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Research paper

Application of Hansen Solubility Parameters to predict drug–nail interactions, which can assist the design of nail medicines

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ABSTRACT

We hypothesised that Hansen Solubility Parameters (HSPs) can be used to predict drug–nail affinities. Our aims were to: (i) determine the HSPs (δ_D, δ_P, δ_H) of the nail plate, the hoof membrane (a model for the nail plate), and of the drugs terbinafine HCl, amorolfine HCl, ciclopirox olamine and efinaconazole, by measuring their swelling/solubility in organic liquids, (ii) predict nail–drug interactions by comparing drug and nail HSPs, and (iii) evaluate the accuracy of these predictions using literature reports of experimentally-determined affinities of these drugs for keratin, the main constituent of the nail plate and hoof. Many solvents caused no change in the mass of nail plates, a few solvents deswelled the nail, while others swelled the nail to varying extents. Fingernail and toenail HSPs were almost the same, while hoof HSPs were similar, except for a slightly lower δ_P. High nail–terbinafine HCl, nail–amorolfine HCl and nail–ciclopirox olamine affinities, and low nail–efinaconazole affinities were then predicted, and found to accurately match experimental reports of these drugs' affinities to keratin. We therefore propose that drug and nail Hansen Solubility Parameters may be used to predict drug–nail interactions, and that these results can assist in the design of drugs for the treatment of nail diseases, such as onychomycosis and psoriasis. To our knowledge, this is the first report of the application of HSPs in ungual research.

1. Introduction

The human nail can suffer from a number of diseases, such as onychomycosis (fungal infections of the nail) and psoriasis [1]. These diseases are common and significantly affect the sufferers' quality of life; however, their current treatment is far from ideal, with long treatment durations and low success rates, even for the newest medicines [2–9]. For effective treatment, drugs must permeate into the nail (their site of action) following topical and/or oral administrations. Ungual (i.e. of the nail) drug permeation depends on the properties of the drug (such as its size, charge), the formulation (such as its pH, which influences drug charge), the nail plate (such as its porosity and hydration), as well as drug–nail, drug-formulation and formulation-nail interactions, such as drug-keratin binding, drug release from the formulation and the latter's adhesion to and residence on the nail plate. The influence of these factors on ungual permeability has been researched to varying extents, and the need for a more rational approach to the development of new therapies is obvious [10]. While the relationship between certain factors and ungual permeation is well-established (for example that of drug size) [11,12], the influence of other parameters such as nail–drug interactions, has been much less investigated.

Drug binding to keratin – the main constituent of the human nail plate – is known to reduce its antifungal effect, as shown by Tatsumi et al. (2002) who reported a direct relationship between a drug's affinity to keratin and the extent of reduction in its antifungal activity in the presence of keratin [13]. Drug binding to nail keratin is also expected to influence ungual drug permeation. For example, in evaluations of topical drug carriers in Franz cell type setups, a high affinity for nail keratin is expected to lead to greater drug partitioning out of the carrier into the nail plate. Concurrently, a high drug–nail affinity will reduce the drug partitioning out of the nail into the receptor medium, resulting in lower drug flux and calculated ungual permeability. This may help explain the lower flux, but greater drug-in-nail levels of terbinafine (which has higher keratin affinity than amorolfine [13]) when UV-cured gels loaded with terbinafine or amorolfine were evaluated as topical nail medicines [14]. Sugiura et al. (2014) also suggested that the greater ungual permeability of efinaconazole, compared to amorolfine and ciclopirox, was related to its lower keratin affinity [15].

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The ability to predict drug–nail interactions will therefore assist effective drug design and the success of therapy. With this in mind, the aims of the research discussed in this paper were to:

(i) Determine the Hansen Solubility Parameters (HSP) of the nail plate, the hoof membrane (a commonly used model for the nail plate in ungual research due to the scarcity and expense of nail plates), and of the anti-onychomycotic drugs terbinafine HCl, amorolfine HCl, ciclopirox olamine and efinaconazole.
(ii) Predict nail–drug interactions based on the determined HSPs, and evaluate whether these predictions reflect literature reports of experimentally-determined affinities of these drugs for keratin.

Solubility parameters – first developed by Hildebrand and coworkers [16], and which help to quantify the statements 'like dissolves like' or 'like seeks like' [16–18], have been widely used to predict materials' compatibilities, including in pharmaceutical drug development [19–22]. Hansen Solubility Parameters divide the total solubility parameter (δ_T) into individual parts arising from dispersion forces (δ_D), permanent dipole–permanent dipole forces (δ_P), and hydrogen bonding (δ_H) [17] such that:

$$\delta_T^2 = \delta_D^2 + \delta_P^2 + \delta_H^2 \quad (1)$$

The HSP parameters of materials can be found experimentally, based on the observation of interaction (or its absence) between the test material and solvents with well-defined HSPs. The solvents are then divided into those which interact strongly with the test material ('good' solvents), and those which do not interact ('bad' solvents). The δ_D, δ_P, δ_H HSPs of all the solvents are then plotted 3-dimensionally, and a computer program locates the 'sphere' in HSP space that includes the 'good' solvents and excludes the 'bad' solvents, with a minimum of error. The centre coordinates of the sphere give the HSPs (δ_D, δ_P, δ_H) of the test material, while the radius of the sphere (*Ro*) describes how large/small the interaction range is.

