Nanotechnology approaches to solving the problems of poorly water-soluble drugs

Traditionally, almost half of new molecular entities identified by pharmaceutical industry screening programmes have failed to be developed because of poor water-solubility, which makes their formulation difficult or even impossible. However, important advances are being made in improving the bioavailability of hydrophobic compounds, so that promising candidate drugs need no longer be abandoned or have their development stalled by sub-optimal formulation. In addition to more conventional methods, tackling this problem has become one of the main applications of nanotechnology in drug delivery. This is also the most advanced approach commercially, as formulation scientists increasingly turn to a range of nanotechnology-based solutions to improve drug solubility and bioavailability.

I t is estimated that the full development of a new prescription medicine from discovery to marketing approval in the United States typically takes 10-15 years and costs more than $800 million. On average, according to the Tufts Center for the Study of Drug Development, only five out of every 5,000 potential drugs are actually tested in clinical trials, and of these only one will eventually be approved for use in patients[1]. The curtailment of this enormous wastage, and consequent reduction in the overall costs of drug development, is clearly a priority for the pharmaceutical industry as a whole.

One essential factor in the development equation is drug solubility and bioavailability. Poor water-solubility has been attributed to almost half of the 150,000 new molecular entities (NMEs) synthesised annually by pharmaceutical companies, and is also claimed to reduce the performance of more than 10% of successfully marketed drugs[2].

Nanotechnologies have numerous and widespread applications but their earliest commercial impact is likely to occur in the fields of biotechnology and medicine. This is because, in addition to novel drug developments using materials in the 0.1-100 nanometre range, nanotechnology has the potential to breathe new life into both sub-optimally performing marketed drugs and also many of those pre-clinically promising candidate NMEs that were 'beached' owing to poor water-solubility.

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Table 1: Nanotechnology approaches to improve the solubility of hydrophobic drugs

COMPANY	TECHNOLOGY	
NANOPARTICULATE TECHNOLOGIES		
Elan	NanoCrystal	NanoCrystal drug particles (<1,000 nm) produced by wet-milling and stabilised against agglomeration through surface adsorption of stabilisers; applied to NMEs eg aprepitant/reformulation of existing drugs eg sirolimus
Eurand	Biorise	Nanocrystals/amorphous drug produced by physical breakdown of the crystal lattice and stabilised with biocompatible carriers (swellable microparticles or cyclodextrins)
SkyePharma	IDD	Insoluble Drug Delivery: micro-nm particulate/droplet water-insoluble drug core stabilised by phospholipids; formulations are produced by high shear, cavitation or impaction
BioSante	CAP	Calcium Phosphate-based nanoparticles: for improved oral bioavailability of hormones/proteins such as insulin; also as vaccine adjuvants
American Bioscience	NAB	Nanoparticle Albumin-Bound technology: injectable suspension of biocompatible protein with drug improves solubility/removes need for toxic solvents; eg paclitaxel-albumin nanoparticles
Baxter	Nanoedge	Nanoedge technology: drug particle size reduction to nanorange by platforms including direct homogenisation, microprecipitation, lipid emulsions and other dispersed-phase technology
NANOSTRUCTURING TECHNOLOGIES		
pSivida	BioSilicon	Drug particles are structured within the nano-width pores of biocompatible BioSilicon microparticles, membranes or fibres; gives controlled release/improves solubility of hydrophobic drugs
iMEDD	NanoGate	Silicon membrane with nano-width pores (10-100 nm) used as part of an implantable system for drug delivery and biofiltration
PharmaSol	NLC8	Nanostructured Lipid Carriers: nanostructured lipid particle dispersions with solid contents produced by high-pressure homogenisation; lipid-drug conjugate nanoparticles provide high-loading capacity for hydrophilic drugs for oral delivery

In addition, nanotechnology offers a means of providing novel formulations for existing marketed drugs as a way of extending the patent lifetime and therefore the exclusivity in terms of sales. The US FDA approved the first drug that specifically uses nanotechnology to increase solubility in 2000. A nanoparticulate formulation of Wyeth's Rapamune (sirolimus), an immunosuppressant to prevent organ transplant rejection, was developed by Elan using its Nanocrystal technology and has become the fastest selling drug in the transplant market.

