



ALTASCIENCES



**UTILIZING NANO PARTICULATE
FORMULATIONS IN THE DELIVERY
OF POORLY SOLUBLE DRUGS**

1. INTRODUCTION

The most common reason for producing sub-micron or nano-sized dispersions is to increase oral bioavailability of poorly soluble drugs. Other advantages include reduced fed/fasted variability, as well as faster onset of therapeutic action.

The physiochemical aspects of dissolution kinetics may have originated with Noyes and Whitney (1), but it was Edwards (2) who, over sixty years ago, realized that oral bioavailability could be improved if dissolution was then rate-limiting step. As the solubility of active pharmaceutical ingredients (API) in new drug molecules continues to trend lower, pharmaceutical companies face increasing pressure to produce smaller and smaller API particles to overcome the dissolution rate problem. The common technique of micronization is insufficient for APIs exhibiting low solubilities – a fact that has driven adoption of other techniques such as wet bead milling and microfluidization. Wet bead milling offers selective and scalable processes and can regularly reduce the particle size to the 100 – 200 nm range, sometimes even smaller.

Products using nano-sized active ingredients have entered the market, with more currently in the clinical trial stage (3-7). Examples of marketed products include Rapamune® (sirolimus, Wyeth Pharmaceuticals), Emend® (aprepitant, Merck & Co.), TriCor® (fenofibrate, Abbott Laboratories), Megace-ES (megestrol acetate, Par Pharmaceutical companies Inc.), Invega Sustenna® (paliperidone palmitate, Janssen Pharmaceutical), and Triglide™ (fenofibrate, Skye Pharmaceutical). The first five examples were manufactured using wet bead milling (Elan's NanoCrystal® technology, now owned by Alkermes), while the last one uses high pressure homogenization (Skye Pharma's IDD-P technology).

Most of the products mentioned in (3-7) were intended for oral administration. The active ingredient in these products had a very low aqueous solubility.

It is BCS class II compounds that primarily benefit from a small particle size, while BCS class IV compounds also benefit to a lesser degree. The BCS classes are depicted in Figure 1 on the next page.

Other routes of administration, such as parenteral and pulmonary delivery, have also benefitted from size reduction. Benefits of particle size reduction for the parenteral route include small dose volumes (resulting from high drug loading) and avoidance of harsh solvents and/or extreme pH conditions. Benefits for the pulmonary route include the ability to use inhalers intended for solutions, as well as the ability to produce spray-dried powders whose particle sizes are optimized for deep lung delivery.

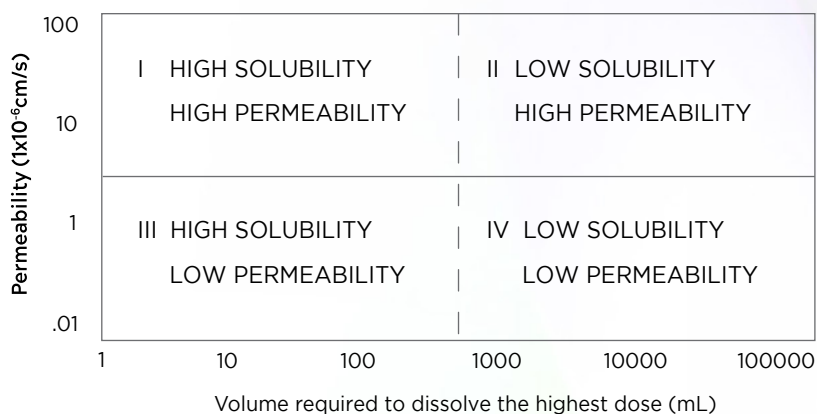


Figure 1. Diagram depicting BCS classes 1 - 4.

2. DISSOLUTION LIMITED ABSORPTION

The dissolution rate from suspended particles, as expressed by Edwards (2), reads as follows:

$$\text{Eq. 1} \quad \frac{dC}{dt} = \frac{DS}{h} (C_s - C)$$

The surface area of the dispersed phase is related to the specific surface area (SSA) by:

$$\text{Eq. 2} \quad S = \frac{m}{\rho} \times \text{SSA}$$

The specific surface area - particle size dependence is depicted below.

