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Small Steps for Mankind: Controlled-Release Gets Smarter Thanks to Nanotechnology

By: Cindy H. Dubin

INTRODUCTION

Issues of solubility, safety, drug delivery, and disease targeting often leave researchers scratching their heads, looking for a way to improve upon these realities of drug development. Nanotechnology is proving itself as the answer to smarter formulation.

"Nanotechnology is the key to optimizing drug delivery," said Dr. Roger Aston, Director of Strategy at pSiVida Limited in Australia. "By presenting drugs at the nanoscale, the immediate impact is making otherwise poorly soluble drugs much more bioavailable, soluble, and safer."

Just about half of all new chemical entities are insoluble, thus improving solubility and bioavailability is the first principal aim of nanotechnology. The second is to enhance release characteristics.

In addition to improved solubility, drugs based on nanotechnology have several other advantages over those developed by other means, according to the Institute of Nanotechnology in Glasgow, Scotland. For example, drugs tend to perform better in nanoparticulate form as the drugs perform more efficiently and with fewer side effects. And, specific nanosized receptors present on the surface of cells will recognize the drug and elicit an appropriate response, thus delivering and releasing the therapeutic exactly where needed.

TARGETING STRATEGIES

It is in this realm of nanotechnology that pSiVida is targeting its strategy: Existing registered proprietary drugs that pose difficulty in delivery; new drugs coming out of the biotechnology sector for which delivery is not yet developed; generics that can benefit from a new commercial life cycle by reformulation (e.g., better safety, efficacy, compliance, etc.); and newly designed products benefiting from the unique properties of pSiVida's BioSilicon (e.g., brachytherapy and chemo brachytherapy and drug-eluting devices for vasculature or bone therapy such as stents and antibiotic or bone growth factor devices).

pSiVida's BioSilicon is a new nanostructured biomaterial that allows drug molecules to be held in nanosized pockets that release tiny pulses of drug as the BioSilicon dissolves. The rate of dissolution can be tuned so that delivery can be achieved over days or months. BioSilicon is a nanostructured drug delivery system based on elemental silicon (the same material as the microchip that runs a cell phone or computer) and has application to a variety of drugs that have problematic delivery and bioavailability characteristics. pSiVida is exploring ophthalmic implants from both a drug delivery perspective and a tissue engineering aspect. Initial constructs involve biodegradable implants for drug delivery from the tissue surrounding the eye.

"The eye is a particularly favored target due to the safety of BioSilicon," said Dr. Aston. "Unlike the degradation products from polymers like lactides and glycolides, silicic acid (the product from BioSilicon) is a very mild acid, expected to cause less irritation."

Dr. Aston also explained that silicon and BioSilicon offer the only technology to generate genuinely "smart" products through the chip potential of the material. "Microprocessors are getting smaller and smaller, and we can already consider delivery devices that release drugs through chip-based intelligence. This will allow delivery characteristics that are essentially processor controlled. Diagnostics in the body would be biodegradable devices that report the health of a patient back to the doctor. No drug delivery system/diagnostic can come close to this yet. BioSilicon can be fashioned into a biodegradable intelligent chip-based device. We still need to do some development here, particularly with safe and biodegradable power supplies; however, this is ultimately where nanotech, electronics, and healthcare come together."

pSiVida's first intelligent products will be diagnostic in-the-body biodegradable devices that will report health through measurement of various biomarkers, such as for

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FIGURE 1

Illustration of the Complex Formation of the Hydrophobic Drug & Amino Acid by Reversible Association

