the consensus reached is that acoustic cavitation, which is the formation and collapse of gaseous cavities, has the dominant role in sonophoresis, particularly under low-frequency conditions [7]. In an attempt to develop an in-depth mechanistic understanding of this technique, recent studies have investigated the interactions of cavitation bubbles with the stratum corneum [7]. Sonophoresis has also been shown to operate in synergy with other enhancers of transdermal drug transport, including chemicals, electroporation and iontophoresis [8]. Understanding the synergistic relationship that exists between various enhancers and selecting the right combination represents a large opportunity to develop potent and safe methods to enhance transdermal drug delivery that as yet has only been sparsely exploited.

While significant advances have been made on the scientific front, technological innovations have also had an impact on sonophoresis. For example, the FDA has recently approved the use of a low-frequency portable ultrasound device for skin permeabilization. In addition, the development of low-frequency, low-profile transducers for sonophoresis was recently reported [9].

Over the past fifty years, sonophoresis has undergone a significant transformation from a technique that was primarily developed for the local delivery of small hydrophobic drugs to a method that can deliver systemic doses of macromolecules. This journey has been facilitated by an infusion of novel research in this area and the technological discoveries that are associated with ultrasound devices. Although research has led to an improved understanding of the sonophoresis mechanism, further investigations are needed to enhance knowledge of this mechanism. Specifically, detailed characterization of cavitation events on the skin surface will prove useful in designing strategies for controlling cavitation with a view to achieving greater enhancement in drug delivery without compromising safety. Future investigations must also concentrate on the collection of supplementary safety data. In addition, the challenges that are linked with practical issues, including the scale-up of doses from animals to humans, device development and regulatory processes, must be tackled.

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Turning from monogamy to strategic promiscuity

Pharmacologists usually like to have therapeutic compounds that are selective for the desired target only. In most cases, this approach reduces unwanted side effects and clarifies the pharmacodynamic activity of the compound. Nevertheless, many patients are non- or poor-responders to a therapy that influences only a single target when multiple factors contribute to the complex biochemical expression of a manifested disease. Taking antipsychotic drugs as an example, it is clear that the action of these drugs on multiple targets, rather than focusing on one neurotransmitter receptor subtype only, results in an optimized therapy. However, the improved understanding of diseases at the molecular level, including receptor activities, enzyme interactions and biochemical cross-talk, complicates the process of identifying potential targets. Progress in the field of proteomics adds valuable information at each level. Therefore, it is reasonable to adopt strategies that address multiple targets simultaneously. Furthermore, there is no doubt that taking one drug that acts at multiple sites with a single pharmacokinetic profile instead of a cocktail of drugs with different pharmacokinetics is advantageous.

In a recent issue of *Drug Discovery Today*, Morphy and colleagues [1] addressed the topic of 'designed multiple ligands'. Whether these potentially therapeutic drugs are referred to as multiple, bivalent, polyvalent or hybrid compounds, the increasing trend in the design of such molecules represents an improved knowledge of the targets for the therapy of different diseases and the potential benefit of targeting more than one molecular receptor and/or pathway. The authors elegantly describe, with several examples, that the modulation of different receptors and/or enzymes could have supporting therapeutic effects. Nevertheless, the addition of another molecular target also adds complexity to the design of compounds.

In this respect, affinity values or inhibition constants alone should not be tracked because *in vitro* results only represent pieces of the therapeutic

 PII: S1359-6446(04)03208-8

mosaic. In their review, Morphy *et al.* [1] propose 'ten aspirations' that they suggest could potentially be used to asses the feasibility of the design of a compound with potentially multiple targets. If these 'aspirations' are followed, with a particular emphasis on the recommended 'balanced modulation of several targets', the possibility that disease conditions could lead to targets having different (patho)physiological distributions, different densities, different cellular environments and different adaptations (e.g. internalization, receptor coupling and receptor upregulation) must be considered. Therefore, of the ten recommendations listed, which encompass topics that are generally applicable to many of the requirements in drug development, particular importance must be placed on the need for a clear understanding of the *in vitro–in vivo* relationship of a compound; an evident relationship between *in vitro* activities, *in vivo* activities and clinical profile is what everybody in drug development desires but hardly ever achieves. Successful drug development depends on interdisciplinary work between specialists in the medicinal chemistry, molecular modelling, crystallography, biochemistry, pharmacy, pharmacology and clinics fields, as well as with those working in life sciences. In general, this seems to be the case in current drug development, but there is an even greater need for cooperation when multiple targets per molecule is the focus of research.

A change in direction for the route to successful drugs from a single target (monogamy) to selected multiple targets (strategic promiscuity) appears to be a highly promising and potentially beneficial therapeutic strategy. However, a superior understanding of the causes, and their complexity, of the disease is essential.

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Medicinal chemistry: new technologies and developments

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The Medicinal Chemistry Division of the American Chemical Society (http://www.chemistry.org) offered a rich menu of drug research papers at the 227th *American Chemical Society National Meeting* in Anaheim, CA, USA (28 March–1 April 2004).

The Chemetics™ technology developed by the Danish firm Nuevolution (http://www.nuevolution.com) appears to take the concepts of combinatorial synthesis and HTS one step further by using a hybrid of wet chemistry and molecular biology. Alex Gouliaev of Nuevolution described this technology as a wet chemistry process in which DNA-directed synthesis is performed in a single reactor to produce ultra-large small-molecule libraries that contain 10^8–10^{14} compounds. The starting materials are synthesized using standard organic synthetic chemistry before library formation, and could include most of the chemical structures that are currently used in medicinal chemistry.

New chemical entities could be isolated from the mixture of compounds by a selection process that mimics natural evolution. Gouliaev suggested that Chemetics™ could revolutionize drug discovery by enabling the one-pot synthesis and the screening of billions of drug-like small molecules in just a matter of weeks. Chemetics™ technology uses DNA-template sequences to direct the synthesis of small organic molecules. On incubation of the DNA-templates with oligonucleotides to which different drug fragments have been attached, the oligonucleotides bind to their complementary base in the DNA-template, which fixes the position of the drug fragment and facilitates their reaction. As a result of the close proximity effect, only drug fragments that are associated with the same complex will react. Thus, the end-result is that a specific DNA-template directs the synthesis of a particular molecule. Moreover, the structural diversity of this large library is much greater than that produced by current combinatorial

1359-6446/04/$ – see front matter PII: S1359-6446(04)03140-X