To compare two materials, *Ra* (the solubility parameter 'distance') between them can be calculated by

$$(Ra)^2 = 4(\delta_{D2} - \delta_{D1})^2 + (\delta_{P2} - \delta_{P1})^2 + (\delta_{H2} - \delta_{H1})^2 \quad (2)$$

where the subscripts 1 and 2 refer to material 1 and material 2.

For high affinity between two materials, *Ra* must be less than the *Ro* of the test material, and a Relative Energy Difference (RED) value is often used to quantify distances *Ra* relative to *Ro* as follows:

$$\text{RED} = \frac{Ra}{Ro} \quad (3)$$

Thus RED < 1 indicates high affinity, while RED > 1 indicates low affinity.

In applying this approach to the nail, knowledge of the nail plate's HSPs and use of drug–nail RED values is expected to assist the design and/or selection of drugs which have the desired (high or low) affinity for the nail plate. A high drug–nail affinity may mean that an antifungal agent's potency is diminished, but it also means that the drug will concentrate in the nail, resulting in a drug depot in the nail which can enable less frequent drug dosing, as evidenced by oral itraconazole pulse therapy in the treatment of onychomycosis. The nail plate's HSPs will also be useful in other industries, such as the nail cosmetic industry, where various chemicals are used, and where chemical-nail interactions are important for the cosmetic's properties such as wear. Knowledge of the hoof membrane's HSPs should help us further evaluate this material's suitability as a model for the nail plate in ungual research.

2. Materials and methods

2.1. Materials

Healthy nail clippings were collected from adult female and male volunteers, aged 15–45 years (ethics approval, REC/B/10/01 School of Pharmacy, University of London, UK). Bovine hoof membranes were obtained from Madras Veterinary College Teaching Hospital (Chennai, India). Amorolfine hydrochloride was obtained from Ranbaxy Research Laboratories (Gurgaon, Haryana, India). Terbinafine hydrochloride was obtained from AK Scientific (Union City, CA, USA). Ciclopirox olamine was obtained from Zhejiang Huadee Chemicals Co. (Taizhou, Zhejiang, China).

Butyl benzoate, decane, dibutyl phthalate, 1,5-dichloropentane, dimethyl phthalate, 2-ethyl hexanol, glycerol triacetate, 1-hexene, octane, 1-octanol, triethyl citrate, 1,2-propanediol, butanol, 1-methyl-2-pyrrolidone, 1-octanol, 1-pentanol, 1-vinyl-2-pyrrolidone, 2,2,4-trimethylpentane, acetone, acetic anhydride, butyl acetate, diethylamine, ethanolamine, diethanolamine, dimethyl formamide, dimethyl sulfoxide, ethylene glycol, formamide, isopropyl myristate, isopropyl palmitate, piperidine, pyridine, diethyl ether, dibutyl phthalate, benzyl butyl phthalate, acetophenone, propylene carbonate, methyl acetate, ethyl acetate, diacetone alcohol, dodecanol, methyl formate, 2-chloroethanol, hexanol, pyrrole, acetaldehyde, 4-chloro-1-butanol, 3-chloro-1-propanol, ethylenediamine, amino-2-propanol, 2-methylamino propanol, 1-methoxy-2-propanol, were obtained from Sigma Aldrich (UK). Acetone, acetonitrile, benzaldehyde, formaldehyde, hexane, methanol, and triethylamine were obtained from Fisher Scientific (Loughborough, UK). Lactic acid was obtained from Fisons Scientific Equipment (London, UK). Heptane was obtained from BDH Chemicals Ltd (UK). Glycerol was obtained from Alfa Aesar (Heysham, UK).

2.2. Methods

2.2.1. Determination of nail and hoof HSPs

Sample preparation: Fingernail and toenail clippings were washed with distilled water and any debris was carefully removed using a spatula without damaging the nail plate. The nail plates were then allowed to dry and equilibrate at room temperature for at least 60 min. The relative humidity in the laboratory was on average about 44%, where, the nail water content is expected to be about 8% w/w (from relative humidity – nail water content profiles reported in [23–26]). While it is possible that the nail's water content could affect the extent of swelling by organic liquids, we opted to air-dry (as opposed to oven-dry) the nails, as the data obtained in this study are more likely to reflect real-life situation (where nails are hydrated to some extent). Slices of bovine hoof membranes were cut from larger pieces using a scalpel, following overnight soaking in water to soften the tissue. The hoof slices were cut into a thickness of approximately 0.40 mm to reflect that of human nail clippings; following measurement of twenty finger- and toe-nail clippings from different donors using a digital micrometre, the average thicknesses were found to be 0.34 mm and 0.5 mm for finger- and toe-nail clippings respectively.

Nail and hoof HSPs were determined by measuring their swelling behaviour in a selection of solvents, of varying and well-defined HSP values. Fingernail and toenail clippings and hoof slices were weighed, then placed individually in glass vials, after which three mL of a solvent was added, and the vials were placed in a water bath at 25 °C. The mass of the nail clipping/hoof was monitored at regular intervals for a total of 35 days, by removing the sample, wiping off the excess liquid and weighing the sample before returning to the vial. The experiments were carried out in