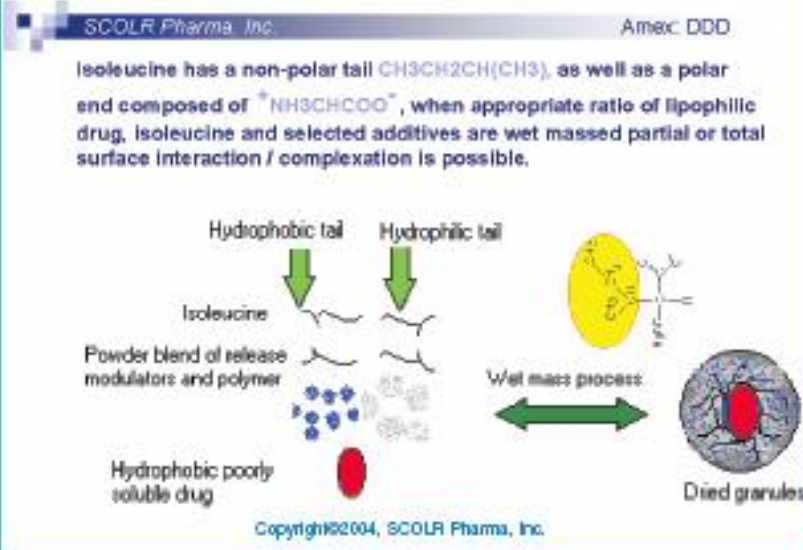
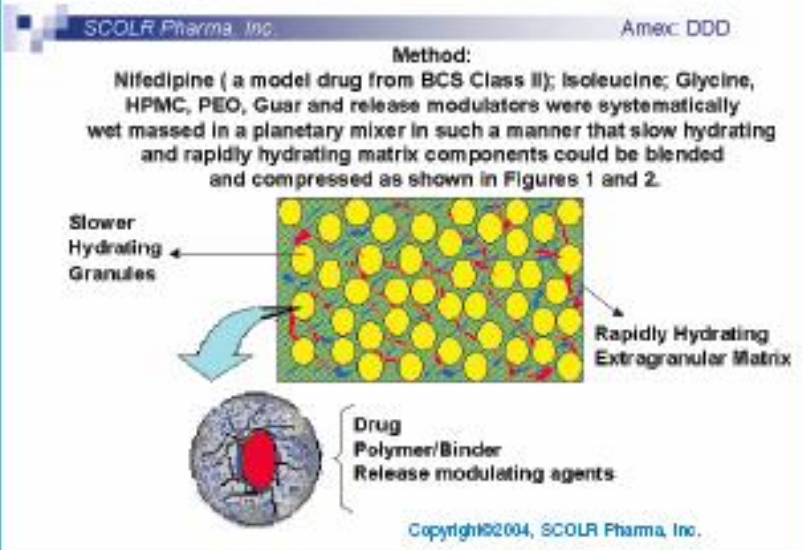


FIGURE 2

Illustration of the Amino:Drug Granules Dispersed Within the "Extra Granular" Polymer Matrix of the Final Tablet Dosage Form



tumors. One issue facing pSivida will be instilling confidence that BioSilicon is safe, in the wake of the negative press surrounding silicone implants in the past, and the more recent concerns voiced about nanotechnology.

Dr. Aston emphasized that silicon and silicone are vastly different materials, the latter being a non-biodegradable polymer that contains other elements such as carbon. Unlike silicone, BioSilicon is safe in that it degrades into silicic acid, a form of silicon found in most foodstuffs. Dr. Aston said that the daily intake of silicon through normal diet will often exceed the doses expected for drug delivery or diagnostic implants.

One distinction between the two is that pSivida's porous silicon breaks down in the body to form BioSilicon. pSivida has already conducted animal studies in which high doses of BioSilicon have been ingested over extended periods, with no evidence of toxicity. Additionally, many concerns surrounding nanotechnology have related to its accumulation in tissues such as the brain. This should not occur with BioSilicon as it is biodegradable.

SCIENTIFIC FRONTIERS

Because oral drug delivery continues to be the preferential route of administration, researchers are seeking ways to incorporate nanotechnology in oral formulations. Oral delivery is a particularly favored route for BioSilicon because the material is resistant to degradation in an acid environment.

And at the 2004 *Controlled Release Society Annual Meeting*, engineers from the University of Texas at Austin described their discovery and research of nanospheres and oral drug delivery. Nanosphere carriers can transport a drug safely through the hostile environment of the stomach and can be formulated into controlled-release tablets or capsules. The spheres were created from hydrogels, which are stable, organic materials that swell at a rate dependent on the acidity of their environment. As a drug-laden hydrogel swells, drug is released.

