

1 Nanosuspensions: Emerging Novel Agrochemical Formulations

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1 Introduction

Whereas nanotechnology and nanoparticle engineering has become ubiquitous in the pharmaceutical research and development arena starting as early as the mid-70s (Rosen and Abribat 2005), it has, quite surprisingly, only recently made its way to the field of agrochemical formulations and delivery systems. Contemporary reviews on pesticide formulations do not refer to dispersed systems in the submicron size range (Rodham 2000; Mulqueen 2003). The 24th Symposium on Pesticide Formulation and Delivery Systems, held in Tampa on October 2003 (Goss et al. 2005), did not have a single presentation on this topic. Even an updated cover story on agrochemical R&D in Chemical and Engineering News (Short 2005), which calls attention to the strong similarities between current agro and pharma research and development, also fails to indicate the great potential in nanoparticulate formulations as novel pesticide-delivery systems. In view of the prediction that “within 10 years nanomaterials will directly affect about half of all human health-related products” (Roco 2001), we strongly believe that a comparable transformation and paradigm shift will also take place in agricultural products and services.

The main drive for nanosizing of drugs, or drug carrier particles, stems from aqueous insolubility, which has become a widespread hurdle in pharmaceutical formulations (predominantly of biopharmaceuticals). It was estimated that close to 60% (Merisko-Liversidge 2002) of the new chemical entities currently in the discovery stage, primarily using high throughput screening practice, are poorly water soluble (solubility below 0.1 mg/l). The problem is far more severe for drugs that are insoluble both in aqueous and organic media (Lipinski 2002). No data exist for the new agrochemical molecules but we can safely assume that the same dilemma exists there. In general, molecules with a poor solubility show, concurrently, also a very slow dissolution rates. The performance of poorly soluble drugs is limited by the dissolution rate, and consequently they exhibit an erratic adsorption profile leading to poor and highly variable bioavailability, which is strongly dependant on experimental conditions (mainly fed-fasted state of the patient). Numerous drug candidates failed to reach commercialization due to solubility problems (Lipinski 2002) as it was realized that it is more expeditious and cost effective to redesign a molecular structure than to move a flawed material through

the development process. Nanosizing of drug particles offers improved solubility but also has the potential for direct in vivo multiple absorption pathways including paracellular and transcellular activities (Kidane and Bhatt 2005). Nanoparticles were also assessed as potential targeted systems (Müller and Keck 2004), including in cancer therapy (Brannon-Peppas and Blanchette 2004; Jain 2005). An excellent demonstration for the advantageous efficacy of a nanoformulation in comparison to other delivery systems is given by Kayser et al. (2003) using the antiparasitic drug amphotericin B. In this study, the nanosuspended drug by far outperforms the liposomal and micronized formulas. A list of other hydrophobic drugs which have been successfully nanosized is given by Date and Patravale (2004) and by Patravale et al. (2004) (also see Rainbow 2004). Nanoparticles as dry powder or aqueous nanosuspension are also highly suitable for aerosol delivery to the lung (Sham et al. 2004) and for transdermal administration (Ceve 2004).

Nanosizing is not utterly new in medicinal science (see early review by Oppenheim 1980). Formulators of parenteral therapies have been preparing colloidal drug carriers since the 1970s. Typical examples are submicron emulsions and microemulsions, nanospheres, nanocapsules, liposomes and lipid or cyclodextrin complexes. The first report on synthetic nanoparticles was made by Speiser and coworkers from ETH in Zurich back in the mid-70s (Kopf et al. 1976). These authors described the preparation of polyacrylamide submicron beads via emulsion polymerization in hexane-water biphasic system initiated by gamma irradiation. The obtained particles were reportedly amorphous, nonhydrated and spheroidal with a diameter of approximately 100 nm and a surface area of 10 m²/g. A 4% aqueous dispersion of the particles showed Newtonian flow properties with a viscosity of 3.52 centipoise at 20 °C. Surprisingly, this paper was cited only 12 times, and all prior to 1984.

