



The Case Against Powder (Active Only) in Capsule Phase I Formulations for Poorly Soluble Drugs: A Comparison of *In-Vitro* Dissolution

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OBJECTIVE

The objective is to compare the *in-vitro* dissolution of non-formulated powder (active only) in capsule against that of a formulated capsule in the case of a poorly soluble drug intended for Phase I trials.

BACKGROUND

Powder (active only) in capsule (PIC) is an increasingly popular approach for first-time in man/Phase I clinical trials. This allows the sponsor to skip time-consuming formulation and analytical development activities and proceed directly into Phase I trials.

However, in the case of poorly soluble compounds (BCS Category II and IV) a PIC approach may result in relatively poor *in-vitro* dissolution compared to a formulated dosage form. One possible reason is the tendency of the active (API) to agglomerate, resulting in a much larger effective (what presents to the media) particle size and significantly decreased effective surface area. Agglomeration is not unusual, especially since poorly soluble compounds are frequently milled or micronized to improve their dissolution-rate limited absorption, the basis of which is the Noyes Whitney dissolution rate equation:

$$DC/dt = \frac{DcS}{h} (Cs-C) \quad \text{whereby,}$$

C= Concentration at time t

Dc= Diffusion coefficient of drug in the medium

S= Surface area of drug particles

Cs= Solubility of API in diffusion layer

h= Thickness of diffusion layer that surrounds the dissolving dosage form

Micronizing or milling of the API is performed to reduce the particle size, which results in an increase in S and dissolution rate (DC/dt). The implication of impaired *in-vitro* dissolution is that it may result in reduced *in-vivo* dissolution resulting in highly variable and limited bioavailability. Rather than accelerate the clinical program, this may actually result in clinical delays or the unnecessary termination of the clinical program.

To test the *in-vitro* aspect, a comparison was performed of the *in-vitro* dissolution between PIC and formulated capsules of a poorly soluble compound intended for use in Phase I clinical trials.

METHODS

Materials

Active Pharmaceutical Ingredient (API), micronized
Pregelatinized Starch, NF (Starch 1500[®]), supplied by Colorcon
Avicel[®] Microcrystalline Cellulose, NF (Avicel[®] PH102), supplied by FMC
Sodium Starch Glycolate, NF (Explotab[®]), supplied by JRS Pharma
Colloidal Silicon Dioxide, NF (Cab-O-Sil MP5), supplied by Cabot Corp.
Sodium Lauryl Sulfate, NF, supplied by Spectrum
Magnesium Stearate, NF (non-bovine Hyqual[®]), supplied by Mallinckrodt
Capsule, Empty Hard Gelatin, Size 0, Swedish Orange (4188), Opaque, Coni Snap,
supplied by Capsugel
Various reagent grade chemicals and solvents to execute required analytical testing

Manufacturing Equipment

Bonapace MiniCap 100 Capsule Machine
20-mesh Hand Screen
Various Mettler and Sartorius Analytical Balances.

Analytical Equipment

USP Apparatus II (Paddles) Dissolution Bath
Standard Gradient HPLC System with Zorbax Aq Rapid Resolution Column, 3.5 μ m, 50 x 4.6 mm i.d.
Olympus BX51 Microscope with DP71 Digital Camera and Image-Pro Software
Malvern Mastersizer S, Particle Size Analyzer
Canon EOS Digital Rebel Xti Camera, approx. 10.50 megapixels with:
EF 28-135mm f/3.5-5.6 IS USM Lens, 28-135 mm 1:3.5-5.6 Focal Length & Maximum Aperture and EF 50 mm f/1.8 II Lens, 50 mm 1:1.8 Focal Length & Maximum Aperture

Physical-Chemical Characteristics of API

Mw: 448
Solubility in water, 37°C: 1.08 μ g/mL
Solubility in SGF (pH 1.2): 187 μ g/mL :
Solubility in Ethanol: 1 mg/mL
pKa:~4
Bioavailability (oral) : 30-50% (rat)
Particle size: See Table 2

Test Subject Batches

Two batches of 100 mg potency capsules were prepared. One batch contained only the micronized active ingredient (API) in a hard gelatin capsule. This batch will be referred to as the PIC (powder in capsule) batch. The other batch was a conventional hard gelatin capsule formulation containing: micronized API, Starch 1500, Avicel, Explotab, Cab-O-Sil, sodium lauryl sulfate and magnesium stearate. This formulation was designed to assist in the dispersion, wetting and dissolution of the API. See Table 1 for a list of ingredients and their functions in the formulated capsules.

