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Invited Review

Prodrugs for dermal delivery

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Summary

The skin is increasingly being regarded as a portal for drug delivery. Unfortunately most of the drugs currently available are unsuitable for delivery via this route if systemic activity is required. The prodrug approach is one of the methods which have been evaluated for improving the systemic delivery of pharmacologically active compounds. In addition to transdermal delivery, dermal delivery has also attracted much attention for a range of skin diseases including psoriasis, eczema, ichthyosis, acne and skin tumours. In this review, prodrugs which have been reported as being possibly suitable for dermal and transdermal delivery are considered. In particular, the different chemical approaches used for providing the skin with enzyme-labile links are considered in some detail along with the potential benefits claimed.

Introduction

Definition of prodrug

The prodrug concept involves the chemical modification of a known pharmacologically active compound into a bioreversible form, with the aim of changing its pharmaceutical and/or pharmacokinetic character and thereby enhancing its delivery, efficacy and therapeutic value. Regeneration of the active drug occurs in vivo by either enzymatic hydrolysis or simply by chemical processes.

Many types of bioreversible derivatives have been exploited to obtain prodrugs of many different drug molecules. Each individual drug presents a new challenge and optimization of delivery is now routinely considered prior to introduction of any new drug to human therapeutics. Considerations taken into account include chemical synthesis and physico-chemical properties and their relationships to the biopharmaceutics and pharmacokinetics of the derivative, as well as the toxicity and bioactivity of the modified drug. An overview of the work that has been done over the last 20 years in the design and development of prodrugs can be found in many reports (Sinkula and Yalkowsky, 1975; Higuchi, 1977; Bundgaard, H., 1985; Higuchi et al., 1987; Svensson, 1987; Smith, 1988).

Prodrugs for dermal delivery

The skin is a highly active metabolic organ (Pannatier et al., 1978; Bickers et al., 1980). It contains a multitude of different enzymes which

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TABLE 1

Prodrugs for dermal delivery

Parent drug	Bioreversible modification	Improvement	Tissue studied	References
α-Amino-*p*-toluene-sulfanilamide	Acetate salt	Absorption	–	Sinkula and Yalkowsky (1975)
Aspirin and salicylic acid	Methylthiomethyl and methylsulfinylmethyl esters	Absorption	Full-thickness mouse skin	Loftsson et al. (1981) Loftsson and Bodor (1981)
Betamethasone	17- and 21-valerates	Prolonged action	Mouse skin homogenates	Cheung et al. (1985a)
Betamethasone	17-Valerate	Prolonged action	Whole human skin	Rawlins et al. (1979)
Cromolyn	Hexanoyloxyethylidene, hexanoyloxymethyl and pivalyloxymethyl-nitrate	Absorption	Whole mouse skin	Bodor et al. (1980)
Diflucortolone	Valerate	Prolonged action	Skin extracts of rat, guinea pig, and human	Tauber and Toda (1976) Tauber (1982)
Dithranol	Triacetate	Removal of irritating effects and discolouration on skin	Mouse and rat skin homogenates	Wiegrebe et al. (1984)
Ephedrine	3,4-Dimethyl-5-phenyl-oxazolidine	Absorption	Full-thickness human skin	Young-Harvey et al. (1986)
5-Fluorocytosine	*N*-Mannich base derivatives	Absorption	Full-thickness mouse skin	Koch and Sloan (1987)
5-Fluorouracil	*N*-1-Acyloxymethyl derivatives	Absorption	Whole human skin	Bundgaard et al. (1983) Mollgaard et al. (1982) Ozaki et al. (1981)
5-Fluorouracil	*N*-Mannich base derivatives	Absorption	Whole mouse skin	Sloan et al. (1984a, 1988)
Hexachlorophene	Ester, ether, hemiester	Absorption	–	Sinkula and Yalkowsky (1975)
Hydrocortisone	Spirothiazolidine derivative	Prolonged action	Animal skin	Smith (1988)
Hydrocortisone	17- and 21-esters	Prolonged action	Hamster and guinea pig skin homogenates	O'Neill and Carless (1980)

