Rethinking neat-API capsule filling for Phase I clinical trials

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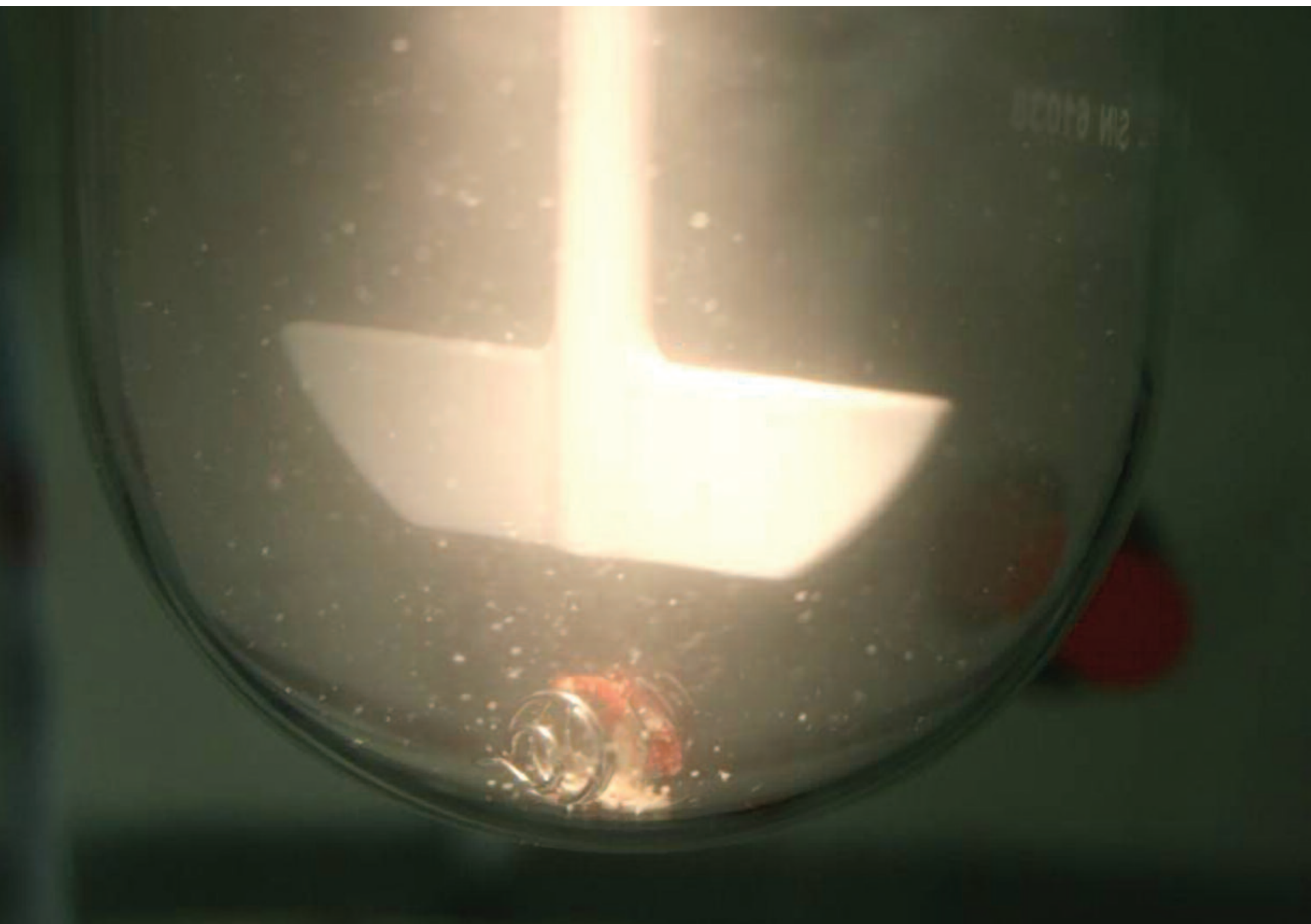

This article discusses the advantages and the disadvantages of filling capsules with a neat active pharmaceutical ingredient (API) for Phase I clinical trials. A case study illustrates when it is not appropriate to prepare neat-API capsules.

