



Assessment of formulation robustness for nano-crystalline suspensions using failure mode analysis or derisking approach



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ABSTRACT

The small particle size of nano-crystalline suspensions can be responsible for their physical instability during drug product preparation (downstream processing), storage and administration. For that purpose, the commercial formulation needs to be sufficiently robust to various triggering conditions, such as ionic strength, shear rate, wetting/dispersing agent desorption by dilution, temperature and pH variation. In our previous work we described a systematic approach to select the suitable wetting/dispersant agent for the stabilization of nano-crystalline suspension. In this paper, we described the assessment of the formulation robustness (stabilized using a mixture of sodium dodecyl sulfate (SDS) and polyvinylpyrrolidone (PVP) and) by measuring the rate of perikinetic (diffusion-controlled) and orthokinetic (shear-induced) aggregation as a function of ionic strength, temperature, pH and dilution. The results showed that, using the SDS/PVP system, the critical coagulation concentration is about five times higher than that observed in the literature for suspension colloidal stable at high concentration. The nano-suspension was also found to be very stable at ambient temperature and at different pH conditions. Desorption test confirmed the high affinity between API and wetting/dispersing agent. However, the suspension undergoes aggregation at high temperature due to the desorption of the wetting/dispersing agent and disaggregation of SDS micelles. Furthermore, aggregation occurs at very high shear rate (orthokinetic aggregation) by overcoming the energy barrier responsible for colloidal stability of the system.

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1. Introduction

Nano-crystalline suspensions are used in pharmaceutical industry to enhance biopharmaceutical performances of highly water insoluble active pharmaceutical ingredient (API). Their colloidal particle size range offers the advantage of large surface area per unit volume that provides the required properties of the final product (Shegokar and Müller, 2010). For the preparation of nano-crystalline suspensions, the particle size reduction is the most commonly used method due to the possibility of controlling particle size by suitable selection of wetting/dispersing agent, as well as by control of milling process parameters (Peltonen and Hirvonen, 2010). The ability of nano-crystalline suspension to

remain in its original state during drug product preparation and administration (processing or in use handling) is critical for since any change could negatively impact its performances. In fact, all suspensions having particle size less than 1 μm are inherently thermodynamically unstable due to the natural tendency decrease the large specific surface area and excess surface energy (Patel, 2010). For this purpose, wetting/dispersing agents are used to stabilize the suspension against flocculation (Holthoff et al., 1996; Lauten et al., 2001) and crystal growth (Ostwald ripening (Ostwald, 1901)).

In a previous work (Nakach et al., 2014), we described a systematic approach to select a suitable wetting/dispersing agent for the preparation of nano-crystalline suspensions. The objective of this paper is to describe the derisking approach implemented for the robustness assessment of the selected formulation with regard to the identified risks that are listed below:

- (i) Particles agglomeration during milling: During high-energy milling, the size of particles decreases to some critical values.

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Further energy supply to these particles of limiting size causes further deformation of particles, energy accumulation in the volume or at the surface of particles, and subsequently leads to aggregation. To evaluate such risk, a long milling duration (13 h) at high shear rate was carried in order to evaluate if the suspension undergoes negative milling phenomenon which is in close relation with aggregation and agglomeration (Anderson and Lekkerkerker, 2002).

