International Journal of Pharmaceutics 406 (2011) 145–152

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Pharmaceutical Nanotechnology

Physical stability of nanosuspensions: Investigation of the role of stabilizers on Ostwald ripening

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ARTICLE INFO

Article history:
Received 8 November 2010
Received in revised form
13 December 2010
Accepted 17 December 2010
Available online 24 December 2010

Keywords:
Ostwald ripening
Nanosuspensions
Stabilizers
Micelles
Physical stability
Particle size

ABSTRACT

The effect of stabilizer type (small molecule vs. polymeric) and the amount of micellar solubilized drug on Ostwald ripening of nanosuspensions was investigated. Indomethacin nanosuspensions were prepared with small molecule stabilizers (sodium lauryl sulfate (SLS) and Dowfax 2A1 (DF)) and a polymeric stabilizer (hydroxypropyl methyl cellulose (HPMC)). Two different drug:stabilizer ratios were used to evaluate the effect of micellar solubilized drug. The Ostwald ripening potential of nanosuspensions was evaluated by subjecting them to various stress conditions (temperature (15, 25, 35 and 45 °C), thermal cycling, and mechanical shaking) for three months. The mean particle size increased in all SLS and DF formulations stored under different stress conditions. No effect of micellar solubilized drug on the Ostwald ripening rate was observed. In the case of HPMC formulations only those stored at higher temperatures (35 or 45 °C) exhibited an increase in mean particle size. The increase in size in the HPMC formulation stored at 45 °C was attributed to dehydration of the HPMC chains and subsequent loss of protection of the nanoparticles. The cube of the mean particle diameter versus time plot was determined to be non-linear for all formulations exhibiting Ostwald ripening. Therefore, according to the Lifshitz, Slyozov and Wagner theory the process was not diffusion controlled. The most probable mechanism for Ostwald ripening was surface nucleation controlled.

1. Introduction

Nanosuspensions are being widely employed for the delivery of water insoluble compounds. High dissolution rates of poorly water-soluble compounds can be achieved with these formulations due to their small particle size and high surface area (Patravale et al., 2004). The high dissolution rate aids in increasing the permeation of these compounds (Jia et al., 2002). Both increased dissolution and permeation greatly improve the oral bioavailability of water insoluble compounds and reduce the effects of fed and fasted states on the bioavailability (Rabinow, 2004). Improvement in oral bioavailability comes with the possible added advantage of dose reduction since less of the administered dose is wasted. Reduced dose not only benefits the patients in terms of reduced side effects and toxicity (Liversidge and Conzentino, 1995; Wu et al., 2004), but also leads to cost savings. In addition, nanosuspensions are very useful in toxicological studies of investigational compounds. The dose administered in such studies often exceeds their aqueous solubility and hence co-solvents are used to achieve solubilization. The use of harsh co-solvents can complicate toxicity studies and sometimes it becomes difficult to pinpoint the cause of toxicity (whether due to the solvents or the investigational compound). No harsh co-solvents are necessary when nanosuspensions are used and therefore these formulations are gaining popularity in early discovery research (Kesisoglou et al., 2007).

The small particle size of nanosuspensions, which is inherent to their success, is also responsible for their physical instability. Nanosuspensions consist of hydrophobic particles dispersed in a hydrophilic medium (usually water). The enormous surface area associated with the small size of these particles results in high interfacial tension, which in turn results in an increase in the free energy of the system. Accordingly, nanosuspensions are essentially thermodynamically unstable systems (Rabinow, 2004). To decrease their free energy nanoparticles tend to reduce interaction with water via flocculation, aggregation or crystal growth. However, these processes adversely affect the central characteristics of nanosuspensions (i.e., small size and high surface area) and consequently the benefits of the nanosuspension formulations, as discussed above, are lost. Stabilizers are added to reduce the free energy of the system by decreasing interfacial tension, and to

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doi:10.1016/j.ijpharm.2010.12.027

prevent nanoparticle aggregation by electrostatic or steric stabilization. Stabilizers constitute an integral part of nanosuspensions and it is important to fully understand their role on physical stability of nanosuspensions (Verma et al., 2009c). Stabilizers can be surfactants, polymers or a mixture of both. Examples of some of the commonly used surfactants include Tween 80, sodium lauryl sulfate and poloxamer 188 (Jacobs et al., 2000). Polyvinylpyrrolidone (PVP), hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), and polyvinyl alcohol (PVA) are examples of polymeric stabilizers (Kesisoglou et al., 2007; Patravale et al., 2004).

Ostwald ripening is the process in which larger particles grow at the expense of the smaller particles (Ostwald, 1901) due to the well known Kelvin effect (Hiemenz and Rajagopalan, 1997). There are two preconditions for Ostwald ripening: (i) the system should be polydisperse and (ii) the dispersed phase should have finite solubility in the dispersion medium. Both these conditions are frequently encountered in pharmaceutical nanosuspensions. In addition, most of the stabilizers used in the preparation of nanosuspensions also increase their solubility and hence may increase Ostwald ripening.