In an effort to speed up the drug regulatory process, the FDA has provided guidance in the form of the Biopharmaceutics Classification System (BCS) with which to identify expendable clinical bioequivalence tests[3]. The BCS recommends a class of immediate-release (IR) solid oral dosage forms for which bioequivalence may be assessed based on *in vitro* dissolution tests. It can be used to justify a biowaiver based on the fact that observed differences in the bioavailability of two such IR products containing the same drug result primarily from *in vivo* dissolution differences in the gastrointestinal (GI) tract[4]. According to the BCS, drug substances are classified as:

Class I – high permeability, high solubility
Class II – high permeability, low solubility
Class III – low permeability, high solubility
Class IV – low permeability, low solubility

Thus, all poorly water-soluble drugs are classed as BCS II or IV.

The BCS biowaiver for *in vivo* bioavailability and bioequivalence studies requires excipients to be in a dosage form used previously in FDA-approved IR solid dosage forms, having a wide therapeutic window and showing rapid and similar dissolution, high solubility and high permeability. BCS-defined class boundaries for drug substances can be summarised as:

● RAPIDLY DISSOLVING – ≥85% of label amount of drug dissolves within 30min *in vitro*.
● HIGHLY SOLUBLE – highest dose strength soluble in ≤250 ml water at pH range 1-7.5
● HIGHLY PERMEABLE – absorption in humans ≥90% of an administered dose

In contrast, poorly soluble drugs present big challenges for the formulation scientist. Compounds with solubilities below 0.1mg/ml face significant obstacles, and often even those falling below 10mg/ml present formulation difficulties related to solubilisation. Those compounds with poor water-solubility that do get through to the market are frequently prone to suboptimal performance owing to low levels of absorption, and the effects of food intake when delivered orally. One answer is to give a higher dose to treat the patient's condition effectively, but this almost inevitably invites increased toxic side-effects and introduces the need for co-therapies to manage idiopathic conditions. There is always a risk for the patient in that the 'cure' might prove worse than the disease.

Poorly-soluble marketed drugs are clearly good candidates for reformulation using the emerging range of different technologies available to target these issues[2]. A recent BCS classification of the 130 orally administered drugs on the WHO model list of essential medicines found that, of the 61 that could be classified with certainty, about one-quarter were poorly soluble (10 [17%] class II and six [10%] class IV)[5].

There is also an excellent opportunity to rescue developmental compounds that were rejected owing to poor solubility[2]. However, prevention is better than cure, and in order to maximise the value of a specific compound it is necessary to solve these problems at an early stage. Accordingly, pharmaceutical companies are increasingly adopting strategies to deal with solubility and bioavailability issues at the earliest possible opportunity.

Technological solutions for hydrophobic compounds

The range of technologies currently available for improving bioavailability (ie, increasing the solu-

bility and/or the permeability or absorption) of poorly water-soluble chemical compounds and high molecular weight drugs can be split broadly (and for the purposes of this review) into conventional methods and nanotechnology. The oral route is the most convenient method of drug administration, but is subject to the bioavailability complications imposed by GI tract physiology and the effects of first-pass metabolism and biotransformation. While current methods may continue to offer fast and cost-effective solutions without compromising product quality, the future appears brighter for new technologies being developed to obtain ultrafine particles in the micro- and nano-scale range.

Conventional approaches to enhancing the solubility enhancement of hydrophobic drugs include:

● Synthesis of molecular species such as salts to facilitate dissolution.
● Drug particle size reduction by physical grinding and milling.
● Amorphous crystal formation for production of solid/resin dispersions: typically melt extrusion technology, in which supra-melt temperatures are used to produce a more soluble amorphous dispersion of chemical drug molecules in a polymer diluent such as polyethylene glycol (PEG).
● Use of surfactants/excipients, eg in self-emulsifying/micro-emulsifying systems: anhydrous lipid-based formulations containing drug dissolved in oil/s, together with surfactants and co-solvents; generally administered in soft gel capsules for spontaneous emulsion on contact with GI fluids.
● Conjugation/derivation (surface chemistry) of delivery system.

