Opportunities for organic nanoparticles

Professor Steve Rannard of **Iota NanoSolutions** introduces the benefits and commercial applications of organic nanoparticles

Many technologies exist which form metal, metal oxide and other inorganic nanoparticles. Applications are mainly found in high technology electronics, catalysts and diagnostics. Such materials are usually hard, insoluble particles which are environmentally persistent, though not necessarily harmful.

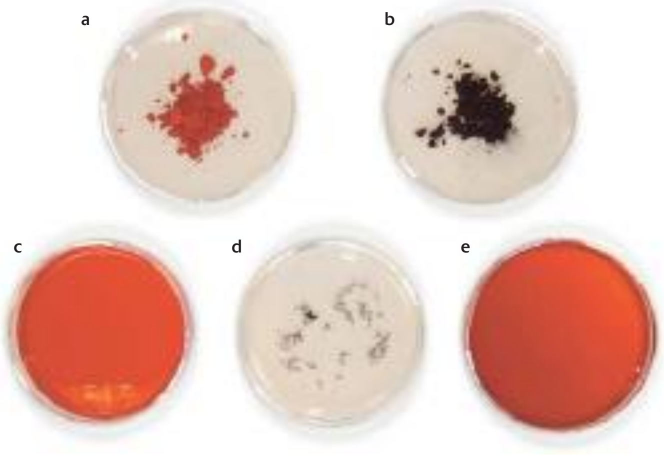
Thousands of organic chemicals are used in various products from pharmaceuticals to consumer products, inks and dyes, flavours and household cleaners. In many products, the organic chemicals are dissolved to aid formulation or are chemically modified to improve their performance.

If a chemical is insoluble in a liquid that is required for formulation, its activity and applicability is significantly limited. For example, pharmaceuticals often have restricted bioavailability and efficacy due to their insolubility in water. This can either restrict the development of new drugs or the scope of current medicines. The same is true for nutraceuticals, biocides and a range of other potentially useful compounds.

By forming very small dispersions of organic compounds, insoluble materials can be made to behave more like truly dissolved molecules without the need to produce new chemicals or use flammable, toxic or volatile solvents. This option is a valuable tool in the manufacture and development of new products because the scope of chemical ingredients that becomes available offers huge potential for innovative and competitive product design.

Organic nanoparticles have received relatively little attention by comparison with inorganic materials, which have seen an increasing level of academic research and commercial investment. The future benefits of inorganic nanoparticles, such as quantum dots, silicas, titania and various catalysts, are not in question but Iota NanoSolutions sees a much larger commercial opportunity in the thousands of insoluble or poorly-soluble organic compounds that are used across many high-technology and commodity product areas.

Iota is a spin-out from Unilever at Port Sunlight based on initial EPSRC-funded work on the formation of organic nanoparticles at the University of Liverpool. Unilever scientists saw potential in the project and, since the initial patent filing by the university, Iota has developed a portfolio of 16 patent filings. The firm was founded in June 2005 with funding from Unilever Ventures and has grown from just three full-time scientists to ten full-time and two part-time employees working in three laboratories at the MerseyBio incubator in Liverpool.



Note: a - Iota-processed Oil Red powder without chemical modification, b - Oil Red powder, c - Nanodispersion of Oil Red after addition to water, d - Oil Red added to water, e - Oil Red dissolved in organic solvent

Figure 1 - Visual comparison of processed & unprocessed Oil Red hydrophobic dye

Previous approaches

The pharmaceuticals industry has led the research into organic nanoparticles over recent years. The search for nano-medicines has driven the development of new materials and the refining of well-established techniques.

The 'bottom-up' synthesis of nanoparticles capable of encapsulating or carrying active molecules has seen the production of dendrimer technologies, protein conjugates, DNA delivery vehicles, liposomes and shell-cross-linked block copolymer micelles, to name just a few. 'Top-down' techniques have focussed mainly on attrition approaches such as wet nano-milling to grind large particles and achieve particle distributions with sub-micron average particle diameters.

Many 'wet' approaches to forming colloidal dispersions from liquid emulsions exist. These typically rely upon the selective removal of the oil phase of an emulsion and the subsequent solidification, via the precipitation, crystallisation or encapsulation of any organic materials that were dissolved within in the solvent droplets. So far, none of these techniques has proved truly generic and they have been limited to specific classes of materials, classified either by their chemical reactivity or by their physical properties.