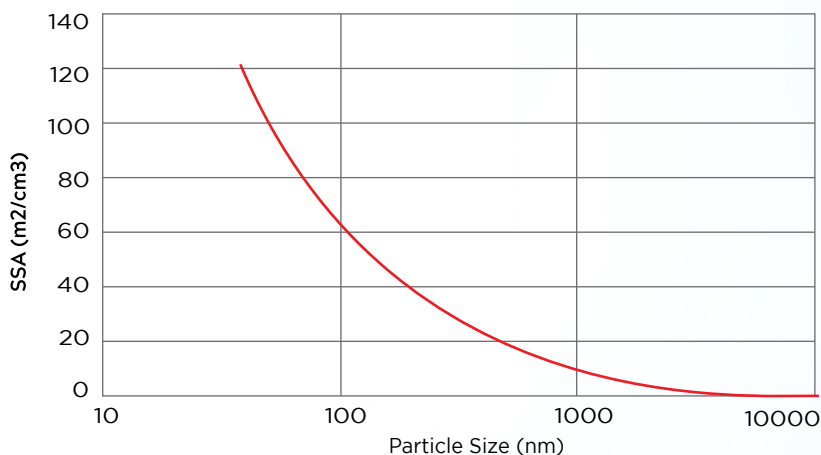


Figure 2. Specific Surface Area (SSA) plotted against particle size.

By decreasing the particle size, the specific surface area increases, which in turn increases the active ingredient's dissolution rate and bioavailability. This trend will continue until the dissolution rate is faster than the absorption rate. This upper limit defines the maximum absorbable dose as described in (8).

GLOSSARY:

- C** Concentration of dissolved drug substance
- CS** Solubility of drug substance
- D** Diffusion coefficient of dissolved drug substance
- h** Thickness of diffusion boundary layer
- k** Intestinal absorption coefficient
- m** Dose
- MAD** Maximum absorbable dose
- S** Surface area of dispersed phase
- SSA** Specific surface area
- t_{Res}** Residence time (time available for drug uptake in small intestine)
- V_{GI}** Volume of gastrointestinal tract
- P** Density of drug

The maximum absorbable dose can be expressed as:

$$\text{Eq. 3} \quad \text{MAD} = k_a C_s V_{GI} t_{Res}$$

It is evident from these expressions that BCS II compounds are particularly strong candidates for improving bioavailability by reducing particle size.

There is no clear limit between the BCS II and IV domains where the particle size reduction is no longer effective. Rather, it is the interplay between intestinal absorption rate, drug solubility and dose that matters. A very small dose of a BCS II compound may still have time to be absorbed even though the particle size is not in the nano range. A very large dose, on the other hand, may not be fully absorbed if it is greater than the maximum, absorbable dose (MAD), no matter how small the particles are.

3. MEDIA MILLING

Stirred media mills, sometimes referred to as bead mills, are highly effective in producing pharmaceutically active nanosuspensions. The process offers flexibility of scale, and is well-contained throughout the production pipeline. The suspending medium is water, which starts as a slurry and becomes a colloid suspension as a result of the milling. The key components required for a stable suspension are compounded into the starting slurry.

A typical media mill in recirculation mode is depicted in Figure 3 (components not shown to scale).

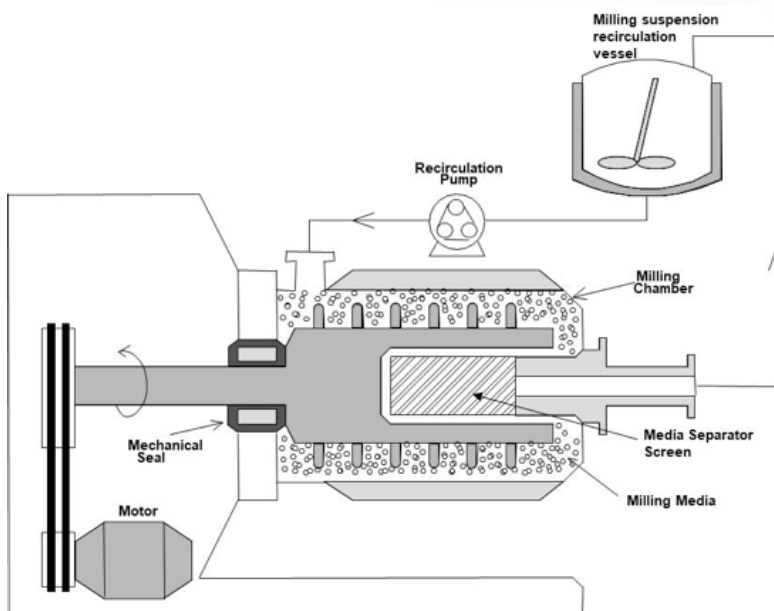


Figure 3. Media mill.

The mill consists of a mill chamber, an agitator, and a media separator screen. The mill is connected to an external recirculation vessel. The content of the recirculation vessel is pumped through the mill, then returns back to the recirculation vessel. The milling media (beads) are contained inside the milling chamber, and are prevented from flowing out by the separator screen.

The media is normally chosen at the front end of milling evaluation. Common types of materials are Yttrium/Zirconium oxide ceramic beads, crosslinked polystyrene beads, and stainless steel beads.