Furthermore, permeability of micro- and nano-sized drug particles is enhanced using a combination of:

● Enteric coating/muco-adhesive.
● Excipient/surfactants.
● Liposome/polymer delivery vehicles.
    ○ [eg poly(lactic-co-glycolic acid) (PLGA) microspheres].

either to prolong attachment to tissues or to increase biocompatibility between the drug delivery system and the tissue surface.

Nanotechnology (1 nanometre [nm] is one thousand millionth of a metre or 10^{-9}m) is extending these existing approaches to the nanoscale, while capitalising on the potentially valuable properties
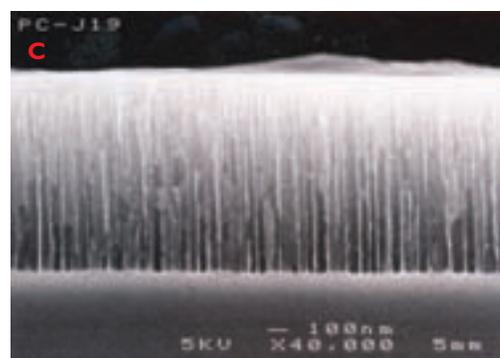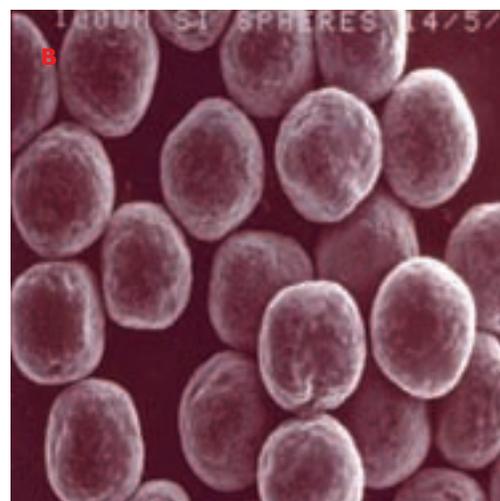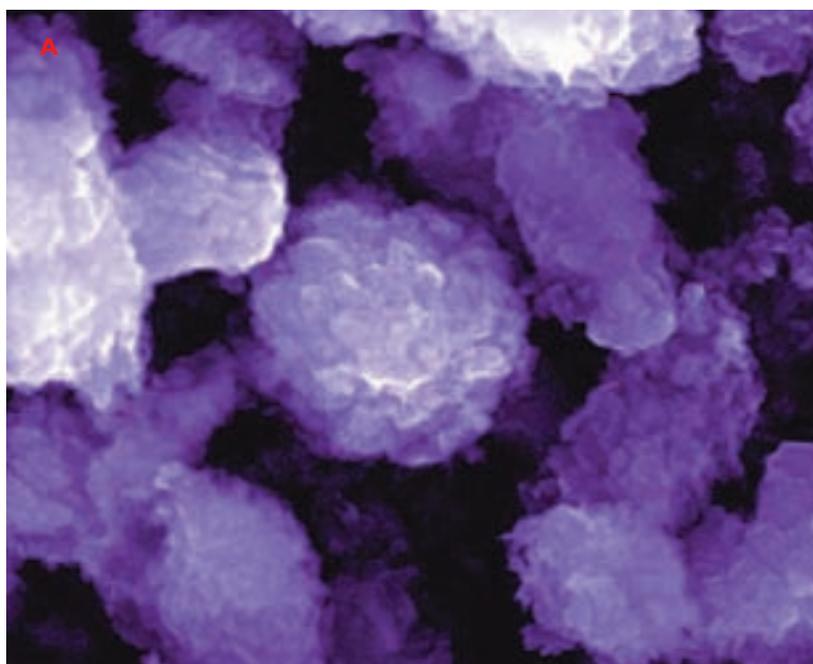
Figure 1: The solubility of hydrophobic drugs can be improved using nanostructured delivery technologies where drug molecules are held within nanometre-width pores of porous microparticles, such as those made from BioSilicon™ (pSivida). The drug is released through the pores as the matrix biodegrades. Solubility is increased owing to the huge surface area created by the nanostructuring process. **A** BioSilicon™ microparticles; **B** High resolution transmission electron micrograph (TEM) of high porosity BioSilicon™ – the bridges of the BioSilicon™ skeleton are tens of atoms across and the pores are tens of nanometres in diameter; **C** Scanning electron micrograph (SEM) of a cross section through a BioSilicon™ film on a bulk silicon wafer showing nanometre-sized pores running longitudinally