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FIGURE 3

Effect of a Combination of Isoleucine (Hydrophobic Amino Acid) & Glycine (Hydrophilic Amino Acid) on Nifedipine Release. Significant Improvement Over Conventional Formulation Strategies Illustrates the Potential for Solubility-Enhancing Complexes of Amino Acids & Hydrophobic Drugs.

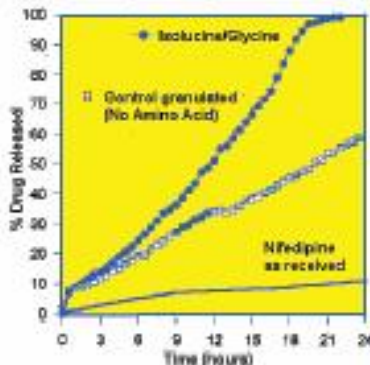
SCOLR Pharma, Inc.

Amex: DDD

Dissolution Studies:

•Dissolution medium: 0.2% SLS adjusted to pH6.8 (buffer system), Modified USP apparatus II, with ring mesh device, paddle speed 50 rpm.

- Drug solubilization and controlled release via a possible "Salt-in" mechanism within a complex hydrophilic matrix



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"Developing smart drug delivery systems that are timed to release drug at a specific time and specific site in the body is very exciting," said Dr. Nicholas Peppas, Professor of Chemical Engineering, Biomedical Engineering and Pharmaceutics at The University of Texas at Austin.

Altair Nanotechnologies, Inc., of Reno, Nevada, is testing its hollow, porous, high-surface area, rigid, ceramic microstructures (TiNano Spheres) in drug delivery and dental compounds. Made from titanium and zirconium, these structures can be coated on the inside, outside, or both with active pharmaceuticals to provide controlled-release characteristics. According to the company, the differentiating characteristic of TiNano Spheres compared to commonly available polymer-based drug delivery systems is that the Altair system can produce a sustained drug delivery system for narcotics. The company plans to license

the technology with pharmaceutical companies interested in incorporating their active pharmaceutical ingredients in the TiNano Spheres.

There is also growing interest in how controlled release and nanotechnology can work together in the field of chronotheapy. This involves using the body's circadian rhythm to maximize a drug's effectiveness.

Consider cardiac therapy. Evidence shows that most heart attacks occur from 4 AM to 6 AM.

"If the last pill a patient takes is before he goes to sleep, his metabolism gets rid of the drug by that time of the morning," explained Stephen Turner, Vice President and Chief Technology Officer at SCOLR Pharma, Inc., in Bellevue, Washington.

"Ideally, controlled-release devices would have the ability to release the drug at specific intervals of the day, allowing a patient's nighttime heart medication to release drug at 5 AM," added Dr. Peppas.

According to the Institute of Nanotechnology, controlled and targeted drug delivery represents a frontier of science. Drugs can be encapsulated in a variety of carriers, such as a carbon nanotube that is like a silicon wafer with antibodies or other molecules that will bind to the drug. Encapsulated drugs can be protected from degradation. The drugs may be in particles with coatings only a few nanometers in thickness. The drugs are normally ingested or implanted and designed to deliver a controlled release of drug, which may last for many months and can be activated at different sites in the body. Nanopores can act as tiny turnstiles for releasing drugs. By making the nanopores only slightly larger than the molecules of drugs, they can control the rate of diffusion of the molecules, keeping it constant, regardless of the amount of drug remaining inside a capsule. Drugs in nanocrystalline form can be administered in smaller doses because they can be delivered directly to the tissue and in controlled doses.

THE PRICE OF NANO

"One does not need large volumes of a drug to treat a disease," said Dr. Peppas. "Smaller volumes are preferential because they are expensive to deliver to the whole body."

Mr. Turner said one hurdle associated with nanotechnology is the cost barrier. He said the physical process of making nanoparticles (milling, crystallization, etc.) is very expensive. "The cost of the drug should be on the mind of formulators as managed care will not reimburse inappropriate drug delivery products. Formulators must consider the financial impact of nanotechnology on the drug."

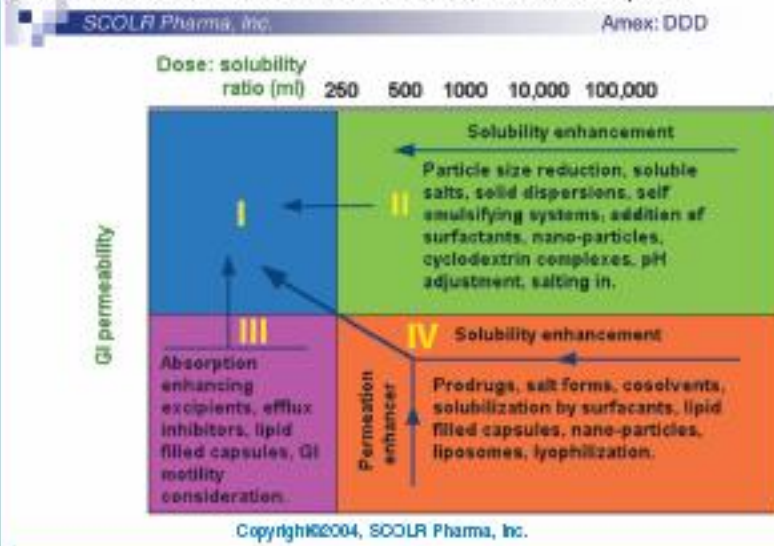
This, however, is not the case for all forms of nanotechnology, according to Dr. Aston. "It depends very much on the manufacturing process. Certainly research costs will have to be borne by the patients as significant sums are being currently invested in this new technology, but the products themselves can be very

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FIGURE 4

Possibilities of Shifting the Solubility-Dissolution Characteristics From a Very Poorly Soluble Drug to D5 Within the Range of Values Encountered in the Human GI Tract (D5 = 250 ml). The Role of Solubility Enhancement is to Attempt to Shift the Classification of the Drug in Order to Eliminate the Problems Associated with Dissolution Limited Compounds.



cheap. Indeed, in the case of BioSilicon, it is less expensive than current marketed polymer-based drug delivery devices.

Mr. Turner said cost is where SCOLR's technology competes with nanotechnology. His specialty pharmaceutical and drug delivery company is focused on oral controlled-release drug delivery, but does not use nanotechnology in its formulation.

SCOLR's platform of patented CDT® technologies enable delivery of active pharmaceutical, OTC, and nutraceutical ingredients from a tablet or capsule over an extended time period. The CDT platform is founded on the art of matrix erosion, changes in gel thickness, electrolyte ionization, and ionic interactions. These are self-correcting systems that lead to carefully controlled erosion as well as a predictable, programmable release of the active ingredient contained in the medicinal core. Previously, this has not been achievable with first-generation delivery systems. This technology enables

successful formulation within two different classes of drugs: Class I (high permeability/high solubility) and Class II (high permeability/low solubility). SCOLR is also exploring the possibility of formulating certain Class III drugs (low permeability/high solubility), which are historically very problematic.

Three CDT patents have been issued to date. The third (the amino acid platform) allows for the controlled release of an active pharmaceutical ingredient during a 24-hour period, independent of its solubility. Figures 1 through 4 demonstrate the amino acid system and its potential.

"We developed the amino acid patent to address the issue of insolubility, like nanotechnology does. We do so in an oral route, which is the most preferential route and has the lowest price point," explained Mr. Turner. "Whether a formulator chooses to use nanotechnology or the CDT platform, at the end of the day, the drug has to be absorbed."

BIOGRAPHY



Ms. Cindy H. Dublin has been a professional journalist since 1988, acting as Chief Editor of various journals and magazines for leading publishing companies. She has spent the past 3 years focusing her writing on pharmaceutical formulation and development. She was recently recognized by the American Society of Business Press Editors for her article on nanotechnology. Ms. Dublin earned her BA in Journalism from Temple University in Philadelphia and a certificate in Business Logistics from Pennsylvania State University.