

Product Pharmacology and Medical Actives in Achieving Therapeutic Benefits

James R. Schwartz

Beauty Care Product Development, The Procter & Gamble Company, Cincinnati, Ohio, USA

J Investig Dermatol Symp Proc 10:198–200, 2005

Scalp skin is physiologically very similar to non-palmoplantar skin of the rest of the body, except for the very high concentration of sebaceous glands (Giacometti, 1965). The scalp environment, however, is much different in being covered by a thick fabric of hair. There are about 250 hair fibers per cm^2 , which results, for a typical individual, in a hair surface area of 50,000 cm^2 relative to the scalp surface area of 600 cm^2 . Together, these parameters indicate the relative inaccessibility of the scalp surface to targeted delivery of actives; relatively low delivery efficiency in this protected environment is an inherent challenge to achieving therapeutic benefits. This is especially true of the most patient-friendly format—shampoos—since a rinsing step is involved and the product cannot interfere with achieving desired hair cosmetic benefits (compliance decreases dramatically if hair cosmetics are poor). This places a large demand on actives with high activity since delivery efficiency will be inherently low as well as development of product pharmacologies that maximize the benefit of the actives employed. This situation will be exemplified for the most common scalp care therapeutic products, those designed to treat dandruff and seborrheic dermatitis (D/SD) utilizing anti-fungal actives to reduce *Malassezia* content on the scalp.

The most common anti-fungal materials used in D/SD scalp therapies include those based on rational chemical design principles (ketoconazole, climbazole, pyriithione zinc (PTZ), piroctone olamine and ciclopirox olamine) as well as materials originating from indeterminate histories (selenium sulfide, sulfur, coal tar, and salicylic acid). Because of the aforementioned demands on activity due to challenging delivery, only those materials with high intrinsic anti-fungal activity should be considered as the basis for therapeutic products. Based on measurement of minimal inhibitory concentrations (MIC) against *Malassezia*, the most potent materials from this group are pyriithione zinc, selenium sulfide, climbazole, and ketoconazole (VanGerven and Odds, 1995; Schmid and Rühl-Hörster, 1996).

For a formulated therapeutic product to be effective, a potent active is a necessary but insufficient condition to achieve activity. The way the active is delivered to the scalp from the product formula, i.e., the product pharmacology, is

Abbreviation: PTZ, pyriithione zinc

at least as strong a determinant of in-use activity as the intrinsic active potency. For example, a comparison of clinical flake-reduction efficacy of a variety 1% PTZ-based D/SD shampoo products demonstrates a wide range of magnitude of therapeutic benefits. Much of this variation is likely due to the varying efficiency of delivery of PTZ, a particulate active, to the scalp surface. Particulate PTZ delivery will be affected by the physical size and shape of the particle (as well as other formulation parameters, which will not be covered further here). Particles which are flat cover the scalp surface more efficiently than those that are not. The particle size is also critical as smaller particles provide better surface coverage but are more difficult to retain on the scalp after rinsing. These two opposing factors result in an optimum size to maximize active delivery. Shampoo product formulations utilizing PTZ particles optimized for delivery outperform those utilizing standard forms of the active (Fig 1). This exemplifies one variable, beyond active potency, that must be considered in selecting a therapeutic treatment.

Another important pharmacological variable that must be considered is the role of the “non-functional” excipients in

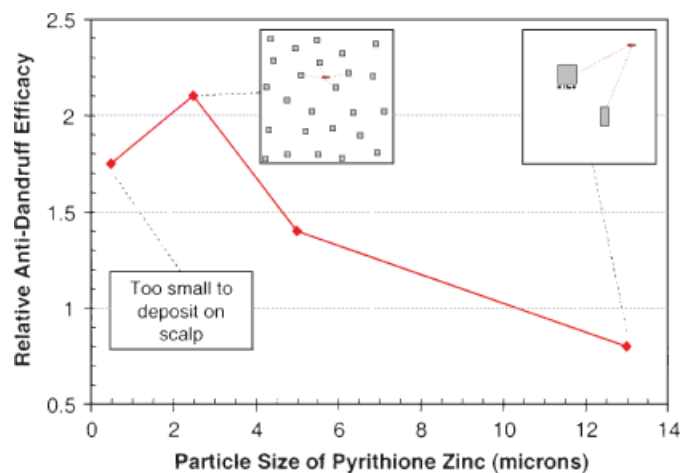


Figure 1
The impact of pyriithione zinc (PTZ) particle size on clinically observed anti-dandruff efficacy from shampoo matrices. Sub-micron particles are difficult to retain on the scalp after rinsing, whereas the distribution of particles on the surface of the scalp (inset) improves as the particles become smaller (note fungal cell target drawn to scale). These off-setting factors result in an optimum particle size for efficacy of 2.5 μm .