Table 1: Formulation

Ingredient	Typical Functionality	Amount per Capsule (mg)
X, micronized	API	100.0
Starch 1500	Diluent, Binder	139.6
Avicel PH102	Diluent	127.0
Explotab	Super-disintegrant	11.70
Cab-O-Sil M5P	Glidant	3.900
Sodium Lauryl Sulfate	Surfactant	3.900
Magnesium Stearate	Lubricant	3.900
Capsules, Empty, Hard Gelatin, Size 0, Swedish Orange (4188), Opaque, Coni Snap	Carrier	1 Capsule

Manufacturing Process

Formulated Capsules were manufactured as follows:

1. Excipients and micronized API were weighed out and screened through a 20 mesh screen.
2. Excipients (excluding the magnesium stearate) and API were blended together for 15 minutes.
3. Resulting blend was blended with magnesium stearate for 5 minutes.
4. Blend was filled into Size 0, Swedish Orange, opaque, hard gelatin capsules using a Bonapace Minicap 100 Capsule Machine to a fill weight to deliver 100 mg of API.

PIC Capsules were manufactured as follows:

1. A sufficient amount of the same lot of micronized API was weighed out. and placed in a weigh-boat.
2. API was filled, as is, into the same lot of Size 0, Swedish Orange, opaque, hard gelatin capsules used for the formulated capsules. Capsules were filled manually using a dredging method whereby the capsule body was used as a scoop to fill to the target weight of 100 mg and then capped manually.

Visual Appearance of Blend

The micronized API and the formulated blend were compared on a black background. Digital images (see Figure 1 and 2) were taken in their “as-is” form with a Canon digital camera with EF 28-135mm, f/3.5-5.6, IS USM lens. Method Reference: Metrics NB 09/665-021.

Optical Microscopy

Photomicrographs of the micronized API and the formulated blend were taken using an Olympus BX51 Microscope coupled with a DP71 Digital Camera and Image-Pro software with a total magnification of 40x. Pictures were taken dry with no dispersant (see figure 3 and 4). Method Reference: Metrics NB 09/665-036.

Particle Size Analysis

The particle size of both blends was measured using a Malvern Mastersizer and a validated wet method including 1:1000 v/v Tween 80 in water dispersant. Two sample preparations (no sonication and 30 seconds sonication) of API and formulated blend were prepared. Particle distributions were generated per USP <851> (see Table 2). Method Reference: Metrics NB 09/665-036.

Dissolution Method

USP Apparatus II (paddles), 100 rpm with sinkers. Media: 2% w/v SDS in water; 37°C±0.5°C. n= 6 capsules. Samples were pulled at 15, 30 and 45 minutes. Method Reference: Metrics NB 09/511-006.

Dissolution Visual Appearance

Photographs were taken of the dissolution of the capsules at various time intervals using the cameras and settings defined under Analytical Equipment.

