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Research Article

Towards Integrated Drug Substance and Drug Product Design for an Active Pharmaceutical Ingredient Using Particle Engineering

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Abstract. A novel experimental approach describing the integration of drug substance and drug production design using particle engineering techniques such as sonocrystallization, high shear wet milling (HSWM) and dry impact (hammer) milling were used to manufacture samples of an active pharmaceutical ingredient (API) with diverse particle size and size distributions. The API instability was addressed using particle engineering and through judicious selection of excipients to reduce degradation reactions. API produced using a conventional batch cooling crystallization process resulted in content uniformity issues. Hammer milling increased fine particle formation resulting in reduced content uniformity and increased degradation compared to sonocrystallized and HSWM API in the formulation. To ensure at least a 2-year shelf life based on predictions using an Accelerated Stability Assessment Program, this API should have a D [v, 0.1] of 55 μm and a D [v, 0.5] of 140 μm. The particle size of the chief excipient in the drug product formulation needed to be close to that of the API to avoid content uniformity and stability issues but large enough to reduce lactam formation. The novel methodology described here has potential for application to other APIs.

KEY WORDS: chemical stability; crystal engineering; crystallization; formulation; particle size.

INTRODUCTION

Pharmaceutical materials science has emerged as a foundation of Quality by Design (QbD) product development with the solid form, crystallization and particle engineering being core elements linking the final steps of the synthetic pathway of active pharmaceutical ingredient (API) manufacture to the drug product attributes. Crystallization is the final step of the pharmaceutical API manufacture and so from a regulatory perspective must be both controlled and reproducible (1–5). In particular, it must provide API of a suitable quality in terms of both purity and appropriate physical properties for dosage form design and robust product processing. In recent years, a greater interest in the latter aspect has resulted in an emphasis of the link between the solid form, particle engineering and formulation aspects being considered in a more integrated holistic fashion. Theoretical strategies (6,7) have been proposed, but there is little literature regarding the integration of drug substance and drug product using particle engineering. These strategies consider using dry milling to control particle properties but the impact on API stability within the formulation is not considered. Furthermore, a low end particle size specification for APIs is also not typically considered.

With relatively small volumes of high-value products being manufactured, it is unsurprising that batch crystallizers, often in cooling mode, are used almost exclusively in the pharmaceutical industry. Crystallization involves both nucleation and growth and controlling the balance of these two phenomena to influence formulation can be challenging. Many complex organic molecules nucleate slowly (8,9). Batch crystallization, therefore, produces particles that are often too large to meet the specification criteria desired by the formulator and further mechanical size reduction by milling is often required (10). Mechanical size reduction, however, can have significant drawbacks.

Crystal and particle engineering involves the control of the crystallization kinetics (nucleation, growth, agglomeration and breakage). It can also involve using particle engineering technologies such as dry impact and high shear wet milling (HSWM) (11) to reduce particle size via particle breakage and sonocrystallization (12) using ultrasound to direct the generation of the desired morphology and particle size distribution (PSD). These methodologies avoid separate process steps such as dry milling, and they are considered attractive in drug development. Ultrasound has been shown to increase the nucleation rate of organic molecules (13–17) when compared to experimentation carried out without ultrasound (control) and, therefore, produces smaller particle sizes with narrower size distributions.

Significant advances have been made in advancing drug product design by defining relationships between API properties and key formulation aspects. These relationships have been documented, for example, linking particle size distributions with content uniformity (18), powder flow (19), surface

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area and mechanical properties (20,21), dissolution (22) and crystal brittleness and milling behaviour (23). Fines typically tend to have poor flow properties (24) and these could have an adverse effect both on blending and the final tableting or encapsulation processes during drug product manufacture. These relationships combined with development of formulation design practices (25,26) have opened up the potential of an integrated product design process consistent with the emerging QbD philosophy. Particle segregation in blends relating to drug product development has also been discussed (27–29). API targets for these attributes are generally specific to the route of delivery and the dosage form (and in some cases devices) under development.

In this research, we consider a novel particle engineering approach to integrate drug substance and drug product design on a laboratory scale by application of particle engineering technologies. This is compared to conventional crystallization processes to form particles with diverse physical properties *e.g.* particle size and size distribution. The impact of these API physical properties on dissolution rate, content uniformity, blend homogeneity, drug product stability and segregation behaviour within medium-scale drug product formulation is also considered. The aim is to define an API particle size target to meet drug product formulation requirements for scale-up and in particular address API instability and content uniformity challenges. This approach provides a route for equipment selection and to scale up the development process.