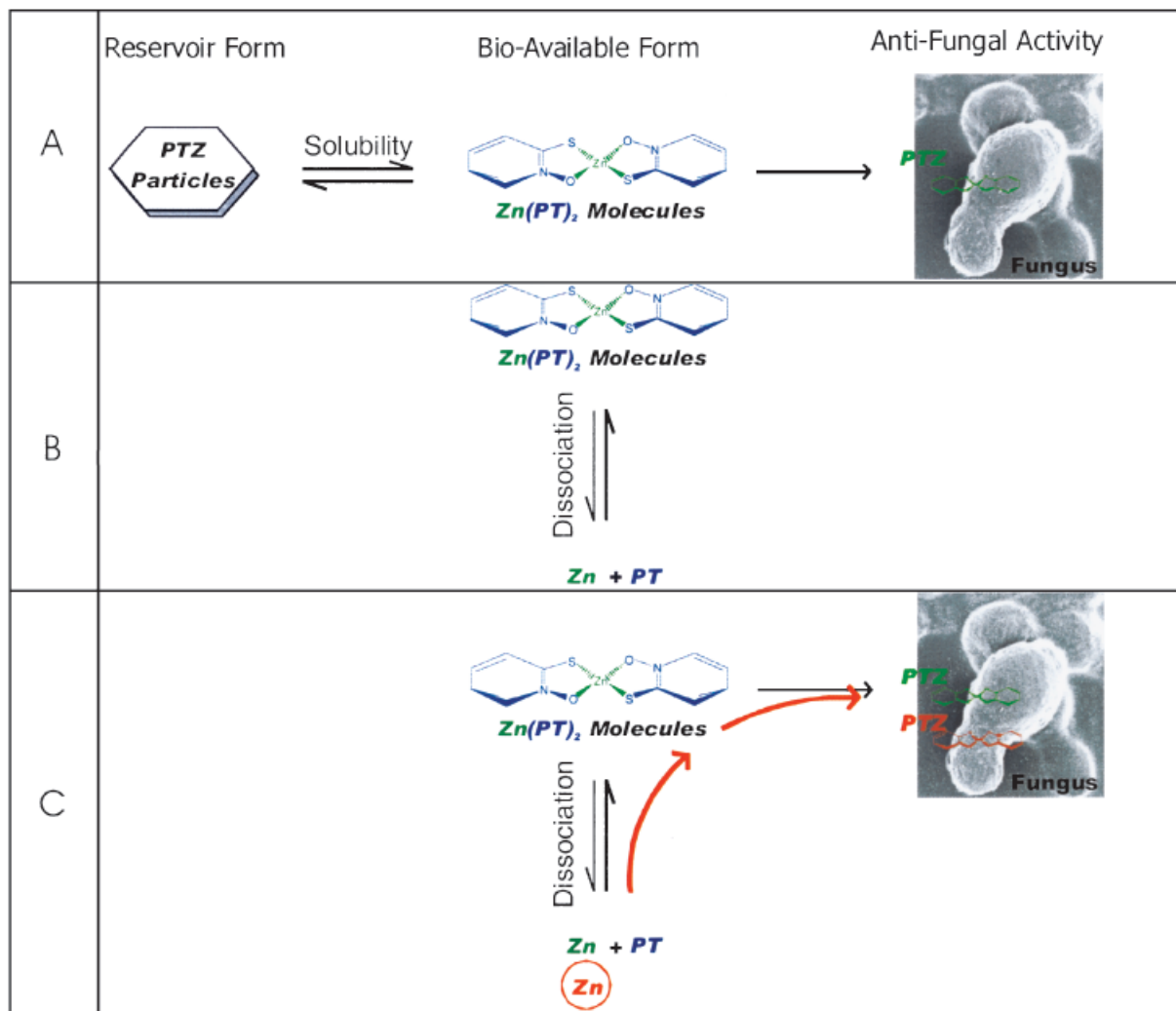


Figure 2

A summary of relevant pyrithione zinc (PTZ) equilibria governing realization of anti-fungal activity. (A) PTZ particles yield a soluble portion of PTZ molecules, which penetrate the fungal cell membrane (green). (B) PTZ undergoes dissociative equilibria, which reduce the portion of the material present in the bio-active complexed form. (C) The addition of an exogenous source of zinc ions (red) shifts the equilibria in the favor of the complexed PTZ form, thereby increasing delivery to the fungal cells (red).

the product formulation—it is well known that they can modulate, either positively or negatively, the activity of the drug active. A specific example of how product excipients can affect the activity of a scalp care formula is the addition of zinc materials to PTZ-based therapeutic products. To understand the mechanism behind this effect requires some understanding of a key component of the anti-fungal mechanism of the active ingredient PTZ itself.

Although the detailed understanding of the biological mechanism of PTZ is beyond the scope of the article, it is important to highlight the importance of the zinc component of the metal-organic complex PTZ. PTZ is based on the organic entity pyrithione (PT) where zinc ion (+2) forms a salt with PT (−1) in a 1:2 ratio. Evaluation of the *in vitro* anti-fungal activity of the organic component (sodium pyrithione) as well as a number of metal salts of this material (including zinc, iron, nickel, and copper), demonstrates a range of over three orders of magnitude (1000-fold) of potency. The zinc salt (MIC of 8 ppm) is almost 10 times more potent than sodium pyrithione (MIC of 64 ppm) alone and approximately

100 times more effective than, e.g., the iron salt (MIC of 500 ppm). This clearly highlights the importance of zinc to the activity of PTZ and establishes the intact PTZ material as the anti-fungal bio-active species. This conclusion becomes the basis for understanding the effect of the formulation containing a zinc excipient on the activity of PTZ.