Pharmaceutical companies seek methods that accelerate or increase the efficiency of drug development. One method is filling a neat API—that is, without excipients or other ingredients—into hard gelatin capsules. This method has many names, including powder in capsule (PIC), API in capsule, active in capsule, and chemical in capsule. PIC is used in this article.

Many articles and presentations discuss the advantages of PIC, which include getting drug candidates into Phase I clinical trials 3 to 6 months faster than conventional methods and decreasing cost [1-4]. However, its disadvantages are not as widely discussed. This article includes a case study that illustrates when this method is not ideal.

Equipment, method

Over the last decade, very precise, low-dose powder filling equipment was developed to prepare drug candidates for Phase I clinical trials. Equipment includes Xcelodose 120S and 600S (Capsugel, Greenwood, SC), Quantos (Mettler-Toledo, Columbus, OH), and Powdernium (Freeslate, Sunnyvale, CA). Xcelodose, which

opens, fills, and closes the capsules, performs so well that it seems to be driving an industry-wide shift from conventional methods to PIC for preparing early clinical trial materials [5]. In fact, nine of the top 10 pharmaceutical companies owned Xcelodose equipment in 2009 [1]. In addition, nearly every contract development organization (CDO) states on its website that it fills neat API into bottles or capsules for early clinical trials, and most CDOs advertise that they own low-dose powder filling equipment. Clearly, PIC has some advantages.

Advantages. PIC gets drug candidates into Phase I clinical trials 3 to 6 months faster than conventional methods [1]. It minimizes technical problems and delays by postponing pre-formulation work, such as excipient compatibility studies, and much of formulation and analytical method development [6-9]. It facilitates drug-candidate screening as outlined in the FDA's Critical Path Initiative strategy, which encourages allowing APIs to fail quickly [10]. PIC also decreases the cost of getting drug candidates into Phase I clinical trials [6]. It conserves the amount of API needed and allows dose adjustments [8, 9]. It eases blinding of clinical trial materials and permits the safe handling of highly potent compounds [6, 7]. Less discussed are PIC's drawbacks.

Disadvantages. PIC may not be suitable for poorly soluble APIs rated Class II or IV under the Biopharmaceutics Classification System (BCS) [6, 9, 11-13]. It also may not be suitable for high-dose, low-bulk-density APIs; APIs that agglomerate or hold a static charge; and APIs that are micronized, sensitive to moisture, or incompatible with gelatin [7, 11, 12, 14, 15]. Indeed, PIC may be suitable only for Phase I clinical trials [6]. For Phase II clinical trials or beyond, it may slow the overall clinical program and increase the total development cost [6, 11, 16]. Furthermore, it does not eliminate the need to develop a formulation and a process, and it may not follow the FDA's guidelines, "International Conference on Harmonization (ICH) Q8 (R1) Pharmaceutical Development" and "ICH Q9 Quality Risk Management" [6].

Comparing the advantages and the disadvantages of PIC reveals two major contradictions. One contradiction is that PIC gets drug candidates into Phase I clinical trials 3 to 6 months faster than conventional methods yet it may slow the overall clinical program. The other is that PIC decreases the cost of getting drug candidates into Phase I clinical trials yet it may increase the total development cost. The contradictions are largely due to undefined milestones. If the milestone is Phase I clinical trials, and that is truly the final goal, then PIC saves time and money. That is especially true for companies that have conservative timelines and risk management. CDOs experienced in fast-track formulation, however, will save only about 2 to 3 months instead of 3 to 6. If the milestone is Phase II clinical trials or beyond, then PIC simply postpones the real development work, slowing the overall clinical program—which can include NDA filing and approval—and increasing the total development cost [11, 16, 17].