MATERIALS AND METHODS

Materials

Two different grades of mannitol (100SD and 200SD) were supplied by Roquette. Talc 200 mesh was supplied by Luzenac.

Equipment

A P500 20 kHz Prosonitron ultrasonic flowcell unit was used at pilot plant scale to manufacture API via a batch cooling crystallization process. The system is used in a recirculation mode and ultrasound introduced at level of 50–150 W/*L* and was used continuously during the cooling crystallization.

A Fitzpatrick Hammer L1A mill was used on a laboratory scale to reduce the particles from the pilot scale conventional batch cooling crystallization process. A 1.6-mm screen size was used with hammers operated in forward mode using an operating speed of 4,000 rpm.

A 1.25- and 4-in. Silverson HSWM was used on a laboratory scale (8,000 rpm) and pilot-scale (4,000 rpm) to reduce particle size post crystallization.

Blending of API and excipients was conducted using a Turbula oscillating mixer. The mode of the mixer was a laboratory Turbula T2F operating at 42 cycles/min using a large securitainer (dimensions 109×130 mm). A high pressure liquid chromatography using a HP 1100 system was used for degradation profiling.

The instability of the API, results in chemical results in chemical degradation when the API particles come into contact with most excipients. Because of this, mannitol and talc were identified as excipients that were compatible with the API. The processing method was also simple to maintain stability, and in this study, capsules were filled by hand. The hand filling process involved weighing excipients and API directly. This ensured that variability in dose, which might arise from using a high-speed automatic capsule filling machine was eliminated. Process control was 'built-in' with the effects of particle size during filling minimised.

Materials Characterisation

Optical light microscopy. An Olympus light microscope with a Nikon camera (Model Eclipse) was used for particle visualisation and image capture.

Particle size distribution. A Sympatec HELOS system was used to measure PSD data. To measure particles, an R6 lens with a size range of 9–1,750 μm was used. A VIBRI feeder in conjunction with a RODOS/M with a 4-mm dispersing line operated at 1.0 bar dispersion pressure was used. Measurements were made in triplicate and showed got reproducibility.

EXPERIMENTAL PROCEDURE

Conventional Batch Cooling Crystallization

The conventional batch cooling crystallization involved using a concentration of 7.14 L/kg API in a 50:50% *v*/*v iso*-propyl alcohol/water solvent mixture. The API was dissolved by heating the starting suspension at a rate of 1°C/min from 20°C to 65°C. The solution was cooled at a rate of 0.3°C/min to 0°C. Nucleation of particles is observed typically between 50°C and 55°C. Furthermore, various process parameters on a laboratory scale such as seed median particle size (10–100 μm), seed load (1–5% *w*/*w*), agitation speed (100–500 rpm), cooling rate (0.1–1°C/min) and concentration (5–15 L/kg) were investigated. Particles with a median size or 50th percentile D [*v*, 0.5] range of 300–600 μm were obtained using the above process conditions. However, smaller particles with a narrow PSD could not be obtained; hence, milling and ultrasound were considered to produce smaller particles.

Continuous Ultrasound

A 5-*L* P500 20 kHz Prosonix ultrasonic reactor was used in recirculation mode with a 500-*L* crystallization reactor. A diaphragm pump was used to circulate the supersaturated solution via the ultrasonic reactor into the main reactor. Ultrasound power was applied continuously using 150 W/*L* to initiate nucleation at 60°C and continuous ultrasound was continued during cooling to 0°C. With the application of ultrasound an increase in the nucleation rate (15) resulted in the formation of smaller more uniformly sized particles with a narrow particle size distribution.

High Shear Wet Milling (Optimal and Non-Optimal)

HSWM was also used at the end of the conventional batch cooling crystallization at 0°C to reduce the particle size and size distribution on a 1 *L* laboratory scale. A mill speed of 8,000 rpm was used to reduce particle size, but a significant amount of fine

particles was produced. To remove the fine particles less than 10 μm which cause stability issues, a temperature cycling step was introduced by heating the suspension to 20°C to dissolve the fines and then cooling to 0°C.

A HSWM process that incorporated the temperature cycling step, forming the basis of an optimised process to remove potential stability issues was transferred to the pilot plant on a 300 *L* scale. The resultant particles from the conventional crystallization were milled at 4,000 rpm for 120 min in combination with temperature cycling.