Despite being a brilliant and innovative idea, the concept of polymeric nanoparticles as drug carriers has never made it to the pharmaceutical market, mainly due to regulatory limitations and some scale-up difficulties. Interestingly, unlike nanosized beads, microparticles of polylactic acid and of polylactic polyglycolic copolymer are accepted for parenteral administrations. It was argued that biodegradation of nanoparticles, which can freely circulate in the blood stream including the smallest capillaries (see Spenlehauer et al. 1997) and are internalized by cells, can cause cytotoxic effects. Another obstacle has been the low drug payload and the lack of cost-effective large-scale production methods. Research in this area still continues (Couvreur et al. 2002; Bialti et al. 2005). More advanced molecular scaffolds such as dendrimers (Aulenta et al. 2003; Gillies and Frechet 2005), fullerenes, nanotubes (Dennis et al. 2004) or nanowires, which are newcomers as drug carriers, are still in the research stage (Martin and Kohli 2004; Kaiser et al. 2005). Conversely, liposomal formulations did enter the market with several successful cosmetic and pharmaceutical controlled-release products, and several others are in the clinical phases. Nonetheless, major obstacles for faster market penetration of liposome-based formulations are limited physical

stability of the dispersions, drug leakage, low and non-specific activity, difficulties in upscaling and high production cost. The further fascinating potential of both polymeric nanospheres and liposomes for site specific delivery (drug targeting) was also never materialized in practice.

Another nanoformulation methodology (introduced in the mid-1990s) is the concept of solid lipid nanoparticles (SLN) including the improved versions of nanostructured lipid carriers (NLC) and lipid drug conjugate (LDC) (Müller et al. 2000). The three versions are all based on particles with a solid lipid matrix with an average diameter in the nanometer range. The particles are composed of lipids (typically triglycerides) that are solid at ambient up to the body's temperature and stabilized by surfactants. Various drugs can be trapped within the solid template. SLN exhibit excellent physical stability, protection of the incorporated labile drug from degradation, controlled drug release, good tolerability and potential site specific targeting. The main drawback of the SLN concept is that it is not fitting for organic non-soluble active ingredients. Other shortcomings are insubstantial loading capacity, potential drug expulsion after polymorphic transition during storage, and the relatively high water content of the dispersions. Despite numerous publications and patents issued for various SLN drug formulations (see a comprehensive list in Müller et al. 2000), no commercial product was yet announced (with the exception of the cosmetic formulation Nanobase by Yamanouchi introduced in Poland (see http://www.nanobase.pl/01_nanobase.html).

The state-of-the-art approach in drug delivery, which is also most pertinent for drugs that are poorly soluble both in aqueous and organic media, is based on the simple and straightforward concept of a carrier free nanosuspension of stabilized nanometer-sized drug particles. Typical trademarks in this field are Nanocrystal from Elan and Dissocubes from DDS. A comprehensive list of nanosuspension-based drug formulations in development and on the market is given by Rabinow (2004). We strongly believe that this methodology is the most significant to agrochemistry due to low production cost and minimal environmental effect. Nanosuspensions consisting of essentially pure active ingredients combined with minimal quantities of surface stabilizing agents may enable high payload with low toxicity and environmental impact (due to total exclusion of solvents). A comparison of technical and economical feasibility of various nanoscale delivery methods is presented by Date and Patravale (2004).

2 Solubility Enhancement Through Nanoization

As cited above, the factor of poor solubility is a major drawback for drugs and drug candidates. Downsizing of a drug particle, particularly to the submicron level, boosts bioavailability due to simultaneous enhancement of both the saturation solubility C_s and the dissolution rate dC/dt . This is described as follows:

The saturation solubility increases with decreasing particle size according to the Ostwald-Freundlich equation (Eq. 1) (also known as the Gibbs-Thomson and as the Kelvin equation):

$$\frac{S(d)}{S_0} = \exp \frac{\gamma V_m}{RTd} \quad (1)$$

where $S(d)$ is the solubility (mol/kg H_2O) of crystals with inscribed diameter $d(m)$ at temperature $T(K)$, molar volume V_m (m^3/mol), surface free energy (surface tension) $\gamma(mJ/m^2)$. R is the gas constant (8314.5 $mJ/mol K$). S_0 is the solubility of the bulk material ($d \rightarrow \infty$). With all other factors kept constant, the solubility increases with smaller particle size. However, for the solubility $S(d)$ to differ significantly from the solubility S_0 of the bulk material (i.e., the ratio $S(d)/S_0 \gg 1$), the exponential term needs to be much smaller than 1. This occurs only with a particle size in the nano range. This aforementioned phenomenon is another demonstration for the transformation of the physio-chemical properties of materials on the nanoscale.

A nifty demonstration for the significance of the Ostwald-Freundlich equation is shown as follows. The relevant physical properties of three minerals (quartz, gypsum, and pyrite) are summarized in Table 1. In Fig. 1, the solubility as a function of the particle size is calculated. It is apparent that for materials with high surface energy (such as pyrite), the change in solubility for a particle size below 100 nm is three orders of magnitude (!).