- (ii) Aggregation during storage or administration due to the lack of electrostatic stabilization: Aggregation occurs if the energy barrier is small or negligible. According to Sato and Ruch (1980), an energy barrier of 15 $k_B T$ is sufficient to prevent aggregation since thermal energy is 1 $k_B T$, where, k_B is Boltzmann constant and T is the absolute temperature. The height of the energy barrier depends on the electrolyte concentration which is directly related to the thickness of the double layer. Basically, when a salt is added to the suspension, the electrical double layer repulsion is screened, and van der Waals attraction becomes dominant and induces fast aggregation of particles (Yu and von Gottberg, 2002). At critical electrolyte concentration (CCC) the energy maximum disappears leading to fast aggregation of particles. In our work, the CCC was determined by quantification of aggregation rate as a function of electrolyte addition.
- (iii) Shear-induced aggregation (orthokinetic aggregation): Aggregation processes are always carried out under conditions where suspension is subjected to some shear by stirring or by flow leading to increase of collision frequency (Potanin, 1991). In our study, Orthokinetic aggregation was evaluated under a fixed shear rate.
- (iv) Aggregation by desorption of wetting/dispersing agent from particles surface: Robustness to dilution is important for nano-crystalline suspension to ensure that the particles formed have similar properties at different dilutions to achieve uniform drug release profile and to ensure that the drug will not get aggregation at higher dilutions in vivo which may significantly impact biopharmaceutical attributes of the product. We had previously, demonstrated that the adsorption of polymeric surfactants (PVP K30) led to high affinity isotherm implying that such process is irreversible (Nakach et al., 2014). To check the irreversibility of adsorbed surfactant, desorption of surfactant from particles surface was investigated by diluting the suspension in water.
- (v) Crystal growth due to Ostwald ripening and/or flocculation by depletion at high temperature: During milling or autoclaving (in case of suspension use in parenteral administration), the suspension could be submitted to high temperature. In this case, large particles grow with time at the expense of the smaller ones (Ostwald, 1901) due to the well-known Kelvin effect (Hiemenz and Rajagopalan, 1997). Furthermore, high temperature can lead to desorption of polymer molecules which become more soluble (Tadros, 2012) or precipitate when the temperature is higher than polymer cloud point (Corti et al., 1984). Consequently, the non-adsorbing polymer molecules can induce flocculation by depletion interaction between colloidal particles (Jenkins and Snowden, 1996). In this paper, we evaluated the sensitivity of suspension to Ostwald ripening and/or flocculation by depletion at high temperature.
- (vi) Flocculation due to pH variation: According to the route of administration, an API experiences a wide range of physiological pH. Accordingly, nano-suspension needs to be robustly designed with regards to pH variations which may significantly affect the effectiveness of electrostatic stabilization (Kiratzis et al., 1999). Indeed, pH is an important parameter to be taken into account because the particle surface is strongly

modified by acid-base equilibria, and the particle charge may vary from negative to zero and to positive values. In fact, by varying the pH, the isoelectric point (IEP) can be reached. The IEP is the pH value at which the zeta potential value is zero, implying no electric charge on the surface of a particle. For that purpose, the sensitivity of our formulation to pH variations was investigated.

2. Experimental

2.1. Material and methods

2.1.1. Materials

A hydrophobic highly insoluble API powder was provided by Sanofi R&D (Paris). It was micronized by jet milling before use. The physico-chemical properties of the API are given in Table 1.

Polyvinylpyrrolidone PVP (K30) (Molar mass: 30,000 g) was purchased from BASF (France), sodium dodecyl sulfate (SDS) was purchased from Univar (France), Vitamin E TPGS[®] (d-alpha tocopheryl polyethylene glycol 1000 succinate) was purchased from Eastman Chemical Company (Netherlands), Solutol[®] HS15 was purchased from BASF (France) and Sodium chloride was purchased from Sigma Aldrich (France).

2.1.2. Methods

2.1.2.1. Suspension preparation

2.1.2.1.1. Preparation of milled suspension for evaluation of perikinetic aggregation, orthokinetic aggregation, sensitivity to temperature and pH variation. The milled suspensions were prepared using API at concentration of 20% (w/w) and SDS/PVP as wetting/dispersing agent at concentration of 1.2% (w/w). An aliquot of 50 ml suspension and 50 ml of Cross-linked Polystyrene beads (500 μm diameter supplied by Alkermes (USA)) were introduced in Nano-mill 01[®] (annular mill purchased from Alkermes, having a stator of 80 mm diameter and rotor of 73 mm). The mill was operated during 150 min at 10.8 m/s. The mill temperature was maintained at 10 °C.

2.1.2.1.2. Assessment of suspension behavior during long milling duration trial. In our previous work, the screening of wetting/dispersing agent was carried out in two parts (Nakach et al., 2014):

- (i) Part 1 focused on qualitative screening to select the lead candidate. At the end of this part two formulations appeared clearly superior to the others: SDS/PVP and Vitamin E TPGS[®].
- (ii) Part 2 focused on quantitative screening aimed to optimize the selected lead. For this part, the SDS/PVP made from ionic surfactant (SDS) and polymer (PVP) considered as more relevant was selected for the optimization.

In the present study, we decided to compare the suspension made of SDS/PVP to that made of vitamin E TPGS[®] (as reference) in

Table 1
Physico-chemical properties of the API used for this study.

Average particle diameter	5 μm
Molecular weight (g/mol)	497.4
Water solubility ($\mu\text{g/ml}$)	0.2
Log P ^a	6.9
Density (g/ml)	1.42
Melting point (°C)	156.7

^a P is the partition coefficient between octanol and water.

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