PIC may also lead to a false negative pharmacokinetic result for poorly soluble APIs, compelling companies to terminate the development of a potentially valuable drug and cause additional delays and expense [11]. In other situations, PIC allows companies to quickly kill drug candidates [10]. The likelihood of clinical success plays a role in whether to use PIC for this reason. Companies bet on the success of their drug candidate if they believe it is exceptional or there is promising safety or efficacy information. Companies bet against the success of their drug candidate if the candidate has no better chance than other candidates and the companies have numerous candidates to screen. PIC quickly gets the drug candidates into Phase I clinical trials: If the results are discouraging, then PIC saves time and money and the next drug candidate can be screened. However, if the results are promising, then companies may face a significant amount of work to get the drug candidates into Phase II clinical trials and beyond. Because of this, companies betting on the success of their drug candidates should use caution when considering PIC.

Furthermore, in cases where PIC is the logical choice, companies need to consider whether it meets the Quality by Design (QbD) requirements in the FDA's guidance on pharmaceutical development [18]. According to the FDA, the guidance "does not apply to contents of submissions for drug products during the clinical research stages of drug development. However, the principles in this guidance are important to consider during those stages as well." In fact, many companies incorporate elements of QbD in early regulatory submissions (e.g., IND/IMPD/CTA). However, PIC is not the simple, early approach to clinical dosing that it seems: The potential for inappropriate use makes it necessary to conduct a risk assessment, like a First Time in Man formulation decision tree [7]. The assessment should evaluate the basic biopharmaceutical and physicochemical attributes of the drug candidate for PIC suitability [6]. Attributes include particle size, solubility, bioavailability, tendency to agglomerate or hold a static charge, moisture sensitivity, and gelatin compatibility, among others. The assessment is especially important for relatively insoluble APIs rated BCS Class II or IV, in which dissolution-rate limited absorption could be a factor [11].

Case study

The purpose of the case study—first published as a poster at the 2009 American Association of Pharmaceutical Scientists Annual Meeting and Exposition in Los Angeles, CA—was to discover whether the in vitro dissolution of a neat API rated BCS Class II was slower than that of capsules containing a formulation with the same API.

One reason PIC could inhibit in vitro dissolution is API agglomeration, resulting in a much larger effective particle size and smaller effective surface area. (The term "effective" relates to the area of the particle that comes into contact with media.) Agglomeration is not unusual, especially since poorly soluble particles are frequently milled or micronized to improve their dissolution-rate

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limited absorption. That concept is the basis of the Noyes-Whitney dissolution-rate equation:

$$DC/dt \quad \frac{D_c S (C_s - C)}{h}$$

where

D_c diffusion co-efficient of API in the medium

S surface area of API

C_s solubility of API in diffusion layer

C concentration in the medium

h thickness of diffusion layer that surrounds the dissolving dosage form.

To test this theory, two batches of 100-milligram (mg) potency capsules were prepared and dissolved. One batch included hard gelatin capsules that contained only the micronized API. The other batch included hard gelatin capsules that contained the micronized API, partially pre-gelatinized corn starch (Starch 1500, Colorcon, Harleysville, PA), microcrystalline cellulose (Avicel PH102, FMC BioPolymer, Philadelphia, PA), sodium starch glycolate (Explotab, JRS Pharma, Patterson, NY), colloidal silicon dioxide (Cab-O-Sil M5P, Cabot, Boston, MA), sodium lauryl sulfate, and magnesium stearate. The formulation was designed to assist the dispersion, wetting, and dissolution of the API. Table 1 lists the ingredients and their functions.

The neat-API capsules were prepared in two steps. First, the micronized API was placed in a weigh-boat and weighed. Second, 100 mgs of the API was manually scooped into size 0, opaque, Swedish orange hard gelatin capsules, which were then manually capped.