Hammer Milling

A L1A Fitzpatrick mill was used on a laboratory scale to reduce the size of the API particles obtained from the conventional batch cooling crystallization process. The mill was operated with hammers forward at 4,000 rpm with a 1.6 mm square hole screen. The mill speed was selected in an attempt to minimise level of fine particle formation to minimise the impact on stability.

The different particle engineering processes implemented did not influence the crystallinity and amorphous content. For the various crystallization processes used, the API was dried under vacuum (50 mbar) at 50°C until the water and IPA solvent levels were below 0.2% *w*/*w*. The yields obtained from conventional crystallization, sonocrystallization and HSWM ranged between 85% and 90%. Using various particle engineering methods, the same polymorphic form was achieved with very high crystallinity and amorphous contents between 1% and 2% *w*/*w* using solution calorimetry. The physicochemical properties of the API play no significant role in this work.

RESULTS

Drug Substance Manufacture

Conventional batch cooling crystallization resulted in the formation of wide distribution of particle sizes with D [v, 0.5] ranging from 283 to 605 μm (Table I). The presence of large particles was determined to be the main cause of the content uniformity issues producing a less homogeneous distribution of the API in the blend. This was supported by content uniformity (30,31) modelling. Particle size control using particle engineering was deemed crucial to successful drug product manufacture. This needed to be balanced against the fact that smaller sized particles showed an increased level of degradation products on storage in this study.

Figure 1 shows optical microscopy images of the API particles obtained using various particle engineering technologies. Conventional batch cooling crystallization produced the largest particles consisting of large plates and flakes, typically 300–800 μm in size. Sonocrystallization resulted in the formation of uniformly sized plate particles, typically 100–200 μm in size from optical microscopy. The non-optimised HSWM process generated irregular plate particles and flakes, typically 200–400 μm in size from optical microscopy. Hammer milling resulted in significant particle size reduction when compared to the conventional batch cooling crystallization particles. The particles formed based on optical microscopy were rounded and irregular possibly due to micro-attrition events on the particle edges and are typically 100–300 μm in size. A significant number of fine particles were formed ranging between 1 and 30 μm size range resulting in a bimodal PSD (Fig. 2) when using Hammer milling. These fine particles would have a significant impact on API, blend and drug product stability. The optimal HSWM with temperature cycling process resulted in a reduction of particle size producing particles typically 100–200 μm in size and significant reduction in fine particles in the 1–30 μm range to address both content uniformity and stability issues. HELOS Sympatec PSD measurements (Fig. 2) using the various particle engineering technologies shows the diversity of particle size and size distributions produced. The PSD information complements the optical microscopy. The impact of diverse drug substance physical properties in drug product formulation will be assessed in the following section.

Drug Product Manufacture

Dissolution Modelling

The API has an aqueous solubility of 21 mg/ml, rising to 45 mg/ml at pH 4.0 and 37 mg/ml at pH=10.6 (1) and has been designated as high solubility according to the Biopharmaceutics Classification System and the projected dose (in the range of 5–50 mg) have alleviated any concerns that drug availability *in vivo* might be adversely affected by changes in drug substance PSD. Experimental dissolution studies performed using a 5–50 mg dose resulted in 100% dissolution being achieved in 2–3 min. These experimental resulted were validated using the Johnson dissolution model (22) which assumes spherical particles. The modelling demonstrated that even when extreme parameters are introduced (*i.e.* an API D [v, 0.5]=500 μm and a clinical dose 100 times as large as the anticipated clinical maximum (500 mg)) 100% drug dissolution is achieved within 10 min (Fig. 3).

As the predictive modelling assessment suggests particle size does not influence dissolution rate over the range investigated, the particle engineering methods evaluated are not expected to influence the API dissolution rate.

Content Uniformity Modelling

Modelling was carried out to determine a desired particle size which would minimise the risk of content uniformity issues in the formulation (30,31). The models are based on the use of spherical particles.

The content uniformity model predicted that where the dose strength ranges from 5 to 50 mg, the USP content uniformity requirements will be met if the D [v, 0.5] of the API lies within the 100 to 300 μm range (Fig. 4). For content uniformity of APIs, a standard geometric deviation of 2 is typically targeted. The standard deviation is driven by the narrowness of the PSD of the API as defined in Fig. 4. A narrower PSD translates to a lower standard deviation as defined by the ratio of the d_{90}/d_{50}. A smaller d_{90}/d_{50} corresponds to a lower standard geometric deviation (Fig. 4). These predictions agree with experimental observations in which particles engineered using the conventional batch cooling crystallization (Table I) did not meet the content uniformity specifications.