The use of Yttrium/Zirconium ceramic beads is common in the pharmaceutical industry. However, the use of crosslinked polystyrene was successfully used by Elan in all of its NanoCrystal® products (3,4).

Although ceramic media are highly effective, they can cause abrasions on the mill surfaces, resulting in elemental contamination in the milling slurry.

Polymeric milling media can be used in higher media loading, and produce a gentler milling. Stainless steel milling media is common in industries (e.g., food processing, pigment and ink manufacture, etc.). The initial process attributes are chosen based on know-how, but may vary as a result of process development.

The formulation aspect of product attributes is driven by the combination of attributes most likely to result in a stable dispersion. The overall concentration may be locked in as the process is optimized. The hardness/friability is an inherent property of the API, while the viscosity is a property of the formulation components and overall concentration. These are not variables in a traditional sense, but reflect attributes that may influence rate of size reduction, as well as the final particles size that can be achieved.

3.1. Theoretical Media Milling Considerations

Theoretical aspects of media milling have been extensively reported. Some of these works have been focused on mechanistic aspects involving stress number and stress intensity (9 - 11). Others, meanwhile, have focused on fracture models and population balance models (12).

The key aspects of the mechanistic approach as shown in (9) will be the main focus of this discussion. It is stated that the milling process can be characterized by the frequency with which a feed particle is hit by the milling beads, and how forceful these hits are. The former is referred to as stress number (SN), while the latter is referred to as stress intensity (SI).

Typical Process Attributes Can Be Represented As Follows:

Milling attributes

- Milling time
- Agitator speed
- Media load
- Media size
- Recirculation flow rate

Product attributes

- Overall product concentration
- Formulation (types of stabilizers, relative concentration)
- Particle size of starting material (API)
- Hardness/friability of solid (API)
- Viscosity of formulation

The stress number is proportional to the number of bead contacts over the course of the milling process. The stress number is therefore proportional to the milling time and agitator speed. A higher stress number is also obtained for a higher media load, as well as for a smaller grinding media (due to the greater number of beads).

The stress intensity, meanwhile, is proportional to the kinetic energy of bead collisions. It is therefore proportional to the bead diameter cubed (proportional to volume), bead density (bead volume times bead density gives mass), and tip speed squared (mass times speed squared is proportional to kinetic energy). There exists a lower threshold below which collisions do not result in particle fracture. The stress intensity must therefore be above this limit in order for milling to occur.

Stress number and stress intensity exhibit significant interplay in various ways. For instance, a smaller grinding media results in a higher stress number, but also in a lower stress intensity.

All key aspects of stress number and stress intensity are captured by defining the process attributes' media type, media size, media load, agitator speed, and mill time.

The particle size reduction in media milling has frequently been found to follow a power law with regards to milling time (c.f. Walker, (13))

This can be stated as follows:

$$\text{Eq. 4} \quad X = a \cdot t^b$$

where a and b are fitted constants. A log - log plot of particle size vs. milling time produces a linear trend with the slope b and intercept $\ln(a)$. This allows one to readily estimate time required to produce a certain particle size (end point) given previous particle size - time data. A typical milling curve is depicted in Figure 4.

It is common to observe an initially faster rate of reduction, which later follows the well-known power law as shown in Eq. 4.

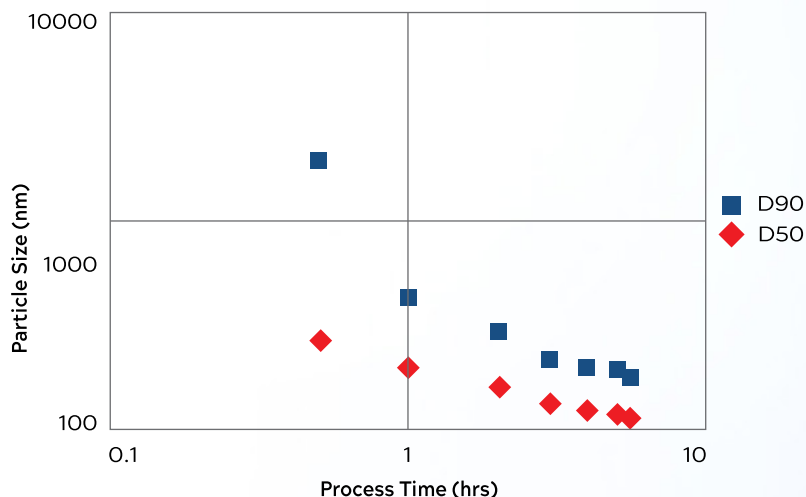


Figure 4. Particle size vs. process time.

GLOSSARY:

- t** Milling time
- X50** 50 percentile of particle size distribution
- X90** 90 percentile of particle size distribution

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About Altasciences

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