



Nano dispersions deliver solutions

In the formulation of pharmaceutical products, the viability of a drug is often linked not just to its efficacy, but to the ability of the formulating company to produce a product with an appropriate dose size, overall performance, stability, format, bioavailability, and with minimal drug-drug interactions, toxicology and side-effects. Poor solubility, particularly in water, may be the cause of up to 40% of new drug candidates failing to be taken into product development programmes and is often considered to be one of the key factors that determine bioavailability.

In a paper last year, researchers estimated¹ that only around 60% of marketed drugs were either 'high solubility/high permeability' or 'high solubility/low permeability' – so-called BCS (Biopharmaceutics Classification System) Class I and Class III materials. These estimates also suggest that 90% of drugs currently being developed for future therapies are classed as 'low solubility/high permeability' or 'low solubility/low permeability', otherwise known as BCS Class II and BCS Class IV compounds.

Pharmaceutical formulators have devised many approaches that seek to overcome this low solubility problem,² including lipid based delivery systems, solid solutions/dispersions, modified release formulations, emulsions and micro-emulsions and many others. However, most of these formulation strategies target the so-called 'grease ball' materials with low solubility but high permeability (BCS Class II compounds). The very hardest materials to formulate are those with low solubility and low permeability, known as 'brickdust' (BCS Class IV compounds).

The agrochemical industry has likewise developed many approaches to allow the formulation of poorly water-soluble organic active ingredients. Many of these involve using solvents to dissolve the compounds, a strategy that is not readily available to the pharmaceutical industry, and one that is increasingly under pressure from legislation. However, the problem of applying an agrochemical to a field at application rates ranging from approximately 100g to multiple kilograms per hectare is a real concern when the water-solubility of the active ingredient may be less than 1 mg/litre. To rely on water alone would require huge volumes of liquid.

Nanotech solutions

Rather than relying on the solubility of an organic compound to formulate products, another approach is to generate particles of organic material that are dispersed or suspended in water, rather than dissolved. The particle size of the dispersion will have

a significant impact on a number of factors, including the stability of the final product and its efficacy. This is not a new approach and companies working in diverse markets have ground up insoluble materials for many years to produce inks, plastics additives and even pharmaceutical products. Most of the particles in these dispersions were, on average, many microns in diameter.

However, advances in measurement in recent years have led to new approaches to form particles with average diameters below 1 micron, at the nanometre scale. To add some context, the HIV virus is approximately 100nm in size and gold nanoparticles are often produced in the 10-100nm range for various applications including sensors. Organic nanoparticle dispersions can now be produced via several techniques including nanomilling and controlled crystallisation or precipitation.

The technology that led to the creation of Iota NanoSolutions (INS) was originally developed in 2002 by chemists Andy Cooper and Haifei Zhang at the University of Liverpool, UK. The potential of this new approach to form organic nanoparticles was quickly recognised at the Unilever R&D laboratories in Port Sunlight by Steve Rannard (now at the University of Liverpool), Alison Foster and Dave Duncalf, and developed into a portfolio of five technology platforms supported by a range of patent filings. INS was founded in 2005 using corporate venture funding from Unilever Ventures and has since grown to include 14 employees, including scientists, business development and management personnel. INS works with partner companies to develop solvent-free nanoparticles of poorly soluble

In Brief

- Poor solubility may be the cause of up to 40% of new drug candidates failing to be taken into product development programmes
- INS works with partner companies to develop solvent-free nanoparticles of poorly soluble organic compounds.
- Many agrochemicals and biocidal compounds are hydrophobic and poorly water-soluble, so aqueous nanodispersions offer new approaches for product formulation
- The INS approaches generate solid nanoparticles of drugs without requiring a 'drug-carrier' and therefore minimise levels of excipients

Hydrophobic dye: unprocessed in water (top); and INS processed dye forming a nanodispersion in water in 1-2 minutes

Dispersions of nanoparticles in water promise to overcome some of the problems of poor solubility that have plagued the development of pharmaceuticals and agrochemicals, write **Dave Duncalf** and **Steve Rannard**

organic compounds. These are mainly water-based products that incorporate water-insoluble materials as nanoparticles. Uniquely, INS forms dry, stable products that redisperse to form a nanodispersion in a single processing step, irrespective of the physical properties of the compound being processed; crystalline, amorphous, high and low melting point and solid or soft solid compounds can all be used to generate nanodispersions.