Hydrocortisone	17- and 21-esters	Prolonged action	Mouse skin homogenate	Cheung et al. (1985b)
Hydrocortisone	Butyrate propionate diester derivative	Absorption, prolonged action	Dog skin and enzyme extract of dog, and rat skins	Ozawa et al. (1985)
Indomethacin	*N*,*N*-Dialkylhydroxylamine	Absorption	Whole mouse skin	Sloan et al. (1984b)
6-Mercaptopurine	S^6,9-Bisacyloxymethyl derivative	Absorption	Whole mouse skin	Waranis and Sloan (1987)
6-Mercaptopurine	S^6-Acyloxymethyl derivative	Absorption	Whole mouse skin	Waranis and Sloan (1988)
6-Mercaptopurine	Mannich base derivatives	Absorption	Whole hairless mouse skin	Siver and Sloan (1988)
Metronidazole	Benzoate	Absorption	Whole human skin	Bundgaard et al. (1983)
Metronidazole	Acetate, propionate, butyrate, valerate, caproate esters	Absorption	Whole human skin and skin homogenate	Johansen et al. (1986)
Mitomycin C	1-a-*N*-substituted derivatives	Absorption	Full-thickness hairless mouse and rat skins	Hashida et al. (1985) Mukai et al. (1985)
Oestradiol	17-Acetate, 3,17-diacetate, 17-valerate, 17-heptanoate, 17-cypionate	Transdermal permeation	Whole skin	Tojo et al. (1986)
Procaine	Polyethylene glycol (carbamate)	Absorption	–	Sinkula and Yalkowsky (1975)
Prostaglandin	Alkylsilyl ether	Absorption	–	Sinkula and Yalkowsky (1975)
Progesterone	Ethyl ester thiazolidine derivative	Prolonged action	–	Bodor et al. (1982)
Theophylline	7-Acyloxymethyl derivatives	Absorption	Full-thickness hairless mouse skin	Sloan and Bodor (1982)
Theophylline	*N*-Mannich base derivatives	Absorption	Full-thickness hairless mouse skin	Sloan et al. (1984a) Sloan et al. (1988)
6-Thiopurines	*S*-Acylheteroalkyl derivatives	Absorption	Full-thickness hairless mouse skin	Sloan et al. (1983)
Vidarabine	5′-Valerate	Absorption	Full-thickness hairless mouse skin and skin homogenate	Yu et al. (1979a and b, 1980a–c)
Vidarabine	5′-Monoesters	Absorption	Full-thickness hairless mouse skin	Higuchi et al. (1983a) Higuchi et al. (1983b)
Acid of viprostol	Viprostol (methyl ester)	Absorption	In vivo blood sampling	Bickers and Kappas (1980)

can metabolize a wide range of synthetic and naturally occurring xenobiotics (Rongone, 1977; Noonan and Wester, 1985). Metabolism of drugs by the skin is gaining interest due to its pharmacokinetic, pharmacological, therapeutic and toxicological implications. One way in which the metabolic capacity of the skin can be exploited in the field of dermal drug delivery is with the use of prodrugs (Bucks, 1984; Hadgraft, 1985).

Most drugs diffuse poorly through the skin and manipulation of the physicochemical properties of the drugs by selecting drug derivatives with lipophilicities conducive to diffusion of the molecules through the skin barrier is often resorted to.

