A pharmaceutics perspective on drug delivery to the nail: recent advances and challenges.

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The rationale behind the development of topical therapies for nail disease is clear. The area is often described as an unmet medical need and is addressed by active research and recent progress in new formulations and actives (1). Diseases of the nail, primarily psoriasis and onychomycosis, have a relatively high prevalence and a significant social (quality-of-life), psychological and economic impact (2-7). Systemic therapies are not usually recommended for patients with nail psoriasis alone (2-4) and application of topical agents or painful local injections of steroids are often unsuccessful (2-4). Onychomycosis affects 2-15% of the general population, 20-30% of the >60 years and ~34% of diabetic patients (5-6); an incidence expected to rise in our progressively aged and overweight societies. Antifungal systemic therapy results in side-effects and drug-drug interactions, a clear disadvantage when treating patients with co-morbidities. Unfortunately, antifungal topical treatments are limited to superficial and less severe infections as their efficacy is limited (5-8). The percentage of patients with onychomycosis attaining complete cure with topical products was 5-9% for tavaborole and ciclopirox products and 12.7-54 % for amorolfine and 15-18% for efinaconazole (8-10). Thus, we are still far from the final target, i.e., the availability of efficient topical treatments with which to replace current oral therapies.

Popular wisdom in the field is that nail topical products fail to deliver sufficient amount of the active to the target areas of the nail apparatus. The general assumption being that the structural properties of the nail plate render this structure a formidable barrier to drug penetration. However, the nail thickness and structure are not the complete story; one should not forget that a formulation performance depends on many factors. First of all, the pharmacodynamics, in this case antifungal activity, dictates the active concentration required at the target site. This concentration must be ensured by the formulation through the release, delivery and local absorption of the active with the right rate and extent. The standard approach to oral formulation development discriminates and characterizes separately the release and absorption processes. Thus, dissolution tests and bioavailability studies provide information later linked through *in vitro – in vivo* correlation procedures. The Biopharmaceutical Classification System divides oral drugs in four categories depending on their high/poor solubility and permeability, further reinforcing the message that good permeability is not sufficient to ensure appropriate bioavailability and performance. Quite differently to dissolution tests, in vitro permeation studies (IVPT) performed with topical, nail and skin, formulations, normally include the corresponding membrane. The assumptions underlying IVPT methodology are: (a) that drug diffusion across the skin and the nail constitutes the rate limiting step to topical absorption and therefore, this approach provides the best information with which to predict *in vivo* performance and (b) that drug partitioning into and diffusion across these membranes are so reliant on interactions between the barrier and the vehicle that both elements are required for any IVPT to be meaningful. This is true indeed, but the composition of some medicated nail lacquers is such that the release of the active, rather than its permeation across the nail plate, becomes the rate limiting step of the process so the first assumption is not met. It is common for nail lacquers to contain solvents that evaporate upon application or permeate the nail themselves. A transient period during which the active is super-saturated in the film may increase penetration but will, eventually, be followed by drug crystallization, rendering the active unavailable for further partitioning into the plate. For example, we have observed that fluxes across agarose gels and dialysis membranes of two antifungals decreased dramatically just one to two hours after application of some lacquers. It follows that improved formulations that maintain the drug solubilized and able to partition into the nail plate for the required period of time provide an

additional strategy with which to improve topical therapies. Indeed the superiority of recently developed aqueous based nail lacquers might be linked to these residual formulation effects (11). Alternatively, colloidal carriers (nanoparticles and hydrogels) have been used as drug reservoirs with this purpose (12). Failing to address this issue will alleviate, but not completely solve, the problems related to low nail bioavailability; indeed even the best permeation enhancer will struggle to deliver crystalized drugs. A first step towards the rational development of efficient nail formulations would be the availability of standardized *in vitro* release (IVRT) and *in vitro* permeation (IVPT) tests with which to establish the efficiency of the release and permeation processes. Ideally, the long term aspiration would be to develop *in vitro-in vivo* correlations, a more complex process requiring identification of the metrics with which to characterize the *in vivo* performance of medicated nail products.

Currently, most *IVPT* are based on diffusion cell methods and employ either human nails or animal hooves; the concentration of the active or alternatively its antifungal activity is measured at the receptor chamber; the drug can be extracted from the complete nail or from microtome sections. The approaches range from keratin disks to toes from cadavers (1,13). As always, it is crucial to avoid extrapolating the predictive value of any model beyond its scope and to objectively assess the limitations of any experimental design before concluding and comparing results. For example, the size of a nail sample can alter significantly IVPT results as recently illustrated (14). Some experiments hydrate extensively the nail before applying formulations but it is known that water causes significant effects -increased porosity and swelling, altered impedance- on the nail structure, and is considered a penetration enhancer itself (12,15,16). Mechanistically, the role of physicochemical properties (log P, molecular weight, ionization) should be characterized in experiments reflecting practical applications and the differential permeation pathways for lipophilic and hydrophilic substances (12) further elucidated.

The lengthy duration of IVPT studies could be alleviated by developing a methodology similar to the dermatopharmacokinetics approach. Presently, to assess drug uptake into the nail post-application of a formulation requires either a destructive extraction technique, which does not provide any detail about the precise localisation of the penetrant or physical dissection/filing, a time-consuming process that yields limited information. In addition, neither approach allows the time course of chemical uptake into the nail to be determined, each method providing only a single datum at one specific time post-treatment. The recent developments based on FTIR spectroscopy (17) and Raman confocal microscopy will provide useful new tools. For example, the permeation of water, DMSO and propylene glycol across the nail has been characterized in a semi-quantitative manner using Raman confocal microscopy (12).

The panorama is not bleak, new developments include new drugs and formulations as recently reviewed (1,13). The need for a wiser integration of formulation, physicochemical and antifungal properties is increasingly recognized. It is crucial to balance a drug's MIC with its ability to permeate the nail as illustrated by tavaborole, a recently commercialized antifungal that compensates a higher MIC with a favourable penetration profile due to its lower molecular weight (1). The potential administration of drugs across the skin adjacent to the nail apparatus is increasingly being explored. Other physical methods to improve topical nail therapies involve the use of iontophoresis and lasers. Nail iontophoresis, a somehow logical extension of transdermal iontophoresis, has shown some positive results (18). Yet, these more complex technologies must demonstrate a clear superiority

with respect to the more economic formulation-based approaches if they are to be embraced by public health systems.

To summarize, significant progress has been made in the last 15 years. The interest of topical nail formulations has become recognized in the drug delivery field and is being looked at from different angles and perspectives. Transungual drug delivery is now firmly positioned in the pharmaceutics arena; we must now embrace a more rational and integrated approach to the experimentation and development of new therapies.

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