The capsules containing the formulation were prepared in four steps. First, the excipients and the micronized API were separately weighed and sieved through a 20-mesh screen. Second, the excipients (excluding the magnesium stearate) and the API were blended for 15 minutes. Third, the excipient-API formulation was blended with magnesium stearate for 5 minutes. Fourth, a Dott. Bonapace Minicap 100 capsule filler (Schaefer Technologies, Indianapolis, IN) filled the formulation into size 0, opaque, Swedish orange hard gelatin capsules to 390 mgs, delivering 100 mgs of the API.

The capsules were observed during six 45-minute dissolution tests, and the percentage of label strength (LS) that dissolved was measured every 15 minutes.

Results

The appearance of the micronized API, both to the naked eye and under a microscope, differed greatly from that of the formulation prior to encapsulation. Figure 1 shows the micronized API, which agglomerated into particles about 0.5 to 3 millimeters in diameter, and the formulation, which remained a fine powder. Figure 2 shows micrographs of the micronized API and the formulation. Again, the micronized API had a much larger effective particle size and smaller effective surface area than the formulation.

Table 2 clearly shows that the neat-API capsules dissolved slower and less thoroughly than the capsules containing the formulation. After 7 minutes, both capsules ruptured and dispersed their contents into the media. The neat-API capsules ejected large agglomerates, and the capsules containing the formulation ejected fine particles. After 45 minutes, the vessel with the neat-API capsules displayed more non-dissolved API at its bottom than the vessel with the capsules containing the formulation (photo on page 8). At the end of the six dissolution tests, the mean percentage of LS that dissolved was 72.7 percent for the neat-API capsules and 93.1 percent for the capsules containing the formulation.

In closing, PIC was not appropriate for the poorly soluble API because the neat-API capsules resulted in slower, more erratic, and less thorough in vitro dissolution than the capsules containing the formulation. Although the clinical relevance of the distinction is unknown, inhibited in vitro dissolution may yield reduced in vivo dissolution,

TABLE 1

Ingredients and their functions

Ingredient	Typical function	Amount per capsule (mg)
X, micronized	API	100.0
Partially pre-gelatinized corn starch[a]	Diluent, binder	139.6
Microcrystalline cellulose[b]	Diluent	127.0
Sodium starch glycolate[c]	Super-disintegrant	11.70
Colloidal silicon dioxide[d]	Glidant	3.900
Sodium lauryl sulfate	Surfactant	3.900
Magnesium stearate	Lubricant	3.900
Hard gelatin capsules[e] (size 0, opaque, Swedish orange #4188)	Carrier	1 capsule

a = Starch 1500, Colorcon, Harleysville, PA
b = Avicel PH102, FMC BioPolymer, Philadelphia, PA
c = Explotab, JRS Pharma, Patterson, NY
d = Cab-O-Sil M5P, Cabot, Boston, MA
e = Coni-Snap, Capsugel, Greenwood, SC

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Figure 1

Appearance of the API and the formulation (no magnification)

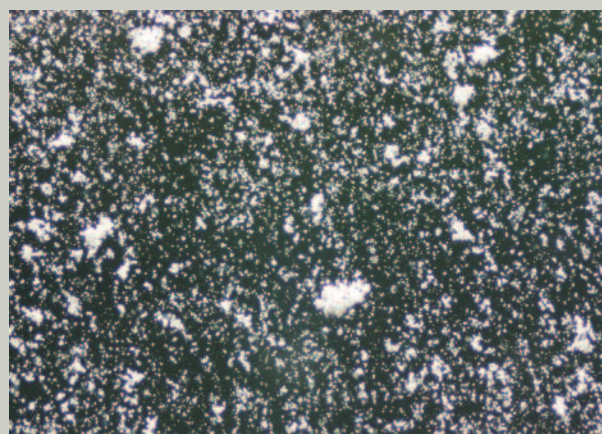
a. Micronized API (agglomerated)

b. Fine powder formulation

Figure 2

Appearance of the API and the formulation (40 magnification)

a. Micronized API (agglomerated)