Agrochemical applications

As many agrochemicals and biocidal compounds are hydrophobic and poorly water-soluble, aqueous nanodispersions offer new approaches for future product formulation. As well as enhancing the bioavailability of these compounds, the potential to modify their activity is also of considerable interest, especially as legislation increasingly restricts the introduction of new biocides. INS has studied the impact of generating nanoparticle dispersions of many antimicrobial compounds and has discovered unexpected increases in activity.³

Figure 1 shows a minimum inhibitory concentration test, comparing the activity of the common toothpaste antimicrobial *Triclosan* dissolved in a water/ethanol solvent mixture (Figure 1 – filled squares) with nanoparticles dispersed in water (Figure 1, filled circles). The concentration of *Triclosan* required to inhibit 50% regrowth of the Gram-negative bacterium *Corynebacterium* is known as the IC_{50} and is shown by the lower horizontal dotted line in the graph. The water/ethanol solution (Figure 1, filled squares) showed substantial inhibition of regrowth of the bacterium at *Triclosan* concentrations >100 ppm, however, inhibition was lost rapidly at concentrations below this point, to give an observed IC_{50} of approximately 50 ppm. The aqueous nanodispersion (Figure 1, filled circles) was significantly more active, with bacterial regrowth inhibited to <50% at 6.25 ppm. The observed IC_{50} of the nanoparticle dispersion is therefore approximately one eighth of the molecular solution.

Similar activity increases have been observed for commercial agrochemicals, leading to the potential for future solvent-free products utilising less biocidal compound and offering both financial and environmental benefits. Figure 2 compares a commercial fungicidal emulsion product and an aqueous nanoparticle dispersion produced by INS, in a glasshouse experiment assessing the level of damage by fungal infection. Both the commercial and INS formulations were applied to a food crop at the identical concentrations, starting from the current recommended dose with subsequent dilutions. Twenty-four hours later, the plants were inoculated with fungal spores. The results show that even after a dilution to 25% of the starting concentration, the

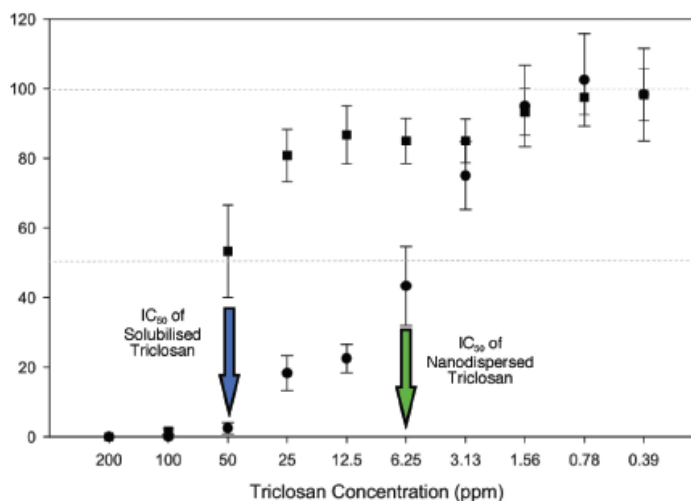


Figure 1: Comparison of IC_{50} for nanodispersed *Triclosan* (●) versus solubilised *Triclosan* (■)

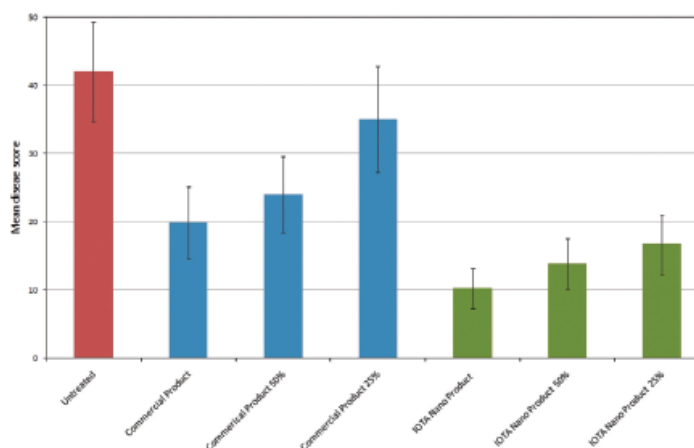


Figure 2: *In-planta* data showing reduced fungal disease in plants treated with nanodispersed fungicide versus commercial product treated at three dilutions

Drug delivery

aqueous nanoparticle dispersion is as effective at reducing fungal damage as the commercial product at the full recommended application level.

Pharmaceutical applications

Several nanoparticle pharmaceutical therapies have been developed commercially, such as Merck's anti-emetic *Emend*, Abbott's anti-cholesterol drug *Tricor*, and Wyeth's immuno-suppressant *Rapamune*, which are now being used routinely. Many new technologies rely on particle carriers such as dendrimers, liposomes and polymer particles to 'solubilise' poorly water-insoluble drugs. For example, 'pegylation' is a common technique used to attach polyethylene glycol chains to a drug molecule in order to improve the compatibility of the drug within the body and also to reduce degradation of the drug by normal bodily functions. In Abraxis BioScience's nano-enabled breast cancer treatment, *Abraxane*, the drug itself is bound to nano-sized albumin carrier particles. However, the INS approaches generate solid nanoparticles of drug without such a 'drug-carrier' and therefore minimise levels of additional ingredients known as excipients needed in potential formulations.

