A New and Versatile Method for Preparing Drug Nanoparticle Formulations for Enhancing Bioperformance

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1. INTRODUCTION

It is well known that a significant percentage of contemporary drugs suffer from poor aqueous solubility, which often results in poor bioperformance (i.e., poor oral absorption and high exposure variability). With this in mind, a wide variety of drug delivery methods have evolved over the years in an effort to address this ubiquitous challenge. Towards this end, the preparation and application of drug nanoparticle formulations was first reported over 20 years ago [1]. In this approach, a drug's particle size is reduced to a median particle size in the nanometer range. This reduction in particle size results in a large increase in surface area (figure 1) and dissolution rate, which can lead to a subsequent improvement in oral absorption. Generally, the drug is maintained in its crystalline state. The success of the crystalline nanoparticle approach in enhancing bioperformance has been born-out by the appearance of several nanoparticle drug products on the market [2] for use in a variety of administration routes.

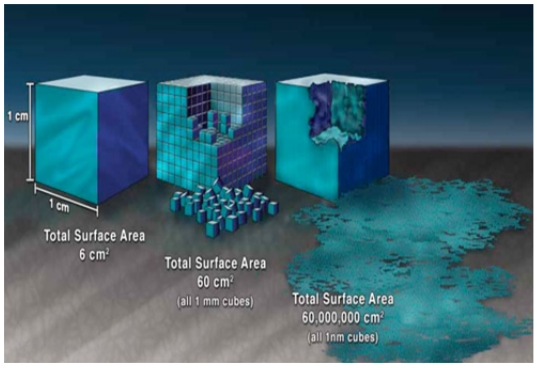

Figure 1. Decreasing particle size and associated increased surface area

One of the most effective methods of producing nanoparticles is *via* high-energy wet media milling using a high-speed impeller mill, which produces an aqueous suspension of nanoparticles. In this method, mixing shear forces and the forces generated during the drug particles' impact with the milling media [3] can reduce the drug particle size to the range of 200 nm in a few hours. It is important to note that a stabilizer (i.e., polymers such as poloxamer) must be added to the resulting aqueous suspension of nanoparticles in order to prevent agglomeration/aggregation. Although it has proven to be effective, typical impeller media-milling processes have some significant limitations. Some of these limitations are tabulated below.

Limitations of impeller media milling methods:

- Relatively large amounts of drug (>20 mg) are generally required to make even the smallest possible nanoparticle formulations.
- Since heat is generated, the milling equipment requires cooling capability.
- Although the mixing rate of a typical impeller media mill is a high-energy process, it often takes hours to reduce the particle size of an average compound into the nanometer size range.
- Impeller mills operate via a batch process, which is not amenable to screening multiple surfactants and milling conditions for optimal performance.

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These limitations make it particularly difficult to investigate nanoparticles early in drug discovery space, where several drug candidates often need to be evaluated at once and drug quantities are very limited.

2. A NEW METHOD FOR PRODUCING CRYSTALLINE NANOPARTICLES

Here we report a useful new method [4] for generating nanoparticles, using a LabRam® [5] high-frequency resonant mixer (figure 2). The LabRam mixer utilizes Resonant Acoustic® technology that applies low frequency, high-intensity acoustic energy to create a uniform shear field throughout the mixing vessel. The result is rapid fluidization and dispersion of material inside the vessel. Resonant Acoustic® mixing (RAM) is a non-invasive mixing technology, where no impellers or wands are used.

The versatility and advantages of using the LabRam for nanoparticle preparation method are several fold. The advantages are tabulated below.

Advantages of the LabRam preparation method:

- Nanoparticle suspensions can be produced in considerably shorter timeframe (often <10 minutes) as compared to impeller media milling. This allows for far more experiments to be run in parallel (i.e., high throughput in multi-well plates).
- Resonant mixing conditions are less stressful (i.e., less heat) as compared to impeller milling, which results in better performing nanosuspensions (i.e., less particle agglomeration or drug degradation)
- A wide range of vessels and preparative scales are accessible – from a few mgs divided into a multi-well plate, through 10s of mgs in vials to multi-gram quantities. Hence, the multi-well plate capability allows for high throughput screening of stabilizer systems, while the multi-gram scale capabilities enable the preparation of nanoformulation supplies to support *in vivo* studies such as a long-term toxicology study.