Table I. Particle Size Distribution Measurements from Various Pilot Plant Batches Using the Conventional Batch Cooling Crystallization Process

Batch no.	D [v, 0.1] [μm]	D [v,0.5] [μm]	D [v, 0.9] [μm]
A	106	283	500
B	73	332	552
C	127	356	601
D	188	580	1,354
E	263	605	1,141

The D [v, 0.1], D [v, 0.5] and D [v, 0.9] is defined as the 10th, 50th and 90th percentile of the particle size distribution on a volume basis

Drug Product (Formulation) Stability

A significant challenge facing the development of this API has been its instability. A shelf life of at least 2 years is required for a drug product to ensure product integrity is maintained throughout the period of clinical evaluation. Initial excipient compatibility studies revealed that lactam formation and Maillard degradation occurred when the API was incorporated into a capsule formulation comprising lactose, talc and starch based on the successful commercially available formulation of a related API with similar stability challenges. In the final formulation, mannitol was selected over lactose as the degradation was reduced. Starch was removed, as it was found to have no effect on the processability or the stability of the capsule formulation. Talc was included for its glidant and flow stabilising properties. Additional studies suggested that the Maillard and lactamisation reactions were surface area related and greater where the ratio of excipients to API was higher.

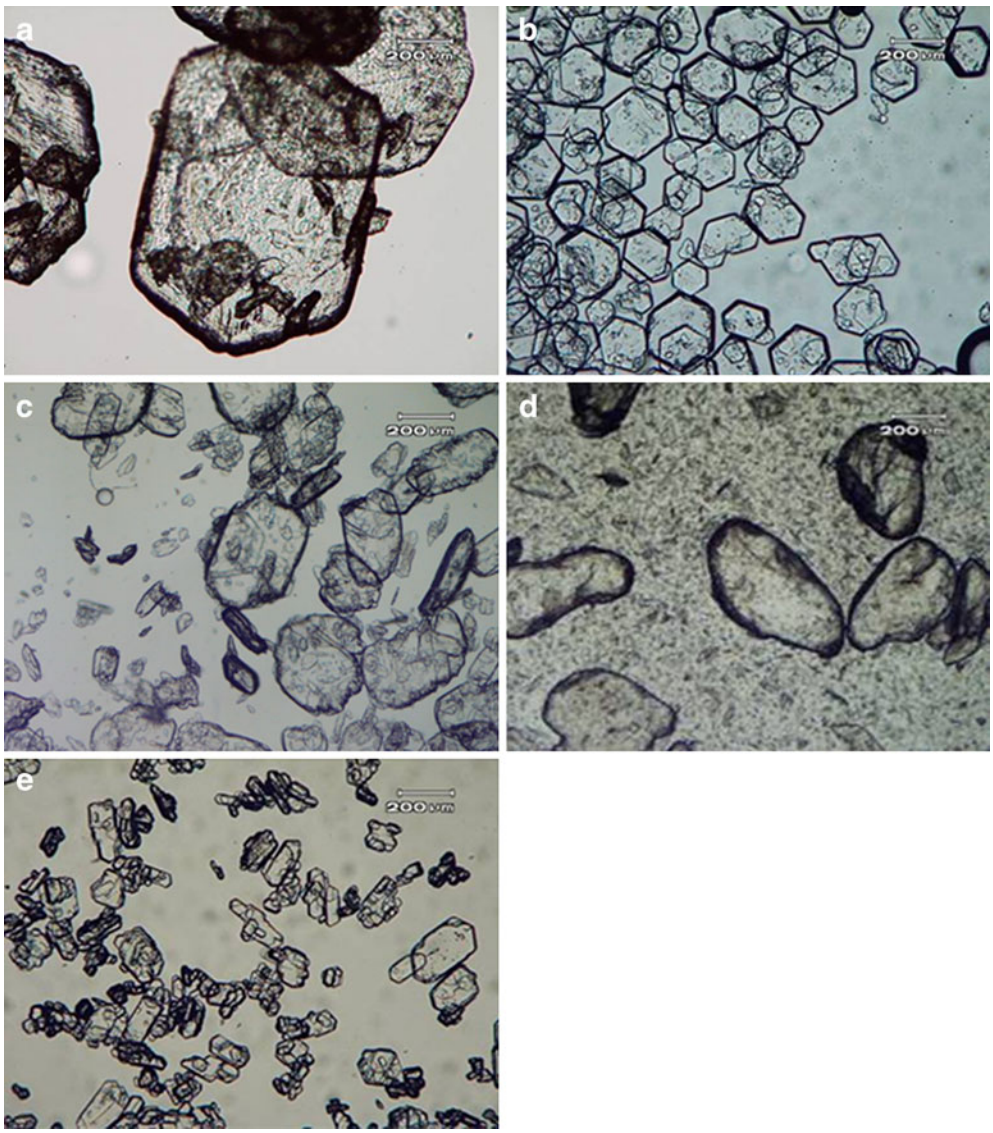


Fig. 1. Optical microscopy images of API produced using various particle engineering methods. **a** Conventional batch cooling crystallization, **b** sonocrystallization, **c** non-optimal HSWM with temperature cycling, **d** hammer milling, **e** optimised HSWM process with temperature cycling

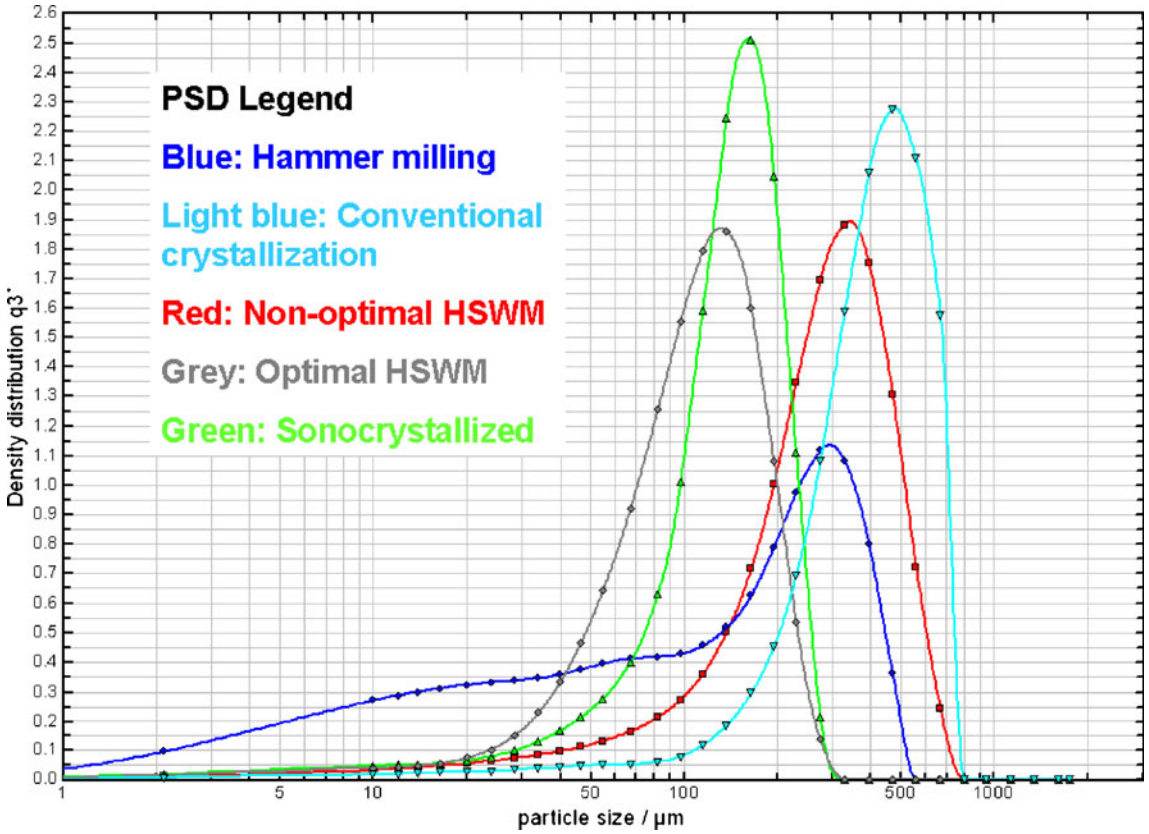


Fig. 2. HELOS Sympatec PSD measurements for the different particle engineering methods evaluated

The stability studies, therefore, focussed on using coarser API particles (D [v, 0.5] >100 µm) and a coarse grade of mannitol (200 SD with a mean particle size=180 µm) in order to minimise the potential for instability. An Accelerated Stability Assessment Programme (ASAP) (32) was conducted to determine the effect of the drug substance particle size on the stability. The study was to determine whether the 5 mg capsule (lowest blend strength) had an acceptable use period at 25°C/60% RH. Table II shows the capsule formulation used for stability testing.