Organic compounds are inherently and ultimately soluble in water or aqueous environments, even if they dissolve very slowly or the amount that can be dissolved in a given volume of water is extremely small. For this reason, unlike their inorganic counterparts, organic nanoparticles will not be persistent in the environment over long periods.

Iota approach

The environmental impact of a commercial organic compound must be studied in detail before products are produced and therefore the development of nanoparticle technologies using existing compounds makes good commercial and environmental sense.

For this reason, Iota focuses primarily on extending the use of existing materials while facilitating the formation of products from NCEs in the pharmaceuticals and healthcare sectors. So far, it has processed over 200 organic compounds, with vastly varying chemical structure, chemical reactivity and physical properties, to produce dry, solid materials that rapidly disperse in water to produce 'solution-like' dispersions.

Several process techniques have been shown to follow the principles of Iota's particle formation strategy. Compounds from reactive peracids through to dyes, pharmaceuticals and even low melting-point waxes have been successfully converted into aqueous nanodispersions.

The speed of nanodispersion formation may be controlled so that almost instant dispersion or sustained release over hours can be achieved. The size of the nanoparticles can also be controlled. Dispersions of approximately 300 nm are typical but sizes ranging from 50 to 500 nm have been routinely formed, depending on the needs of the specific application.

Unlike attrition methods, Iota's approach does not require longer processing times to achieve smaller particles. In addition, the approaches are not limited by the self-assembly of small molecules or polymers. No chemical changes are made to the compounds and therefore there are no new supply chain issues and existing understanding of long-term environmental effects and fate can be used to evaluate new product technologies.

Iota has a number of ongoing programmes. In some cases, an increase in bio-activity has been seen for bioactive compounds such as biocides and pharmaceuticals. When such an increase is seen, opportunities exist to decrease the dosage or concentration of the active ingredients to avoid overdosing or unnecessary cost. Where molecular solubility limits the concentration of a chemical, the application of particle dispersions allows far higher loadings to be achieved, with concentrations over 50 times higher than saturated micelle concentrations having been seen for some compounds.

Iota's aqueous dispersions do not contain organic solvents and therefore have obvious benefits over products reliant on emulsions, concentrates or other solvent borne formulations. In addition, the removal of high-temperature, high-shear processing may be of particular value if the compound in question has hydrolytic or thermal instability.

No new molecules are involved. Iota produces dry solids that are physical blends of existing water-soluble compounds and the insoluble 'problem ingredient'. When the media-soluble portion of the blend dissolves on contact with water, the insoluble components are dispersed on a nanometre scale. This approach can be used to disperse water-insoluble materials in water, water-soluble compounds in lipophilic liquids and hydrophobic compounds in hydrophilic solvents.

The solid blends may be converted to a tablet format, blended with other powders or added to a liquid and used as dispersions. The formation of a solid that will form a dispersion on demand also offers the potential for large cost savings, as solids are cheaper to transport than liquid dispersions. An Iota powder stored for 30 months under typical non-stringent laboratory conditions has been shown to disperse just as readily, producing identical nanodispersions, as freshly produced materials.

The loading of the active ingredient within the blends varies with different compounds but typical values of 40-60% are regularly achieved and values as high as 85% have been observed in several cases.

Drivers for nanoparticles

Legislative constraints are increasingly impacting product development. For example, the Biocidal Products Directive, the Cosmetic Products Directive - especially the 7th Amendment, banning animal testing of cosmetic ingredient, - and the Plant Protection Products Directive all regulate and restrict the development, use, proliferation and marketing of active compounds within a range of products across Europe.

In each case, annexes to the directive contain lists of acceptable materials. The addition of new chemicals is only possible after successfully following a lengthy and expensive process of assessment.

The BPD specifically requires an extensive dossier of toxicological data, including an environmental impact assessment, and a full understanding of the chemical efficacy of the active. The addition of a substance to the annex, even after the compilation of the dossier, may be denied if less harmful and more suitable alternatives are available for the intended application.

The impact of this new approach to biocidal legislation is that, unlike previously where the industry would spread the costs of safety data generation over many years as market share and active use increased, the regulatory bodies now require the testing to be complete before any forecast of sales and long-term revenue can be attained.

The estimated costs of the data package are in the region of €3.5-5 million/active substance. This cost implication will significantly reduce the development of new biocides and also limit the number of current candidates that are worthwhile registering.