The prodrug approach in dermal drug delivery has been the subject of many recent investigations and various drugs have been considered (see Table 1). In studying dermal delivery, it is important to

TABLE 2

Bioreversion mechanisms of prodrugs

Mechanism	Prodrug derivative	Parent drug	Reference
Chemical hydrolysis	*N*-Mannich bases	5-Fluorocytosine	Koch and Sloan (1987)
		5-Fluorouracil	Sloan et al. (1984a)
			Sloan et al. (1988)
		6-Mercaptopurine	Siver and Sloan (1988)
		Theophylline	Sloan et al. (1984a)
	N,*N*-Dialkylhydroxylamine derivatives	Non-steroidal anti-inflammatory carboxylic acids e.g. indomethacin	Sloan et al. (1984b)
	Oxazolidines	β-Amino-alcohols e.g. ephedrine	Young-Harvey et al. (1986)
Enzymatic reactions: hydrolysis	*S*-Acylheteroalkyl derivatives	6-Thiopurines e.g. 6-mercaptopurine	Sloan et al. (1983)
			Waranis and Sloan (1987, 1988)
	N-1-Acyloxymethyl derivatives	5-Fluorouracil	Bundgaard et al. (1983)
			Mollgaard et al. (1982)
	1a-*N*-substituted derivatives	Mitomycin C	Hashida et al. (1985)
			Mukai et al. (1985)
	Esters	Corticosteroids	Cheung et al. (1985a and b)
			O'Neill and Carless (1980)
			Pannatier et al. (1978)
			Sinkula and Yalkowsky (1975)
			Smith (1988)
			Tauber and Toda (1976)
		Hormone	Tojo et al. (1986)
		Prostaglandin	Bickers and Kappas (1980)
		Aspirin and salicylic acid	Loftsson et al. (1981a)
			Loftsson and Bodor (1981b)
		Cromolyn	Bodor et al. (1980)
		Dithranol	Wiegrebe et al. (1984)
		Hexachlorophene	Sinkula and Yalkowsky (1975)
		Metronidazole	Bundgaard et al. (1983)
			Johansen et al. (1986)
		Vidarabine	Higuchi et al. (1983a and b)
			Yu et al. (1979a and b, 1980a–c)
oxidation	7-Acyloxymethyl derivatives	Theophylline	Sloan and Bodor (1982)
	Ester	Dithranol	Wiegrebe et al. (1984)
reduction	Pivalyloxymethylnitrate ester	Cromolyn	Bodor et al. (1980)

identify two distinct alternative objectives. The first is optimisation of systemic delivery (e.g. antihypertensive agents and oestrogens) and the second optimisation of delivery to the dermis (e.g. topical corticosteroids and agents for the treatment of skin abnormalities such as eczema and cutaneous tumours). The physicochemical attributes necessary for the prodrug to meet these distinct requirements are clearly going to be different.

Skin metabolism of prodrugs

Maintenance of the activity profile of the parent drug demands reversion of the prodrug to the active agent by enzymatic or non-enzymatic reactions. Many prodrugs possess an ester linkage (Bundgaard and Nielsen, 1988) capable of undergoing enzyme-catalyzed cleavage to the parent drug and it is well documented that dermal enzymes are effective in promoting such metabolism (Pannatier et al., 1978; Tauber, 1982; Bucks, 1984). Pannatier et al. (1981) have studied the enzymatic hydrolysis of a series of aliphatic esters of *p*-nitrobenzoic acid in mouse skin homogenate while Johansen et al. (1986) investigated the transport and bioconversion of a series of aliphatic esters of metronidazole in the skin. There is, however, still a great need to explore new prodrug types, even among the esters. Such derivatives are probably the most common prodrugs, mainly because of the predominance of carboxylic and hydroxyl groups in drug molecules along with the ready availability of enzymes in the body capable of hydrolyzing most esters.

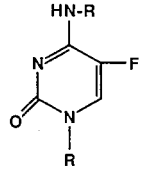


Fig. 1. The *N*-Mannich base prodrugs of 5-fluorocytosine.