Hence, using the LabRam®, we now have the ability prepare and evaluate nanoparticle formulations during the drug discovery lead optimization stages all the way to the preparation of long-term toxicology supplies and even the clinic.

Figure 2. The Resodyne LabRam Resonant Mixer

2.1 Nanoparticle Preparation and Stabilizer Screen Example Case Study

An example of the utility of the LabRam preparation method is shown with a nanoparticle stabilizer screen we executed with a highly insoluble compound. In this study, we compared the LabRam method to a process using a typical high-speed impeller mill. Firstly, using the LabRam, we were able to quickly screen 5 different stabilizers in parallel in less than an hour, as compared to an all-day sequential batch process using the impeller mill. Table 1 shows the stabilizers evaluated by the 2 milling methods along with the resulting particle sizes generated.

Stabilizer[1]	Impeller Mill D50 / D90 (nm)[2]	LabRam D50 / D90 (nm)[2]
HPMC/SDS	311 / 585	256 / 356
HPC-SL/SDS	111 / 1330	192 / 247
PVP K28-32/SDS	157 / 2510	170 / 276
Pluronic F127	1126 / 1580	391 / 599
Tween80	269 / 1031	186 / 360

Table 1. Nanoparticle stabilizer screen and resulting particle size. [1]HPMC: Hydroxypropyl methylcellulose; SDS: Sodium dodecyl sulfate; HPC: Hydroxypropyl cellulose; PVP: Polyvinyl pyrrolidone; Pluronic: Poloxamer. [2]Particle size measurement by dynamic light scattering.

From table 1, it is easily seen that some stabilizers performed better than others in preventing agglomeration (larger particle sizes generated).

Again, using the LabRam, these critical screening data were obtained in less than an hour using only a few mgs of drug, vs. an entire day using an impeller mill (with significantly more drug consumption).

Figure 3 shows light microscope images of representative nanoparticles prepared by an impeller mill and the LabRam®, using the same stabilizer. From the images, it is clear that the nanoparticles prepared by the LabRam were significantly less aggregated, even though the same stabilizer was employed.

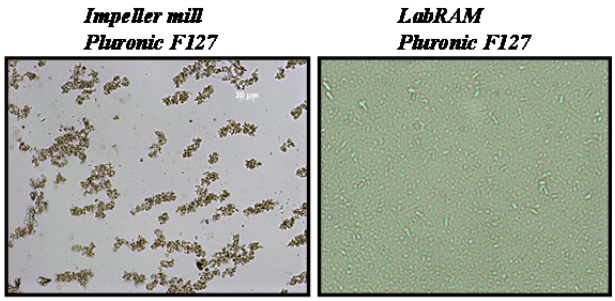

Figure 3. Nanoparticles prepared by an impeller mill and the LabRam, using the same stabilizer (Pluronic F127)

3. CONCLUSIONS

Application of a LabRam has proven to be a versatile and advantageous method for producing nanoparticle formulations. This method is compatible with a wide range of drug structural types and can efficiently produce aqueous nanoparticle formulations that are amenable to various routes of administration. With this new method in hand, the evaluation of nanoparticle formulations is now routine in early drug discovery space, using minimal drug supplies and time resource.

4. REFERENCES

1. See for example, Liversidge, E., et.al., Eur. J. Pharm. Sci., *18*, 113-120, **2003**
2. For example, oral Aprepitant (Emend®)
3. An effective milling media is, for example, Yttrium stabilized Zirconium oxide 0.5 mm beads; 95% ZrO2 + 5% Y2O3.
4. D. Leung et al., Int. J. Pharm., *473*, 10-19, **2014**
5. http://www.resodynmixers.com