of materials at this size-range. The significance of the nanoscale (internationally defined as from 100nm down to the size of atoms [approximately 0.2-1nm][6,7]), depends on these potential differences, which naturally raises safety concerns, at the same time as raising hopes.

Some of the key nanotechnology-based approaches to the enhancement of drug solubility are summarised in **Table 1**. Many of these methods rely on reducing drug size to nanoparticles, thereby greatly increasing the surface area and leading to enhanced dissolution. As with conventional methods, however, stabilisers are often required to prevent recrystallisation and reagglomeration, while mechanical size-reduction processes can damage delicate molecules.

Nanostructured delivery technologies such as BioSilicon™ (pSivida) avoid these problems related to physical stress, as the drug is retained within a biocompatible nanoporous matrix and is released through pores in a controlled manner as the matrix biodegrades (see **Figure 1** on honeycomb structure, cross section and microparticles). The nanostructured silicon crystal-lattice scaffold

of BioSilicon provides a huge surface matrix for hydrophobic drugs and can be produced in diverse forms to suit a variety of drug delivery requirements. This technology exemplifies the critical difference in the scientific concept of the nanostructuring approach compared with nanoparticle-based technologies.

Controlled release of hydrophobic compounds

Sustained drug action may be achieved in various ways, including enhanced circulatory persistence of the drug and cellular targeting, as well as by controlled-release methodologies.

Effective controlled-release drug technologies focus on solid dose formulations of hydrophobic compounds rather than lipid-based systems, the exception being liquid gel formulations with osmotic pumps such as Alza's OROS osmotic system. In general, however, solid dosage methods for precise linear release of poorly soluble compounds are simpler and less expensive to develop.

The kinetics of drug release from the majority of controlled-release formulations are less than ideal,

often comprising an initial burst of enhanced solubility but failing to ensure complete delivery and absorption of the drug dose. This is a common problem for oral BCS class II drugs (with low solubility but high permeability) formulated with surfactants, as the surfactant that aids on-site drug dissolution or dispersion at one level will suppress it at a higher concentration.

Novel methods of reducing this reliance on release-accelerating agents, and prolonging controlled delivery of oral drugs such as nifedipine and glipizide from hydrophilic matrices, were recently described: one based on electrolytic control of pH, and the other on formation of hydrophobic associations and hydrostatic interactions in the matrix using polar or amphoteric excipients[9].

Therapeutic efficiency is enhanced by controlling the release of drugs over specific periods. The structuring of biocompatible nanomatrices for controlled drug release is an important application of nanotechnology as it avoids the dependence on chemical modifications of the matrix to suit individual drugs, which is typical of polymer-based systems. This immediately simplifies the drug delivery system as well as reducing the toxicity potential.

Essential characteristics in nanostructured materials include biocompatibility, accurate control of nanostructuring to provide consistency in terms of drug release kinetics, and drug-loading efficiency.

Nanostructured silicon is emerging as a material that is showing great promise not only for controlled release of drugs, but also for increasing the bioavailability of poorly water-soluble drugs. Decades of experience in micro-electronics has meant that extremely pure silicon is readily available and the technology for creating micro- and nanostructured forms is also established.