Ostwald ripening kinetics in disperse systems is governed by two basic processes: (i) diffusion of the solute molecules; and (ii) attachment or detachment (crystal growth and dissolution) to and from the particle surface. If crystal growth/dissolution at the particle surface is rapid then diffusion becomes the rate determining step (diffusion controlled growth). Whereas, if diffusion of the solute molecules is faster than their incorporation or removal to or from the solid particles then the coarsening of the system is governed by the mechanisms of crystal growth (including, surface energy and the presence of defects) (interface controlled growth). Depending upon the nature of the interface and crystal growth mechanism three different types of interface coarsening can be identified: (i) continuous growth, (ii) surface nucleation and (iii) spiral growth. The kinetics of diffusion controlled growth and two of the interface controlled growth (continuous growth and spiral growth) are given by:

$$d^n - d_0^n = k \times t$$

where d is the average diameter at time t, d_0 is the average initial diameter at $t = 0$ and k is the ripening rate. The exponent n is 3 for Lifshitz, Slyozov and Wagner (LSW) diffusion controlled processes (Lifshitz and Slyozov, 1961; Wagner, 1961) and continuous growth processes (Dehoff, 1984; Wagner, 1961) and 2 for spiral growth (Kahlweit, 1975; Ratke et al., 1995). The ripening rate is a given by:

$$k = \frac{64\, D C_\infty V_m \gamma}{9\, RT}$$

where D is the translational diffusion coefficient of the dissolved solute molecules, C_∞ is the bulk solubility of the dispersed phase, γ is the interfacial tension and V_m is the molar volume of the dispersed phase. R and T are the universal gas constant and the absolute temperature, respectively. The surface nucleation controlled growth of particles follows a logarithmic dependence on time (Cabane et al., 2005; Solomatov and Stevenson, 1993) and is given by

$$d - d_0 = k_1 \log\left(1 + \frac{t}{\tau}\right)$$

where τ and k_1 are constants with dimensions of length and time, respectively.

Although, the importance of Ostwald ripening on the physical stability of nanosuspensions has been underlined in a number of literature reports (Chaubal and Popescu, 2008; Eerdenberg et al., 2008; Jacobs et al., 2000; Lindfors et al., 2006; Moschwitzer et al., 2004; Pace et al., 1999; Verma et al., 2009a,b), detailed studies on the stability of nanosuspensions including the role of Ostwald ripening have not been reported. In this work Ostwald ripening of nanosuspensions has been investigated in detail with special emphasis on the stabilizer characteristics. The first aspect of this study deals with investigation of the effect of the micellar solubilized drug on Ostwald ripening. For this, indomethacin is used as a model drug and nanosuspensions were prepared at two different drug:stabilizer ratios (high and low) with two small molecule surfactants (sodium lauryl sulfate (SLS) and Dowfax 2A1 (DF)). Ostwald ripening of nanosuspensions was followed for three months under various stress conditions (elevated temperature, thermal cycling and mechanical shaking).

Both surfactants and polymers can be used as stabilizers in nanosuspension formulations. However, interfacial film characteristics differ significantly for these different types of stabilizers. Surfactants are usually small molecules; as a result their interfacial films are more dynamic as compared to the polymers which generally exhibit irreversible adsorption (Walstra, 1983). Adsorbed polymer layers are normally more robust and can prevent or slow down the attachment/detachment of drug molecules at the surface of dispersed particles and hence can affect Ostwald ripening. Moreover, polymers have been known to prevent crystal growth (Raghavan et al., 2001, 2003; Ziller and Rupprecht, 1990) in a number of cases. Therefore, the other aspect of this study deals with the effect of the characteristics of the interfacial layer on Ostwald ripening. For this, indomethacin nanosuspensions were prepared using a polymeric stabilizer; hydroxypropyl methylcellulose (HPMC). Ostwald ripening of these nanosuspensions was then compared to those prepared with small molecule surfactants (under similar stress conditions) to evaluate the role of the interfacial layer characteristics on Ostwald ripening.

2. Material and methods

2.1. Materials

Indomethacin USP, 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid, γ polymorph, was purchased from PCCA (Houston, TX). Methocel (hydroxypropyl methylcellulose) E5 Premium LV (HPMC E5) and Dowfax 2A1 (alkyldiphenyloxide disulfonate) (DF) were a generous gift from Dow Chemical Company (Midland, MI). Glycerin USP was purchased from PCCA (Houston, TX). Sodium lauryl sulfate (SLS) was purchased from Sigma–Aldrich (St. Louis, MO). Methanol HPLC grade was purchased from Fisher Scientific (Fair Lawn, NJ).

2.2. Preparation of nanosuspensions

The required amount of indomethacin was dispersed in 100 ml of the stabilizer solution using a mechanical stirrer to form a macro-suspension of the drug. The macro-suspension was homogenized at 10,000 rpm for 10 min using a PowerGen 700 D (Fisher Scientific) lab homogenizer to break up any lumps of the drug that may be present in the macro-suspension. Particle size reduction was carried out by processing this pre-conditioned macro-suspension through a microfluidizer model 110Y (Microfluidics, Newton, MA) at 18,000 psi for 70 min. The bulk temperature of the nanosuspension was maintained within $15 \pm 1\,^\circ$C during processing using a circulating water bath (Grant Ltd. 6, Grant Instruments, Cambridge, U.K.).

2.3. Characterization of nanosuspensions

2.3.1. Particle size analysis

The particle size distribution of the nanosuspensions was determined via dynamic light scattering (DLS) using Submicron Particle Sizer Autodilute Model 370 (Nicomp Particle Sizing Systems, Santa