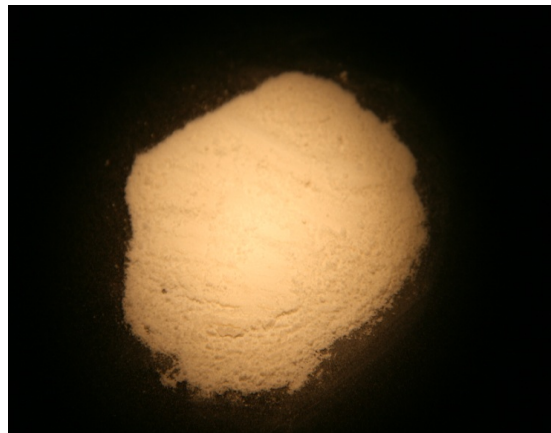
RESULTS AND DISCUSSION

Visual Appearance of Blend

Figure 1-API



Figure 2 – Formulated Blend



The visual appearance of the two materials just prior to encapsulation is quite different. The micronized API in Figure 1 is clearly agglomerated. Agglomerates are approximately 0.5 to 3 mm in diameter. By comparison the formulated blend in Figure 2 consists of a fine powder with the micronized API dispersed throughout the blend.

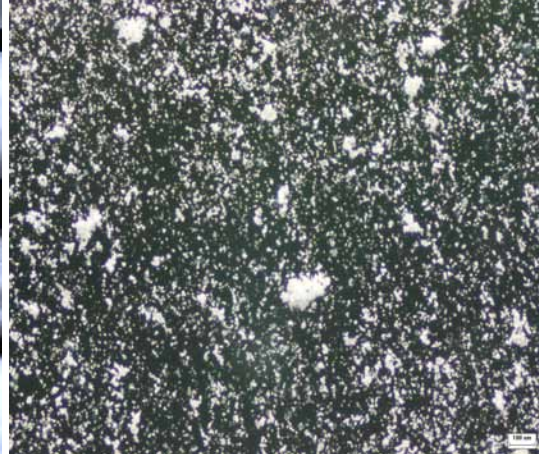
Optical Microscopy

Figures 3 and 4 are photomicrographs of micronized API and the formulated blend.

Figure 3
API



Figure 4
Formulated Blend



The above photomicrographs were taken using 40x magnification. Again, the agglomerated API is shown to have a much larger effective particle size (and reduced effective surface area) than the blend.

Particle Size Analysis

The particle size of the fill materials for the two batches was measured by Malvern Mastersizer. The results are as follows:

Table 2: Malvern Particle Size (volume mean diameter)

	PIC (um)		Formulated Blend (um)	
	no sonication	30s sonication	no sonication	30s sonication
D10	0.38	0.40	16.64	8.51
D50	7.57	6.29	129.64	93.14
D90	17.29	12.80	275.31	260.76

Interestingly, the Malvern shows the opposite result as the visual and microscopic photos. The particle size of the API (PIC) is shown to be much smaller than the formulated blend. One possible explanation is that the Malvern process (sonicated or not) was sufficiently energetic to break down the agglomerates seen in the API. However, the Malvern results do confirm the micronized nature of the API, with most of the material sub-10 micron.

Dissolution

Table 3: PIC (API only)

	15 min	30 min	45 min
1	33.5	55.9	73.3
2	28.8	51.7	67.0
3	52.6	75.6	86.5
4	35.7	59.2	70.8
5	46.0	64.7	76.1
6	28.1	46.6	62.3
Average	37.5	59.0	72.7
SD	9.83	10.24	8.33
%RSD	26.3	17.4	11.5
Minimum	28.1	46.6	62.3
Maximum	52.6	75.6	86.5
Range	24.5	29.0	24.2

Table 4: Formulated Capsule

	15 min	30 min	45 min
1	70.2	89.4	95.4
2	68.7	87.7	94.0
3	68.1	86.7	92.9
4	67.2	85.1	91.2
5	67.0	84.8	90.7
6	70.4	88.4	94.4
Average	68.6	87.0	93.1
SD	1.45	1.83	1.85
%RSD	2.1	2.1	2.0
Minimum	67.0	84.8	90.7
Maximum	70.4	89.4	95.4
Range	3.4	4.6	4.7

Clearly, the dissolution of the PIC is slower and less complete under this dissolution method. The mean % dissolved for the PIC at 15 minutes was only 37.5% Is, while that of the formulated capsules was 68.6%. In addition, the inter-capsule variability at 15 minutes for the PIC was significantly greater (26.3%RSD) than the formulated capsule (1.45%RSD).