Three 5 mg API capsule blends were prepared using three API lots obtained from three different particle engineering technologies (sonocrystallization, non-optimal HSWM with temperature cycling and Hammer milled). Each different particle engineering technique having a different PSD (Table III). The lowest capsule strength was chosen as previous studies indicated that the instability was greater where the ratio of excipients to API was higher.

Blends were filled into size four gelatine capsule shells at a fill weight of 100 mg. To exclude the possibility of capsule shell deterioration at high humidity from influencing the

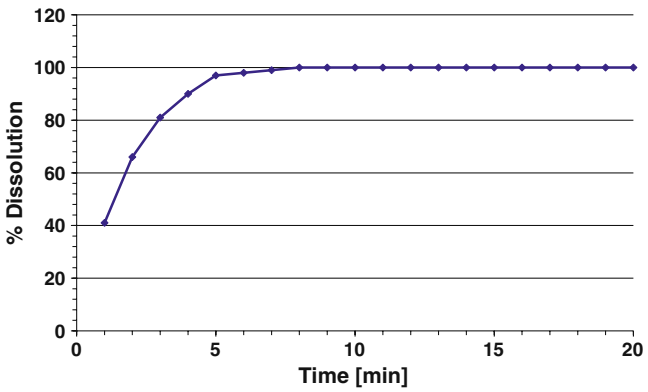


Fig. 3. Dissolution rate predicted as a function of time based on an input D [v, 0.5] size of 500 µm

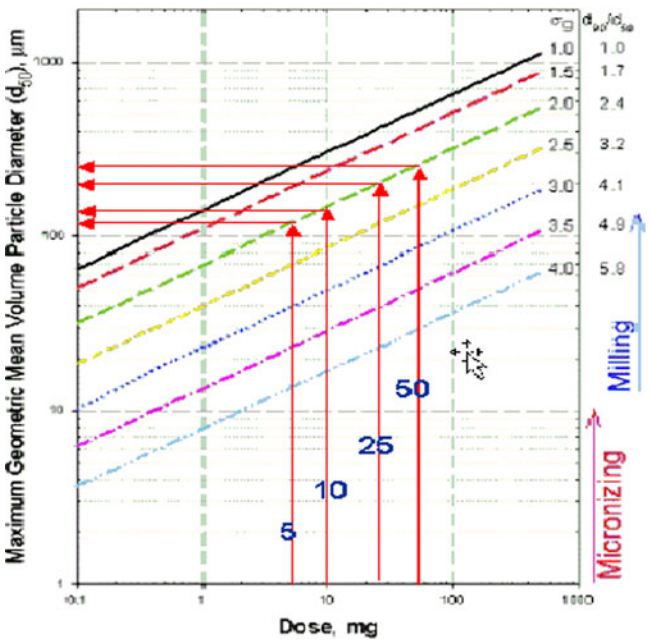


Fig. 4. Maximum mean volume particle diameter, d_{50} [µm] predicted to pass USP Content Uniformity Test (99% Confidence) as a function of geometric standard deviation (σ_g) and dose (mg)

Table II. Pharmaceutical Formulation Used for Stability Testing

Component	[mg]
Active Pharmaceutical Ingredient	5.0
Mannitol (Pearlitol 200 SD)	85
Talc 200	10
TOTAL	100

Table IV. ASAP Temperatures, Relative Humidity and Duration of Testing

Temperature [°C]	Relative humidity [% RH]	Study period [days]
5	5	21
50	75	21
60	5	21
70	5	21
80	40	4

RH relative humidity

results both loose blend and filled capsules were placed on accelerated stability studies. Data is only presented on the filled capsules as there was no difference with the loose blends. The conditions used for ASAP testing are defined in Table IV.

