps develop suitable matching bitter placebos for blinded clinical trials, and helps optimize taste-masked formulations (3). This investigation may lead to the inclusion of a sweetener such as sucrose, fructose, a polyol (sugar alcohol) such as mannitol, or a high-intensity sweetener such as aspartame or saccharine (4). It may be necessary to include an excipient such as ethanol or glycerin to wet the surface of the API particles before the vehicle is added, thereby increasing the API's solubility in the vehicle.

Filling API in a dispensing-bottle manufacturing process is neither complicated nor time-consuming. The time for assay-method development is short because excipients interfere less during method qualification. The excipients may be a sweetener and a vehicle such as Ora-Sweet. When a bottle contains API and excipients, a minimum amount of developmental stability data are needed because the API in a bottle is manufactured in a CRO facility and the volume is prepared by the pharmacist or a clinician administering the dose. Once the bottles are prepared at the clinic and given to clinical subjects, they are consumed in a specified amount of time, which further reduces the requirement for developmental stability data. The general tests are appearance, completeness of solution, pH, microbial limits, assay, and impurities.

If early clinical data indicate a need to bypass first-pass metabolism, spraying a suspension below the tongue mucosal area is suggested (5). Considerations of taste-masking, solubility, mucoadhesive excipients, and local irritation by the API should be evaluated before choosing the approach of spraying a suspension. A quick evaluation using an electronic tongue and a Franz-type diffusion study should be conducted to provide additional taste and mucosal-layer diffusion data (6).

Liquid in a capsule

Liquid in a capsule is a method for not only improving the bioavailability of poorly water-soluble compounds, but also for enhancing low-melting point and low-dose–high-potency drug candidates. The challenge of this approach is solubilizing the API in a favorable surfactant, solvent, and cosolvent system.

When it comes to solubility, the rule of thumb is “like dissolves like.” Physical mixtures, solid solutions, solid dispersions, or a self-microemulsifying drug-delivery system may be used (7). The developed system can be filled into appropriately sized capsules and banded (e.g., “STI Lab Model” capsule bander, Schaefer Technologies, Indianapolis, IN) or filled and sealed (e.g., “CFS 1200” encapsulator, Capsugel, see Figure 2).

Banding capsules using the STI Lab Model can be manual or semiautomatic. The process involves a significant amount of labor and additional time for drying the capsules. The CFS 1200 machine uses liquid encapsulation microspray sealing technology (“LEMS,” Capsugel) to create a robust and an impervious capsule seal (8). The process involves spraying approximately 50 μL of a water–ethanol microspray solution to penetrate the space surrounding the cap and the body joint of the capsule. The melting point must be lowered at the sealing area of the capsule. The entire filling and sealing process is quickly completed (0.33 s/capsule) with warm air (40–60 °C) gently blown across the capsule body and cap-joint surface to form a seal.

The CFS 1200 encapsulator, which operates at a speed of 1200 capsules/h, completes early-phase batches in 1–2 days. A high dose or a poorly soluble compound can be accommodated to a volume range between 0.1 and 1.2 mL in capsule sizes between 000 to 4. Another advantage of the CFS 1200 unit is its ability to fill a liquid between 20 and 70 °C, which makes it suitable for a semisolid dosage form as well. A semisolid formulation with excipients such as polyethylene glycol (“Carbowax Sentry,” The Dow Chemical Company, Midland, MI) or polyoxyglycerides (“Gelucire,” Gattefossé, Paramus, NJ) can enhance bioavailability to attain positive clinical data (9).

Capsugel used the “Coni-snap” two-piece hard-gelatin capsule as the basis for its “Licaps” product, which is more suitable for liquid fills. Licaps is a six-dimple design that protects the filled material from leaking into the zone between the body and the cap of the capsule. It also has the low oxygen permeability necessary to protect the liquid system from oxidation (10).

Including a placebo in a developmental stability study is recommended to justify any chemical data surprises. The stability study is worth initiating for both gelatin and hydroxypropyl methylcellulose capsules. The benefits of the developed liquid-in-capsule process can be well supported for large-scale manufacturing by high-speed commercial equipment such as “IN-CAP 130-01” Dott. Bonapace, Milan), “MG2 Futura” (Futura, MG America, Fairfield, NJ), and “Liqfil Super Hicapseal” (40 and 100 models, Qualicaps, Whitsett, NC).

Binary blends

Manufacturing multiple binary blends is another option to expedite formulation development for immediate-release products. Binary-blend prototypes are combinations of API and an excipient encapsulated with a manual process using encapsulators such as “Feton” (ChemiPharm, Ramsey, NJ) or “MF30” (Pam Pharmaceuticals and Allied Machinery Company, Kandivli, Mumbai), which are capable of manufacturing thousands of capsules for early-phase clinical trials. This technique not

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only serves the goal of acquiring API, excipient, and capsule compatibility data, but is a short process that can save development time.

Assay and impurities methods can be developed and qualified quickly because there is less interference from excipients. With minimal analytical work, the final product can be at the clinic in 11–12 weeks. When the API enters clinical trials, the clinical data obtained by using binary blends provide a starting point for the development of a commercially acceptable dosage form such as a tablet or a capsule.

Conclusion

The methods of active pharmaceutical ingredient in a capsule, drug in a bottle, liquid in a capsule, or multiple binary blends provide options for getting drug product into the clinic in a short period of time. Although not all the options are capable of reaching commercial scale, they are all capable of supporting early clinical studies and may be used as a path to an eventual commercial dosage form.

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