In collaboration with the Liverpool School of Tropical Medicine, INS researchers have recently investigated the activity of an antimalarial drug by comparing the effectiveness of nanoparticles of the drug dispersed in water with a solution of the active ingredient dissolved in the solvent DMSO. Figure 3 shows the IC_{50} of the drug when it is applied to human blood infected with the *Plasmodium falciparum* malarial parasite. When the drug is conventionally dispersed in water by grinding, the IC_{50} is very high (Fig 3, far right), indicating that a high dose is required to control the parasite.

When the drug is processed into an aqueous nanoparticle dispersion, the IC_{50} is very similar to the DMSO-solvent dissolved drug. As can be seen from the six different INS aqueous nanoparticle formulations, the particle size has a dramatic effect on the drug's efficacy.

INS is currently developing oral and injectable therapies with various partners, using excipients that are already used in commercial products. Figure 4 shows *in vivo* data for an intravenously delivered drug. In this case the drug has a very low solubility in water – classed as BCS IV 'brick dust' – and could only be delivered in solution using a solvent based formulation. Obviously the use of solvent is not a preferred dosage form when a drug needs to be injected and so an aqueous nano-dispersion provides an effective answer to this problem. The bioavailability of such insoluble drugs can be very low, particularly when a solvent borne formulation encounters the aqueous environment of the blood or in the stomach, which behaves as an anti-solvent for the drug. INS aqueous nanodispersions are compatible with such fluids and have shown impressive increases in bioavailability.

The *in vivo* comparison data in Figure 4 show that the INS nanodispersion performs very well against a milled/micronised suspension; the INS formulation showing a much higher overall exposure to the drug (AUC) and hence increased bioavailability, together with a higher peak drug concentration (C_{max}), which

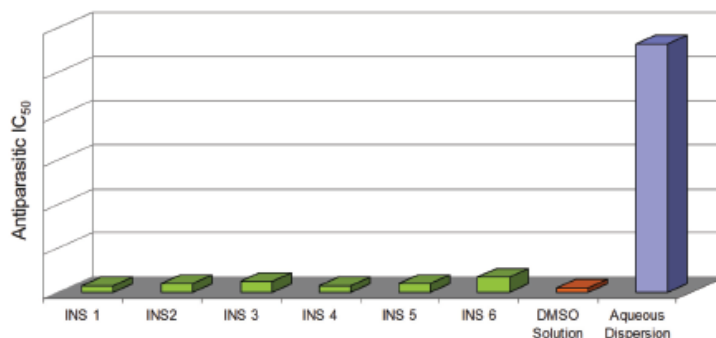


Figure 3: An antimalarial drug, usually administered as an aqueous dispersion, shows significant reduction in IC_{50} when applied as a nanodispersion (*ex-vivo* data)

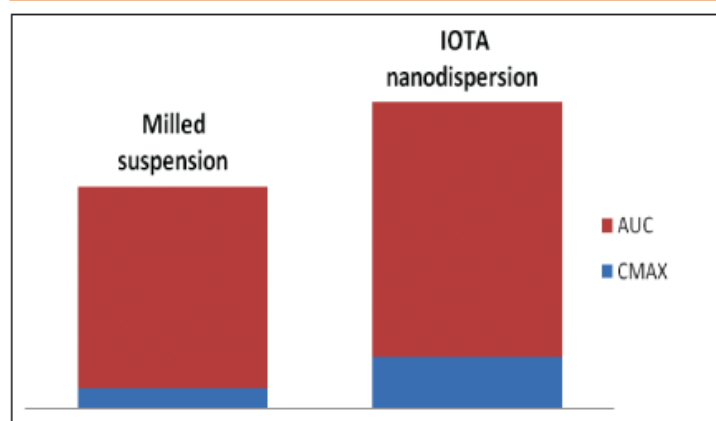


Figure 4: *In vivo* data show that administering a drug as a nanodispersion gives a significant increase in peak drug concentration (C_{max}) and overall drug exposure (AUC) values

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ensures that the threshold efficacy level is reached quickly.

The introduction of INS technology has generated significant interest across many market sectors. The ongoing programme of development with third parties has seen INS produce good manufacturing practice (GMP) materials for evaluation in storage situations and it is hoped that the INS pharmaceutical materials will be evaluated in a partnered 'first in man' trial in the near future. Field trials of agrochemicals are already under way.

INS technology potentially provides new life

for existing molecules, in addition to enabling the development and optimisation of new candidate materials. For agrochemicals, legislation is aimed at increasing productivity whilst limiting damage to the environment. The formation of poorly soluble pharmaceuticals is another increasingly important issue. Financially, the revitalisation of old materials makes excellent sense, as registration, supply and distribution are already in place. INS expects to have materials in advanced stages of product development in the next two years but as any poorly soluble organic compound is a candidate for this approach, the options are almost endless.

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