Commercial development

Clearly, if new uses can be found for existing compounds that are enabled by organic nanotechnologies, the hurdles for commercialisation will be lower, with product development and innovation timescales significantly reduced. The Solvent Directive restricts one possible avenue for product development, therefore new aqueous approaches are needed that can serve many market sectors.

Iota does not specifically introduce new products into any market sector. Rather it forms partnerships with companies active in various fields. The nanodispersing solids it has produced have been widely evaluated by customers in five distinct markets: pharmaceuticals and diagnostics, biocides and agrochemicals, foods and nutraceuticals and functional additives for home and personal care and for polymers, inks, coatings and adhesives.

With the pharmaceuticals sector, these materials have been evaluated *in vitro* and *in vivo*, showing significant benefits over solvent-borne formulations and enhanced bioavailability and pharmacokinetics. The company is also working on the transfer of APIs from traditional treatment formats to new application methods.

In biocides and agrochemicals, aqueous formulations have shown dramatic increases in activity, potentially paving the way to products with reduced biocide concentrations in commercial anti-parasitic, anti-fungal, anti-bacterial and anti-yeast compounds. In food and nutraceuticals, high loadings of vitamins and health-benefit actives have been achieved and stable flavour and natural food colouring dispersions have been developed.

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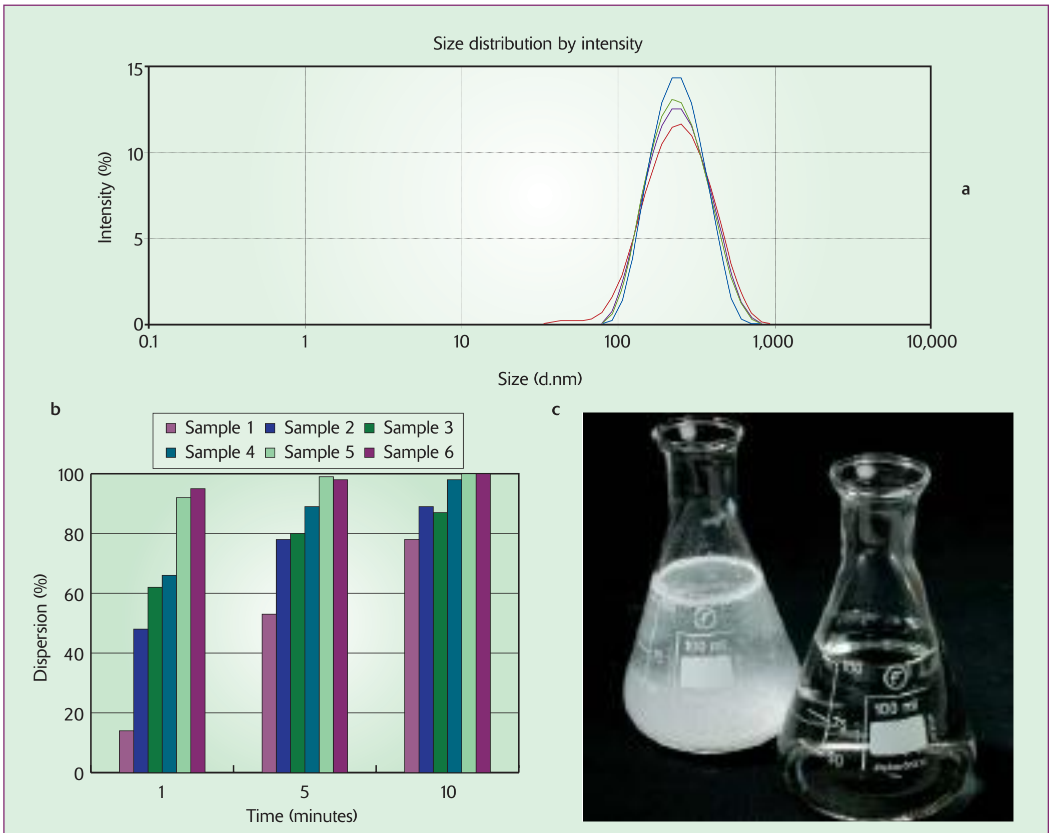

Figure 2 - Dynamic light scattering particle size distribution of an Iota-processed anti-inflammatory pharmaceutical. (a), demonstration of controlled release of nanoparticles from Iota powders & dipsersion of a hydrophobic anti-inflammatory drug in water (c) using conventional (left) and Iota powders (right).