At the final, 45 minute time point, the mean dissolution of the PIC (72.7% Is) was still slower, more variable, and less complete than the formulated capsules (93.1%Is).

Note: The dissolution method was designed to be a discriminating *in-vitro* method that would provide a profile over 45 minutes. It is unknown if the method is biorelevant or if an *in-vivo/in-vitro* correlation (IVIVC) is possible.

Dissolution Visual Appearance

The appearance of the capsules during dissolution appear in Figures 9-18

Figure 9 – PIC, Initial



Figure 10 – Formulated Capsule, Initial

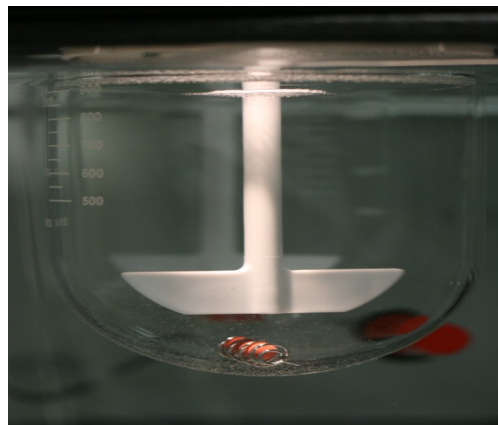


Figure 11 – PIC, T = 7 mins

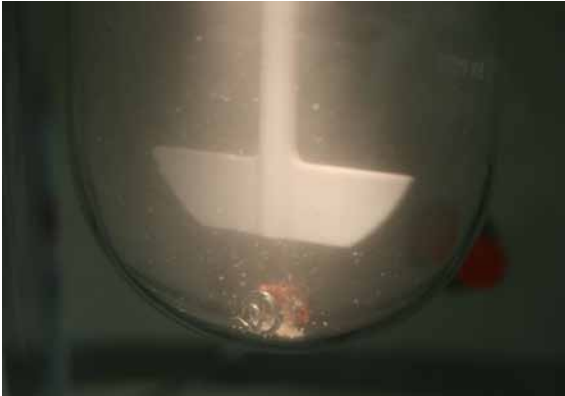


Figure 10 – Formulated Capsule, T = 7 mins

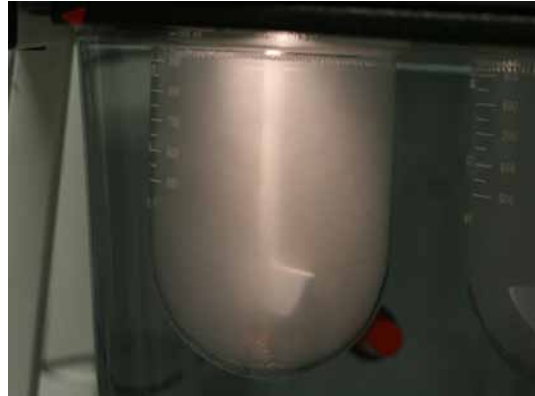


Figure 13 – PIC, T = 15 mins

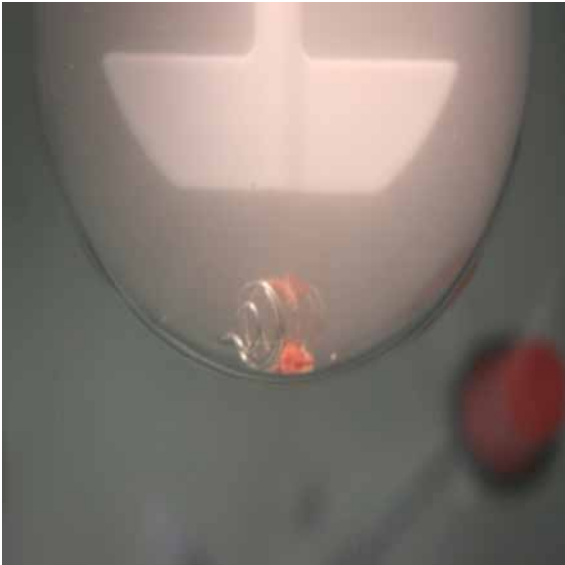


Figure 14 – Formulated Capsule, T = 15 mins

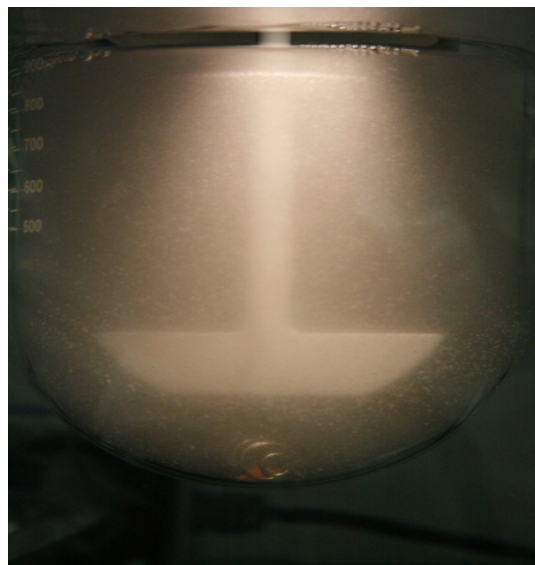


Figure 15 – PIC, T = 30 mins



Figure 16 – Formulated Capsule, T = 30 mins

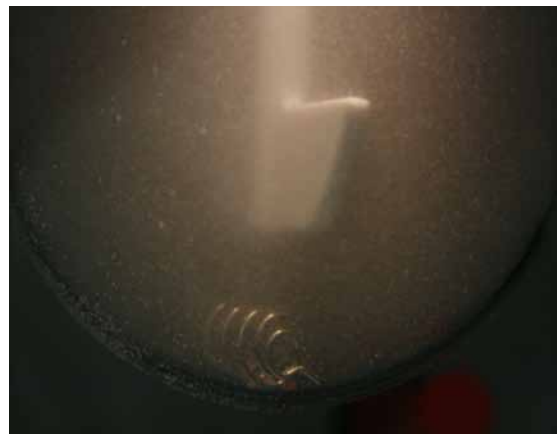
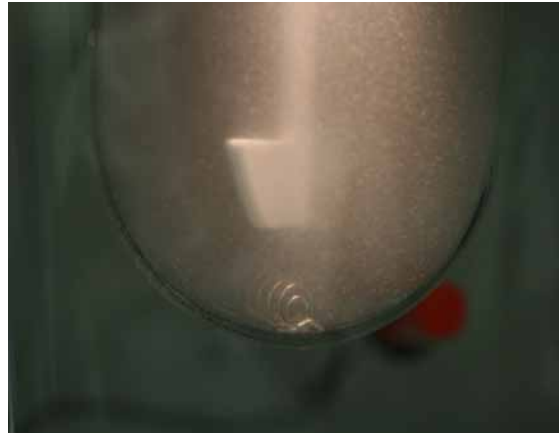


Figure 17– PIC, T = 45 mins

Figure 18 – Formulated Capsule, T = 45 mins



After only 7 minutes, the shells of both products have ruptured and contents are being dispersed into the media. Large agglomerates of API are visible in the PIC vessel, whereas finer particles are noted in the formulated product. At each time point, the PIC vessel appears to have less visible dispersed material than the formulated product. At 45 minutes, there is significantly more undissolved /undispersed API present in the bottom of the PIC vessel. These visible observations correlate well with the analytical results showing that the PIC has slower and less complete dissolution than the formulated product.

CONCLUSIONS

For this poorly soluble compound, a powder in capsule (API only) presentation had significantly slower, more erratic and less complete *in-vitro* dissolution than a formulated capsule. Although the clinical relevance of this difference is unknown, it is theoretically possible this could impact *in-vivo* dissolution-rate limited absorption and result in unacceptable Phase I clinical results. Therefore, for such compounds (BCS Category II and IV), a powder in capsule approach, while allowing early entry into Phase I, may actually delay the overall clinical program.