

lower than in the liver and often at the limit of detection) [94]. Sometimes, UV light is required for transformation (see Section 2.17).

Biotransformation changes the drug or chemical. This change can be in the drug's physicochemical properties or in its pharmacodynamic activity, or it may be both. This can result in (1) the active agent becoming inactive (a degradation process); (2) the inactive agent becoming active (an activation process for a pro-drug); or (3) a lipophilic agent becoming more water soluble (via various metabolic pathways e.g. oxidation, hydroxylation, acetylation, etc.). These changes can affect the drug's penetration through skin.

For example, highly lipophilic compounds, often large, do not penetrate through skin well (a good thing). However, the highly lipophilic preservative butylparaben (one example) can be metabolized to p-hydroxybenzoic acid in skin—this metabolite is less lipophilic and thus more readily penetrates through skin [3, 95]. Cutaneous metabolism of endogenous substrates such as vitamin A and vitamin D also occurs [3].

There are many examples of cutaneous steroid metabolism. The sex steroid hormones testosterone, estradiol, and progesterone are all metabolized by skin, as is dehydroepiandrosterone and hydrocortisone [2]. Skin contains the enzymatic processes for not only steroid biotransformation but also for elimination of polar materials via sulfate conjugation [2].

### 21.2.17 DOES PHOTOCHEMICAL TRANSFORMATION OCCUR DURING TOPICAL ABSORPTION AND IF SO, HOW AND WHAT?

Similarly to Section 2.16, the effect of UV light on a drug or chemical applied to the skin can cause a photochemical transformation (degradation or activation, etc.) In particular, photochemical changes to a drug or chemical can induce a phototoxic or photoallergic reaction.

A *phototoxic* reaction is caused by a drug or chemical absorbing UVA and causing direct damage to sun-exposed skin, whereas a *photoallergic* reaction requires the drug or chemical to be changed by UVA into an allergen—with skin damage occasionally spreading beyond the sun-exposed skin areas.

*Photosensitivity*—an adverse cutaneous response to normally harmless doses of UV radiation—is a property related to the drug chemistry and can be seen with topical or systemic administration. Examples of phototoxic agents include amiodarone, tetracyclines (e.g. doxycycline), coal tar, psoralens, and sulfonamides. Examples of photoallergic agents include sulfonamides, sulfonyleureas, thiazides, chloroquine, carbamazepine, etc. Practically, if a drug or chemical is known to cause photosensitivity, sun protection is recommended if used during the day; application/dosing at night rather than in more sunlit hours may minimize photosensitivity.

### 21.2.18 HOW DOES METABOLISM AFFECT EXCRETION PHARMACOKINETICS OF THE DRUG OR CHEMICAL? AND HOW DO EXCRETION PHARMACOKINETICS RELATE TO TOPICAL ABSORPTION?

A drug or chemical can be excreted from the body unchanged, or it may undergo metabolic changes before excretion. Thus, the factors discussed in Sections 2.16 and 2.17 regarding biotransformation in the skin will affect excretion pharmacokinetics. For example, a highly lipophilic drug or chemical that is biotransformed into a more water-soluble metabolite will not only be more easily absorbed through the skin, it will also be more easily excreted in the urine. Water-soluble drugs often do not require metabolic changes for urinary excretion, and a greater proportion of the administered dose may be excreted unchanged.

Metabolism and excretion are two mechanisms for elimination of drug or chemical, which can be affected by numerous factors [15]. Note that metabolism and excretion pharmacokinetics can differ greatly between structurally similar drugs or chemicals. Thus, depending on the substance, elimination (i.e. drug clearance) may or may not be in proportion to the dose absorbed. For researchers