PTZ, like all metal-organic complexes when in a liquid medium, is governed by an equilibrium between the associated zinc-pyrithione complex (i.e., PTZ) and dissociated zinc and pyrithione components (Seymour and Bailey, 1981). Since PTZ is the bio-active species, dissociation has negative consequences on efficacy. The greater the dissociation, the less PTZ is present in the medium in a form leading to anti-fungal activity. This is represented in the equilibria summarized in Fig 2.

Zinc ion has essentially no anti-fungal activity of its own, but enhances the anti-fungal activity of PTZ by over an order of magnitude in *in vitro* evaluations (Fig 3). The mechanism involves shifting the equilibrium between PTZ and its dissociated components. The basis for this effect is the

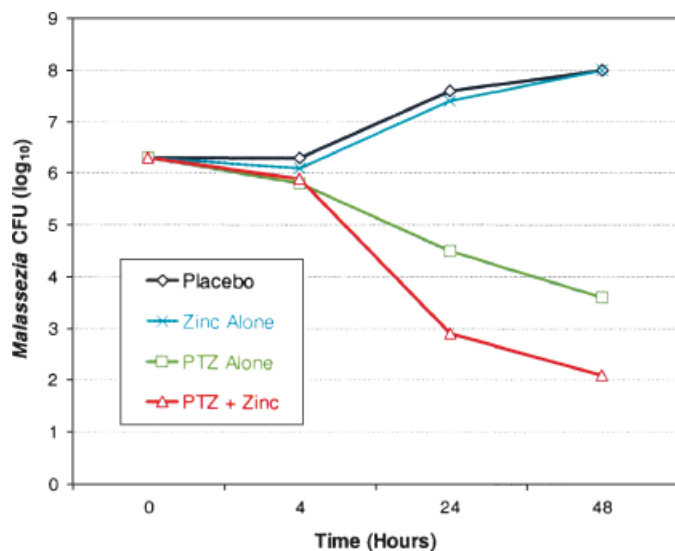


Figure 3
Kill rate microbiology evaluation of shampoo prototypes containing no active (placebo), pyriithione zinc (PTZ) alone, added zinc alone and the combination. Zinc alone has no activity, but it potentiates the activity of the PTZ formula.

well-established principle in chemical equilibria called LeChâtelier's Principle. Briefly, it states that a change imposed on a system at equilibrium shifts the equilibrium in a way that reduces the effect of the change. In practical terms, this means that the addition of a material which appears on one side of the equilibrium shifts the equilibrium in the opposite direction. In the case of the PTZ equilibria, added zinc forces the equilibrium towards the bio-active PTZ complex. In effect, additional zinc is acting in the formula to increase the bio-availability of PTZ to exert its anti-fungal activity and is therefore considered a potentiated PTZ formula.

Support for the mechanism comes from quantitation of PTZ penetration into model mammalian cells. This can be monitored by evaluating zinc levels within cells (modeling delivery to *Malassezia* yeast cells) using fluorescent techniques (Kim *et al*, 1999). Comparison of the zinc levels in cells exposed to either PTZ or PTZ plus zinc, shows much higher levels of intracellular PTZ (as zinc) in the case of added zinc. This is the result of the effect additional zinc has

on increasing the bio-availability of PTZ as the equilibria in Fig 2C demonstrate.

The zinc-enhanced PTZ activity observed *in vitro* and understood in terms of increased bio-availability results in increased performance *in vivo* in complex matrices as well. Quantitation of *in vivo Malassezia* reduction from shampoo matrices demonstrates PTZ formulation with zinc to be more effective than PTZ formulations alone. This benefit also translates to significantly improved clinical flake reduction from shampoos containing added zinc as an excipient.

In summary, whereas potent scalp actives must be selected to achieve therapeutic activity, the product pharmacology must be considered in both the design and selection of the product. Utilizing the example of PTZ-based D/SD treatments, wide variability in clinical performance has been observed. The origins can be understood in terms of how efficiently the product delivers the active to the scalp surface as well as the role that excipients play on modulating activity of the product formulation containing the drug active.

This work was funded by the Procter & Gamble Company. The author wishes to acknowledge David Kaufman for microbiological assessments and Durk Domaschko and Matt Chestnut for visualization of intracellular zinc delivery.

DOI: 10.1111/j.1087-0024.2005.10105.x

Manuscript received September 20, 2004; revised November 23, 2004; accepted for publication December 2, 2004

Address correspondence to: James R. Schwartz, PhD, The Procter & Gamble Company, 11511 Reed Hartman Hwy, Cincinnati, OH 45241, USA. Email: Schwartz.jr.2@pg.com

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