A related graph was presented by Kipp (2004) who calculated the change in solubility of a hypothetical drug particle (molecular weight of 708, an interfacial surface tension of 50, 75, or 100 dyn/cm and density of 1 g/cm^3) as a function of the particle diameter.

Another reason for the increase in $S(d)$ was postulated by Müller and Peters (1998) who suggested that upon nanoization, lipophilic surfaces from the inner part of the crystal are exposed to the aqueous dispersion medium. This will alter the surface tension γ consequently affecting the saturation solubility. The change in packing density (V_m) and differences in interfacial energy (γ) are the reasons for the variation in $S(d)$ of different polymorphic forms. Methods of morphological manipulations to enhance a drug's solubility are reviewed by Shefter (1981) (see also the recent manuscript by Huang and Tong (2004)). Dissimilarity in solubility between pure enantiomeric crystals and racemic solids was also attributed to increased packing density of the latter

Table 1. Physical properties of minerals

Name	Formula	$\gamma/mJ/m^2$	$M_w/g/mol$	$\rho/g/cm^3$	$V_m/m^3/mol$
Quartz	SiO_2	350	60.085	2.649	22.68×10^{-6}
Gypsum	$CaSO_4 \times 2H_2O$	26	172.17	2.32	74.21×10^{-6}
Pyrite	FeS_2	4,733	119.98	5.02	23.90×10^{-6}

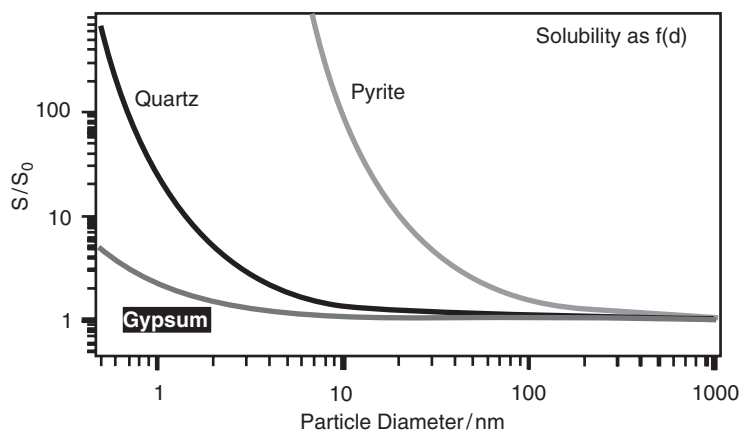


Fig. 1. Saturation solubility as function of particle size of minerals

(“Wallach’s rule”, Brock et al. 1991). In general, amorphous particles are more soluble and encompass a higher dissolution rate (see later) in comparison with crystalline particles of the same size.

The Ostwald-Freundlich equation is also one of the main reasons for the phenomenon of crystal coarsening in suspension known the Ostwald ripening (see next chapter). The theory correlating particle size with saturation solubility has been challenged by several authors (Wu and Nancollas 1998; Tang and Nancollas 2002) but it is still widely cited in the pharmaceutical literature. In a unique experimental work, Müller and Peters (1998) have demonstrated that the saturation concentration of the drug RMPK 22 is indeed dependant on the particle size of the preparation. Thus, for suspension with a mean diameter of 2.4 μm , the saturation solubility was measured to be under 2 mg/ml. For nanosuspensions with a mean diameter of 800 and 300 nm, the measured saturation solubility was 3.2 and 3.6 mg/ml, respectively.

The nanoization process of a particle in a given dispersed system, until complete solubility, is realized in association with an increase in the positive surface energy in relation to negative volume energy, which makes the solution more energetically favorable (Van der Gun et al. 2001). The free energy change for dissolution (or nucleation) developed by Gibbs and Volmer is the sum of the free energy change for the formation of the nucleus surface ΔG_s and the free energy for the phase transition ΔG_v (a volume effect). For a spherical nucleus we have: (Eq. 2)

$$\Delta G = \Delta G_s + \Delta G_v = 4\pi r^2 \gamma + 4/3\pi r^3 \Delta G_v \quad (2)$$

where r is the nucleus radius. A free energy change as a function of r is shown in Fig. 2.

The two free energy terms ΔG_s and ΔG_v have opposite signs so that ΔG as a function of r passes through a maximum which corresponds to the critical



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