From the ASAP stability data, one Maillard degradation product was identified as being most likely to breach the impurity specification limits of 0.3% *w/w* within 2 years. The data relating to this impurity were separated out from that for the summed monosaccharides and fed into a humidity corrected Arrhenius equation (32) in order to calculate in use periods for the three capsule blends using the API engineered from various particle engineering technologies. Table V shows the predicted shelf life of the capsule blends incorporating the three types of API particles.

Table V shows that there is an effect of API particle size on capsule stability. Hammer milled API gave a reduced predicted product shelf- life, compared to sonocrystallized and high shear wet milled API. Hammer-milled API had a much lower D [v, 0.1] compared to sonocrystallized and HSWM API. This D [v, 0.1] has the greatest influence on the stability and, therefore, requires a lower limit to be set for the formulation.

A potential 2-year acceptable use period was predicted by the model for the 5 mg capsule stored at 25°C/10% RH when using HSWM or sonocrystallized API. In addition, predictions based on lactam formation show a shelf life >10 years before a specification of 1.0% *w/w* would be breached; hence, this impurity would be unlikely to limit the acceptable use period. These results indicated that to achieve a 2-year shelf life for the API in a capsule formulation, the API should have a D [v, 0.1] of at least 55 μm and a D [v, 0.5] of at least 140 μm.

Blend Homogeneity Testing

Six capsule blends were prepared at a 150-g scale to assess the effect of mannitol and API particle size on content uniformity. Four blends contained 5% *w/w*, 6.7% *w/w*, 24% *w/w* and 30% *w/w* of API obtained using Hammer milling. Two blends contained 5% *w/w* of API obtained from sonocrystallization. A small (S) and large (L) particle size of mannitol (100 SD with a mean size of 100 μm and 200 SD with a mean size of 180 μm) was used. The manufacturing technique involved tumbling a portion of the mannitol prior to blending in order to coat the surface of the blending vessel and all blends were screened using a co-mill.

Figure 5 indicates that blends containing sonocrystallized API had better content uniformity. There was little difference in content uniformity between the 5% *w/w* and 30% *w/w* blends using sonocrystallized API. Dry-milled API blends (24% *w/w* and 30% *w/w*) made with larger sized mannitol had a higher content uniformity than compared to dry milled API blends (5% *w/w* and 6.7% *w/w*) made with smaller sizes mannitol but was still lower than that of sonocrystallized API blends.

Table III. API PSD from Various Particle Engineering Methods Used for ASAP Stability Testing

Particle Eng. method	D [v, 0.1] [μm]	D [v, 0.5] [μm]	D [v, 0.9] [μm]	D [4,3] [μm]
HSWM	92	289	519	302
Hammer milled	7	112	351	150
Sonocrystallized	55	140	209	138

The D [4,3] is defined as the volume mean size of particles

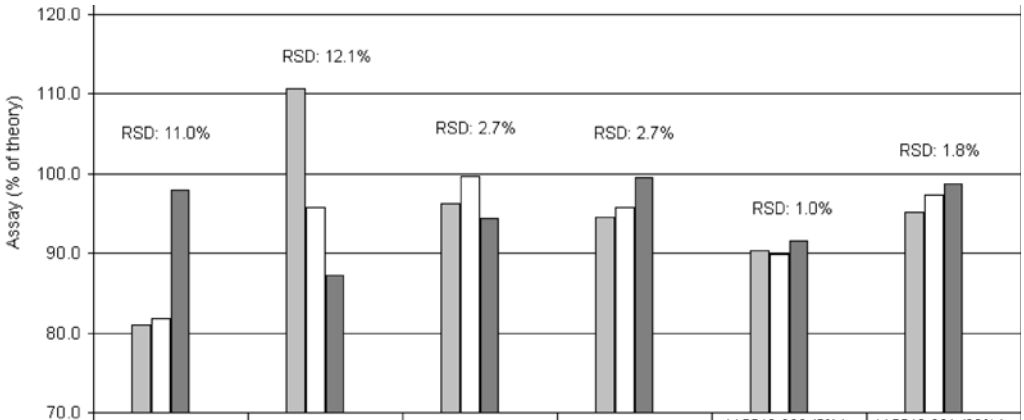
Fluidisation Segregation Testing

Three blends at 5% *w/w* and 30% *w/w* API loadings were further tested using a purpose-built small-scale fluidisation segregation tester to assess their potential to segregate as a result of fluidisation (Table VI).

