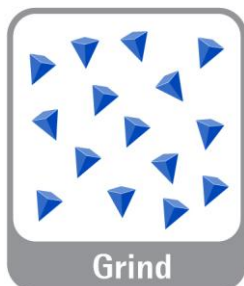


PHYSICAL FORM:**TECHNOLOGY TYPE:****1. What is Grind?**

'Grind' is a method of producing very small particles by abrasion and attrition in a ball mill. It is a similar process to the way finer and finer sand particles on a beach are ground by tidal waves on pebbles and shells. However, much harder ceramic or metallic (materials) balls can be used for grinding drugs either dry or slurry in wet-grinding. Therefore, the time required for size reduction in ball mills is a matter of hours rather than years.

The discrete particles formed by attrition are considerably smaller compared to micronized drugs from mechanical and air-jet mills (often significantly below 1 μ m diameter by using appropriately sized balls and grinding conditions). Extremely small, statically charged particles require stabilization with wetting agents/stabilizers to prevent particles clumping back to larger agglomerates which would defeat the object of the process. Dispersions of fine particles are also referred to as nano-suspensions when the particles are predominantly in the sub-micron range. The mean particle diameters by weight can be as small as 100 nm.

2. Which administration route is our Grind technology suitable for?

This approach can potentially be used across multiple administration routes such as oral, intramuscular, possibly intravenous and topical. However, in real terms it is most useful for orally administered, poorly soluble compounds.

3. Which types of compound are suited to Grind?

Poorly soluble drugs that remain in a physically stable crystal form after grinding. Milling generally increases dissolution rates because of the smaller particles and larger surface areas created for drug dissolution and absorption. Usually, downsizing will not increase the intrinsic solubility of a poorly soluble compound.

Salt forms or compounds that are subject to change after physical processing may be unsuitable for this technique as the physical structure can be disrupted. Often, amorphous particles are unsuited if they have a tendency to agglomerate during processing.

4. How does Grind increase bioavailability?

Due to the significantly smaller particle sizes which offer maximum surface areas in contact with gastro intestinal fluids, poorly soluble compounds dissolve more rapidly compared to the coarse drug. If the solubility is sufficiently high and the drug is very permeable across the intestinal membrane, dissolution rates determine the amount of orally absorbed drug.

For intravenous administrations, there is risk of embolism where more rapid dissolution of the particles in the systemic circulation may be a controlling factor.

5. Which Phares services use the Grind technology?

It can potentially be applied across all service platforms. During Survey, the physical and chemical suitability of the compound for Grind can be carried out. Often, early stage compounds are amorphous and may be unsuitable for effective grinding. Particle characteristics and physical form of the drug are essentially examined to find out if the crystal form can be suitably controlled.

During our tox service Speed, this technique is potentially a very useful tool because liquid formulations with sufficient suspended drug using small amounts of excipients may be more readily obtainable.

Grind can be applied during development of a clinical form in our Icebreaker service. The pros and cons should be weighed impartially against conventional particle size reduction methods (e.g. micronized) since ball milling is more involved and adds to cost. If technically justified and after drying (where necessary) the ground particles are physically stable (i.e. no polymorphic transformations or agglomeration) oral dosage forms can be developed. The payload may not be as high as desirable in early-stage testing since stabilization which lowers the drug load is required to make the formulations more robust.

6. The advantages and disadvantages of Grind

Advantages

- Liquid forms can be rapidly developed for early stage testing (pre-clinical) that can be converted into solids for later clinical development
- Typically, low excipient to drug ratios is required
- Formulations are generally well tolerated provided that strong surfactants are not required for stabilisation
- Generally, crystal forms are chemically and physically more stable than amorphous particles
- A method to consider for stubborn compounds that defeat previous attempts to increase solubility

Disadvantages

- Due to the high surface charge on discrete small particles, there is a strong tendency for particle agglomeration
- Developing a solid dosage form with a high pay load without encouraging agglomeration may be technically challenging
- Technically, development of sterile intravenous formulations is even more challenging

7. Phares Grind expertise

Successful development of Grind as a technique for formulating poorly soluble drugs involves skillful processing and analytical expertise to make sure a reproducibly small particle size is obtained that is physically stable (i.e. consistent size and no crystal transformations). We use our knowledge of colloids along with solid state characterization to identify and develop suitable formulations. Some third party patents cover the use of particular grinding media and processing. Phares can provide guidance on this.

8. Ball milled products

This process is widely used in non-pharmaceutical applications particularly in cosmetics to obtain ultra fine particles for sun block. Examples of pharmaceutical products include rapamycin (Rapamune®, 1 mg and 2 mg tablets, Wyeth).

KEY SERVICES:

