Implications

By this time, many of you will have guessed that LaRue's paper is a serio-comic jibe at this area of nursing. However, it does have implications in the way that oral dosage medications, such as tablets, are formulated and presented. Many patients do have problems with swallowing tablets whole, and hence size and shape are important. These are also important considerations for patients who might lack the coordination to pick up small tablets. In recent times, fast dissolving or chewable formulations have been introduced to aid patients with swallowing difficulties.

'Where there's a pill, there's always a way'

A more intractable problem is the dose of the drug because, if this is large, as in the case of some antibiotics, the formulator is on the horns of a dilemma – providing one large dose will necessitate a large tablet but dividing the dose will result in an increased number of tablets, albeit smaller in size. Both options are associated with potential problems. However, formulators will invariably provide the answer – where there's a pill there's always a way!

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Sonophoresis: a 50-year journey

In 1954, Fellinger and Schmid [1] reported the successful treatment of digital polyarthritis using hydrocortisone in combination with ultrasound. Fifty years later, this technique, which is named sonophoresis or phonophoresis, has emerged as a powerful method for the facilitation of transdermal drug delivery. In a recent issue of *Drug Discovery Today*, Lavon and Kost [2] present an excellent review of the current status of sonophoresis.

Following the first report by Fellinger and Schmid, a number of studies were reported on the sonophoretic delivery of small molecules through the skin [3]. These studies were typically performed using ultrasound with frequencies in the range 1–3 MHz. Enhancements in the levels of drugs transported through the skin were only observed for particular drugs. For example, improvements in the transport of hydrocortisone and indomethacin were observed but not in the transport of lidocaine and salicylate [4]. This variation between drugs raised controversy about the use of sonophoresis for drug delivery. An explanation for the variation was recently offered based on the differences in physiochemical properties of drugs, for example, lipophilicity and molecular weight [4]. Specifically, small lipophilic drugs, which rapidly diffuse through the skin under passive conditions, do not show enhanced transport after application of ultrasound.

Several research groups from diverse disciplines, including engineering, pharmacy, physics and medicine, have worked collectively over the past five decades, and particularly over the past ten years, to gain a mechanistic understanding of sonophoresis and to improve the delivery efficiency of this methodology. In the 1990s, sonophoresis received a major boost from the identification of low-frequency conditions (20 kHz < frequency <100 kHz) [5,6] that enabled the application of sonophoresis to the delivery of macromolecules through the skin. To date, *in vitro* and *in vivo* experimental data exist for the sonophoretic transdermal delivery of insulin, heparin and the tetanus toxoid vaccine. The challenge now lies in converting these exciting laboratory investigations into useful products.

The mechanism of sonophoresis has been the focus of considerable attention;

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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

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