All three sample sets were richer in API in the upper layers, indicating that API had migrated towards the top of the column during fluidisation. The segregation potential for the three API blends as indicated by the RSD of the assay results is given in Table VI. Despite having a tighter uniformity before segregation testing (Fig. 5), the sonocrystallized API material shows a "moderate" tendency to segregation by fluidisation. Although sonocrystallized material contains fewer fines, the sonocrystallized material may flow better and, therefore, segregate more readily than the hammer-milled API or exhibits less adhesive interaction with mannitol.

Table V. Predicted Shelf Life for API Capsule Blends with Different API Particle Engineering Methods

Particle eng. method	Shelf-life predicted at 25°C/60% RH [days]	Shelf-life predicted at 25°C/10% RH [days]
HSWM	105	791
Hammer milled	56	409
Sonocrystallized	99	689



	115546-026 (5% S)	115546-027 (6.7% S)	115546-028 (24% L)	115546-029 (30% L)	115546-030 (5% L, sono API)	115546-031 (30% L, sono API)
Assay (% of theory)- Left	81.0	110.6	96.2	94.5	90.3	95.1
Assay (% of theory)- Middle	81.7	95.7	99.5	95.7	89.8	97.3
Assay (% of theory)- Right	97.9	87.2	94.3	99.5	91.5	98.6
Mean (% of theory)	86.9	97.8	96.7	96.6	90.5	97.0

Fig. 5. Blend homogeneity data based on diverse API physical properties obtained from Fitz milling (first four columns) and sonocrystallized (last two columns) with large (*L*) and small (*S*) mannitol particle sizes

DISCUSSION

A novel approach of integrating drug substance and drug product design is presented for an API using particle engineering technologies such as sonocrystallization, HSWM and hammer milling resulted in the production of diverse particle size and size distributions. The particle engineering approach discussed is applicable to most APIs, in particular to address both stability issues, which has not been discussed in the literature. Traditionally, dry milling has been used and proposed (6) to control particle size but the influence on API stability has not received much attention, which is subject to investigation in this research. Content uniformity modelling was used to predict the median particle size required to meet the USP criteria for dose strengths ranging from 5 to 50 mg. The predictions indicated that a D [v, 0.5] of ca. 300 μm would be too large to meet the USP requirements for uniformity for all dose strengths. This provides an explanation for the failure of API manufactured using the conventional batch cooling crystallization to meet the content uniformity criteria. Based on modelling, a D [v, 0.5] of less than 250 μm should be acceptable. The non-optimal HSWM with temperature cycling yielded a D [v, 0.5] of 283 μm and poses a high risk with regards to content uniformity. To reduce the risk of segregation, the particle size of the mannitol should be as close as possible to that of the API. For these studies, mannitol 200 SD with a means size of 180 μm was compared with mannitol 100 SD with a mean size of 100 μm. The use of 200 SD mannitol led to an increase in content uniformity issues compared to 100 SD mannitol grade with a reduction in the levels of the lactam derivative formed.

The use of hammer milled API should be avoided as this process generated a high proportion of fine particles which in turn reduces the content uniformity of both 5% *w/w* and 30% *w/w* API capsule blends in comparison to sonocrystallized and non-optimal HSWM API. Furthermore, an increase in the formation of lactam and Maillard degradation products is observed with dry milled material. An assessment of stability indicates that the API should have at least a D [v. 0.1] of 55 μm and a D [v, 0.5] of 140 μm to ensure that at least a two potential year shelf-life can be obtained.

To meet all drug product requirements for content uniformity, and stability sonocrystallized API or an optimised HSWM process with a D [v, 0.1] of ca. 50 μm and D [v, 0.5] of ca. 130 μm should be targeted.

CONCLUSIONS

Various particle engineering methodologies were applied to produce diverse particles in order to assess the impact on content uniformity and stability and define a particle size distribution to produce an acceptable drug product formulation and performance.

AFTERNOTE

This information proved vital to inform the bulk API synthesis and drug product manufacturing at pilot plant

Table VI. Segregation Potential of API Blends

API loading [% *w/w*]	Particle eng. method	API D [v, 0.1] [μm]	Assay RSD [%]	Segregation potential
30%	Hammer milled	7.8	3.04	Low
5%	Sonocrystallized	55.3	9.55	Moderate
30%	Sonocrystallized	55.3	5.91	Moderate

production scales. Both the API PSD control and drug product manufacture were successfully transferred on plant to yield acceptable material for Phase 2 clinical supplies of this candidate.

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