



Engineering of nano-crystalline drug suspensions: Employing a physico-chemistry based stabilizer selection methodology or approach



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ABSTRACT

This paper describes a systematic approach to select optimum stabilizer for the preparation of nano-crystalline suspensions of an active pharmaceutical ingredient (API). The stabilizer can be either a dispersant or a combination of dispersant and wetting agent. The proposed screening method is a quick and efficient way to investigate a large number of stabilizers based on the principles of physical-chemistry and employs a stepwise approach. The methodology has been divided in two main parts; the first part being focused on the qualitative screening with the objective of selecting the best candidate(s) for further investigation, the second part has been focused on quantitative screening with the objective to optimize the ratio and amount of wetting and dispersing agents, based on wettability, surface charges measurement, adsorption evaluation, process-ability evaluation and storage stability.

The results showed clearly that SDS/PVP 40/60% (w/w) (sodium dodecyl sulfate/poly(vinyl pyrrolidone)) at a total concentration of 1.2% was the optimum stabilizer composition, at which the resulting nanosuspensions were stable for more than 50 days at room temperature.

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1. Introduction

At present, the small molecular entities produced by the current pharmaceutical discovery are showing an increasing trend toward poor aqueous solubility (Lee, 2002), (Sharma et al., 2009), (Savjani et al., 2012). Such low water solubility is a challenge to achieve adequate bio-availability (Kipp, 2004) after oral administration. It also limits the types of formulations suitable for parenteral administration (Wong et al., 2008). In the recent years, nano-crystalline suspensions have been applied for the delivery of highly water-insoluble active pharmaceutical ingredients (APIs) (Shegokar and Müller, 2010), (Kawabata et al., 2011), (Singh et al., 2011), (Wang et al., 2012). By reducing the particle size of the API, the rate of the dissolution which is directly proportional to the specific surface area, as well as the solubility of the API can be significantly enhanced

(Kesisoglou et al., 2007; Noyes and Whitney, 1897). Indeed Ostwal-Freundlich equation (Borm et al., 2006) shows that the solubility increases exponentially with decrease of particle radius, r . Significant increase in solubility is typically observed when r is less than 200 nm. In addition, in contrary to the formulations made from poor tolerable solvents, such as Polysorbate, the injectable dose can be increased using nano-crystalline suspensions. Indeed they are essentially made of pure drug and typically use a relatively small amount of excipients (Bazile, 2011)

Top down process (particles size reduction by milling) is an efficient way to prepare nano-crystalline suspensions. This method is the most commonly used one thanks to the possibility of controlling particles size by a proper choice of wetting/dispersing agent, as well as by controlling the milling conditions (Leena Peltonen, 2010). The generated nano-crystalline particles in the dispersion must be stabilized against flocculation (Holthoff et al., 1996; Lauten and Nystrom, 2001) and crystal growth (Ostwald ripening (Ostwald, 1901)), thus the selection of appropriate stabilizer composition is a crucial step in achieving stable nano-crystalline suspensions.

The present paper proposes a physico-chemistry based method for the selection of suitable wetting/dispersing agent

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for manufacturing nano-crystalline suspensions using top-down process.

2. Scientific background of formulation strategy

According to [Tadros \(2005\)](#), in a API powder of any material the aggregates and agglomerates are held together by very strong attractive forces. When these aggregates and agglomerates are dispersed in a liquid medium, the attractive forces are reduced but still sufficient to keep the particles strongly attached together. To separate the particle in such aggregates or agglomerates and to disintegrate them, a combination of milling process and supplementing wetting/dispersant agents is required to overcome such attractive forces.

Depending on both the wetting/dispersant agent used and on the drug material properties, the particle sizes will decrease down to an equilibrium value during milling (water solubility, density, molecular weight). Different drugs will require different wetting/dispersant agents. Approach for selecting the most suitable wetting/dispersant agent for specific API, is therefore desired.

From our point of view, an ideal wetting/dispersant agent should satisfy several criteria:

- (i) It should achieve a maximum reduction in the surface energy of the powder. In fact, Reh binder and his collaborators investigated the role of surfactants in the grinding process. They found that, as a result of surfactant adsorption at the solid/liquid interface, the surface energy at the boundary is reduced and this facilitates the process of particles deformation or disintegration. The adsorption of surfactants at the solid/liquid interface in cracks facilitates the propagation of this phenomena. This mechanism is referred to as the Reh binder effect ([Monteiro et al., 2013](#)). Furthermore, for an efficient milling, the migration of wetting agent should be as fast as the propagation of cracks ([Tadros, 2005](#)).
- (ii) The suspension should be stable to avoid Ostwald ripening and flocculation or aggregation during the storage. Typically colloidal stability can be obtained either by electrostatic or steric stabilization or a combination of both: “electrostatic stabilization”. Electrostatic stabilization is brought by adsorption of charged species, like ionic surfactant or phospholipids. The efficiency of electrostatic repulsion can be assessed from the knowledge of the ionic concentration and ion valency, as well as by measuring the zeta potential of the particles ([Hunter, 1988](#)). It is well known that the electrostatic repulsion increases with a decrease of electrolyte concentration, a decrease of ion valency and an increase of zeta potential ([Adler et al., 2000](#)). The zeta potential measurements allow estimating of colloidal suspension stability ([Cosgrove, 2010](#)). The colloidal system is stable when a dominant role is played by the forces causing the mutual repulsion of the particles. Higher is the absolute value of the zeta potential, greater is the probability that the studied suspension will be stable. A small value of the zeta potential (from +5 to –5 mV) indicates a tendency for the system destabilization ([Iwona Ostolska, 2014](#)). Reported typical absolute zeta potential value for stable suspension is between 20 and 30 mV, although value as higher as 100 mV can be obtained ([Dery, 2012](#)). Non-ionic dispersants reduce flocculation through steric repulsion ([Adler et al., 2000](#)). These agents, mostly polymers, form adsorbed layers with thickness (Δ) which is strongly hydrated in water. When two particles each having an adsorbed layer of thickness (Δ) approach each other at a surface-to-surface distance h that is smaller than 2Δ , strong repulsion occurs as a result of two phenomena: (i) unfavorable mixing of the stabilizing chains when these are in a good solvent. (ii) Reduction of the

configurational entropy on considerable overlap of the stabilizing chains ([Fisher, 1958](#); [Sato, 1980](#)).

- (iii) Minimizing Ostwald ripening: firstly, in order to limit the material transport, the API solubility should be maintained as low as possible. Indeed, due to Ostwald ripening, the average particle size may increase over time. The driving force for Ostwald ripening is the higher solubility of smaller particles than the larger ones ([Hiemenz, 1997](#)). This results in a shift of the particle size distribution to larger values during the storage of nanosuspension, especially at higher temperatures. Secondly, the adsorption of polymer at the surface of particles may also efficiently inhibit the crystal growth ([Simonelli et al., 1970](#)).
- (iv) The formulation should be easy to handle and to process in a bead mill, it should in particular not be too viscous. Indeed, rheological parameters are critical during milling ([Gordana Matijasic and Glasnovic, 2008](#)). High viscosity may require longer processing time ([Lee et al., 2005](#)).

3. Experimental

3.1. Materials

A model hydrophobic and non ionisable highly insoluble API was obtained from Sanofi and the API was micronized by jet milling before use. The physico-chemical properties of the API are provided in [Table 1](#).

The dispersant/wetting agents used for the investigation and their intended use in suspension stabilization are listed in [Table 2](#) (See [Appendix A](#)). Several chemical categories were used (cellulose derivatives, povidones, phospholipides, poloxamers, polyethyleneglycol and derivatives, fatty acids and fatty acid esters, SDS, sodium ployacrylate).

3.2. Methods

3.2.1. Preparation of nanosuspensions

For the screening of dispersant/wetting agents using low shear milling, a suspension containing 20% (w/w) of API, 3% (w/w) of dispersant/wetting agents, and 77% (w/w) of water for injection (WFI) was prepared. An aliquot of 10 ml of the suspension and 20 ml of Zirconium oxide beads (700 μm diameter supplied by Netzsch (Germany)) were introduced in 30 ml glass vial. The vial was shaken in orbital roller mill for 5 days at 0.03 m/s and at room temperature.

For the assessment of process ability using high shear milling, a suspension containing 20% (w/w) of API, 3% (w/w) of dispersant/wetting agents and 77% (w/w) of WFI was prepared. An aliquot of 50 ml suspension and 50 ml of Polymill[®] Cross-linked Polystyrene beads milling media (500 μm diameter supplied by Alkermes, Inc., (Waltham, MA, USA) were introduced in a Nano-mill[®] 01 milling

Table 1
Physico-chemical properties of the API.

Average particle diameter	5 μm
Specific surface area (m^2/g) ^{**}	1.5
Molecular weight (g/mol)	497.4
Water solubility ($\mu\text{g}/\text{ml}$)	0.2
pKa	No pKa
Log P [*]	6.9
Real density (g/ml)	1.42
Melting point ($^{\circ}\text{C}$)	156.7

^{*} P is the partition coefficient between octanol and water.

^{**} Measurement is performed using Blaine method ([Kaye, 1967](#)).

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