Nanostructured silicon also has the benefit of being made biodegradable where the kinetics of drug release depend on the rate of biodegradation of the matrix. The rate of degradation can be customised for a range of drugs and depends on matrix porosity and pore width. Also, in this case, the porous structure presents a massive surface area, which has the effect not only of increasing the solubility of hydrophobic drugs loaded into the nanopores, but also allowing a very high drug-loading potential compared with other drug carriers.

The nanostructuring of silicon has also permitted the targeted heat ablation of experimental tumours in mice (eg Nanospectra Biosciences' nanoshell-assisted photothermal therapy [NAPT][11]). Intravenously injected nanoshells, having a silicon core sealed into an outer shell of gold and 'tuned' to near infrared optical absorption, accumulate in tumours via the abnormal vasculature, enabling selective ablation of the tumour by the conversion of directed laser light into heat. In addition, non-biodegradable nanoporous silicon membranes are being used in implanted devices to control the prolonged release of drugs (for up to six months) from enclosed polymer reservoirs (iMEDD's NanoGate; DebioTECH's DebioSTAR), also to screen implanted islet cells from the host's immune defences: letting out insulin produced by the pancreatic cells and letting in nutrients and glucose but not the relatively large antibodies (University of Boston Department of Medical Engineering)[10].

Nanotechnology issues

Nanosciences promise to be the key technology of the future, with multifaceted applications including major developments in drug therapy. The potential of nanotechnology in pharmaceuticals, medicine and healthcare is undeniable, as the natural biological (cellular) interface operates at the nanoscale (from 1-100nm).

Inevitably, however, this raises safety concerns, as the known properties of familiar materials can change when they enter the nanometre range. The knowledge that exposure of animals to nanoparticles can lead to neurological damage[12,13], as well as respiratory and circulatory problems[14], has driven governmental research into the safety of these new technologies. For example, in addition to US regulatory considerations[7], the recently reported European Union (EU)-funded Nanosafe project was concerned with the opportunities and risks associated with industrial applications of nanoparticles[15].

A new EU project, Nanosafe2, is aimed at development of methods for the safe use of nanoparticles, including measurement techniques and researching their toxicological properties[16]. This project involves 24 partners from seven EU countries, with a total budget of approximately €12.4 million (about €7 million being provided by the EU research funding programme and the rest by the companies involved).

In the United Kingdom (UK) an independent study by the Royal Society and the Royal Academy of Engineering was commissioned to assess effects of nanotechnology on the environment, safety, health and ethics[6]. This was published in July 2004 and concludes that most products based on nanotechnology are harmless, with the possible exception of free nanoparticles and (carbon) nanotubes. Any danger lies in the very properties being exploited,

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such as high surface reactivity and the ability to cross cell membranes: it is likely that nanoparticles will penetrate cells more readily than larger particles, and until unresolved questions are answered, both of these specific nanoproduct classes should be treated as new substances under EU chemical substances legislation.

Fixed nanoproducts such as controlled release hydrophobic drugs are less likely to be affected by these safety considerations, especially in the absence of chemical modifications. In particular, the production of 'nano-holes' to incorporate drug molecules simply avoids the safety issues associated with nanoparticles.

Conclusions

The pharmaceutical and biotechnology industries continue to generate promising NME candidates; however, many potential drugs create challenges for their successful development to commercial dosage forms and products. In particular, low solubility and bioavailability present limitations for a large proportion of new therapeutics, in addition to the requirement to mediate clinically-relevant effects for an appropriate period of time.

Clearly, nanotechnologies offer new ways to address these drug delivery challenges and are being applied in a wide range of healthcare settings. Given a responsible Research & Development strategy, including the early consideration of public safety concerns, significant therapeutic advances are to be expected from this growing field within the next few years. Looking further into the future, nanomedical concepts such as dissolving 'smart' applications, ticking tablets, and implantable systems able to monitor disease biomarkers and deliver the appropriate therapeutics are transforming science fiction into fact as the supporting technologies advance.   DDW

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