b. Fine powder formulation

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Table 2

Percentage of label strength dissolved

	Neat-API capsules			Capsules containing formulation		
	15 min	30 min	45 min	15 min	30 min	45 min
1	33.5	55.9	73.3	70.2	89.4	95.4
2	28.8	51.7	67.0	68.7	87.7	94.0
3	52.6	75.6	86.5	68.1	86.7	92.9
4	35.7	59.2	70.8	67.2	85.1	91.2
5	46.0	64.7	76.1	67.0	84.8	90.7
6	28.1	46.6	62.3	70.4	88.4	94.4
Average	37.5	59.0	72.7	68.6	87.0	93.1
SD	9.83	10.24	8.33	1.45	1.83	1.85
RSD	26.3	17.4	11.5	2.1	2.1	2.0
Minimum	28.1	46.6	62.3	67.0	84.8	90.7
Maximum	52.6	75.6	86.5	70.4	89.4	95.4
Range	24.5	29.0	24.2	3.4	4.6	4.7

resulting in highly variable and limited bioavailability. As a result, PIC could slow the overall clinical program and increase total development cost. However, PIC provides numerous advantages when used appropriately and should still be considered when preparing drug candidates for Phase I clinical trials. *T&C*

References

1. Micro-dosing equipment fills niche in R&D, clinical trial materials, Tablets & Capsules, (March 2009), pp. 22-24.

2. Xcelience reduces time to Phase I studies by 17 weeks using API into capsule services, website: www.xcelience.com.

3. Several articles that discuss Xcelodose can be found at www.capsugel.com.

4. Fagan, P., Hood, M., Johnson, J., and Woolven, H. An assessment of the suitability of the Xcelodose 600 in the filling of blended products, The American Association of Pharmaceutical Scientists Journal, (November 2006), abstract 2942.

5. Bryant, S., et al. Advances in powder-dosing technology, Innovations in Pharmaceutical Technology, (June 2002), pp. 95-100.

6. Perspectives on accelerated early drug development using precision neat drug substance filling equipment, website: www.aaipharma.com.

7. Hariharan, M., et al. Reducing the time to develop and manufacture formulations for first oral dose in humans, Pharmaceutical Technology, (October 2003), pp. 68-84.

8. Skultety, P. Formulation development options to the clinic, Contract Pharmacal, (June 2009).

9. Edwards, D. Accelerating drug development with precision dosing techniques, Pharmaceutical Manufacturing and Packing Sourcer, (Autumn 2004), pp. 46-50.

10. Edwards, D. Shortening timelines to Phase I formulation, Innovations in Pharmaceutical Technology, (May 2009), pp. 74-76.

11. Ruff, M., Xian, G., and Vinson, R. The case against powder (active only) in capsule Phase I formulations for poorly soluble drugs: A comparison of in-vitro dissolution, The American Association of Pharmaceutical Scientists Journal, (November 2009), abstract 3145.

12. Wang, J. and Lee, Y. First in human (FIH) oral drug product design and delivery, American Association of Pharmaceutical Scientists Annual Meeting and Exposition, (November 2008), PowerPoint presentation.

13. Kadri, B. Recent options for Phase I formulation development and clinical trial material supply, Pharmaceutical Technology, (August 2008).

14. Beale, D., Woods, P., and Edwards, D. Can automated API dose dispensing be accurate at 10 µg?—An analysis of limiting factors, The American Association of Pharmaceutical Scientists Journal, (November 2009), abstract 2995.

15. Mouro, D., et al. Enhancement of Xcelodose capsule-filling capabilities using roller compaction, Pharmaceutical Technology, (February 2006).

16. Daviau, T. API in capsule vs. the lost art of formulation development, website: www.corerxpharma.com.

17. Daviau, T. Is the API in capsule method overshadowing the science of formulation development?, Life Science Leader, (January 2010).

18. International Conference on Harmonization–Q8 (R1) Pharmaceutical Development, website: www.fda.gov.

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