I : R = $-H$
II : R = $-CH_2-NC_5H_5$
III: R = $-CH_2-N(C_2H_5)_2$
IV: R = $-CH_2-N(CH_3)_2$
V : R = $-CH_2-NC_4H_4$
VI : R = $-CH_2-NC_4H_4O$
VII: R = $-CH_2-N_2C_4H_4-CH_3$

Besides the presence of esterases in skin, other cutaneous enzymatic activities have also been identified (Wester et al., 1986; Guy et al., 1987; Martin et al., 1987). Therefore it is important to understand how such enzyme systems might modulate the activity of topically applied drugs and then to optimize the design of the prodrugs accordingly (Higuchi, 1977; Bucks, 1984; Higuchi and Yu, 1987). Table 2 is a summary of the mechanisms of bioactivation of prodrugs upon dermal absorption.

Prodrugs regenerated by chemical hydrolysis

Mannich base prodrugs

Bundgaard et al., 1983, Sloan et al., 1984a, 1988, Koch et al., 1987, and Siver et al., 1988, derived and studied the Mannich base prodrugs of 5-fluorocytosine, 5-fluorouracil, 6-mercaptopurine and theophylline (Figs. 1–4). They found that these derivatives enhanced the delivery of their parent drugs through the skin because of enhanced water solubility, as well as enhanced lipid solubility. Those more polar prodrugs are also more effective in improving topical delivery than prodrugs that have been designed to incorporate only lipid solubilizing groups into the structure of the parent drugs (Sloan and Bodor, 1982). Therefore, with the exception of polar heterocyclic drugs, water as well as lipid solubility should be a design goal in the future development of prodrugs for improved topical delivery of nitrogen-containing heterocycles and the Mannich bases appear to be attractive candidates for consideration to accomplish that goal, especially since they are chemically labile and do not require enzymatic assistance to regenerate the parent drugs under protic conditions. However, as formaldehyde is liberated upon hydrolysis of these prodrugs, there is concern about its acceptability and possible toxicity on the skin. Instability of the products during storage may also be a problem.

N,N-dialkyl hydroxylamines

N,N-dialkylhydroxylamines appear to be attractive candidates as derivatizing agents for carboxylic acids (Fig. 5) as they are relatively

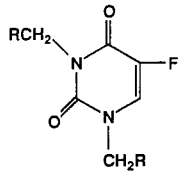


Fig. 2. The Mannich base prodrugs of 5-fluorouracil.

I : R = -H
II : R = $-N(CH_2)_5$
III: R = $-N(CH_2CH_2)_2O$
IV: R = $-N(CH_2CH_2)_2NCH_3$

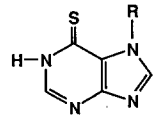


Fig. 3. The Mannich base prodrugs of 6-mercaptopurine.

I : R = $CH_2N(C_4H_9)_2$
II : R = $CH_2N(CH_2)_5$
III: R = $CH_2N(CH_2)_4$

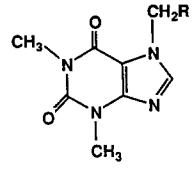


Fig. 4. The Mannich base prodrugs of theophylline.

I : R = H
II : R = $N(CH_3)_2$
III: R = $N(CH_2CH_3)_2$
IV: R = $N(CH_2CH_2CH_3)_2$
V : R = $N(CH_2CH_2CH_2CH_3)_2$
VI : R = $N(CH_2)_5$
VII : R = $N(CH_2CH_2)_2O$
VIII: R = $N(CH_2CH_2)_2NCH_3$
IX : R = $N(CH_2)_4$

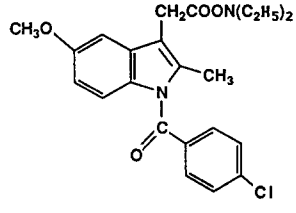


Fig. 5. The *N,N*-diethyl-hydroxylamine derivative of indomethacin.

stable and yet sufficiently labile to serve as activated esters in amination reactions when the reaction is catalyzed by a weak acid (Sloan et al., 1984b). They should be stable as long as they are kept out of contact with protic solvents. In addition, the derivatizing agents exhibit a low order of acute toxicity. Amines have been used as penetration enhancers in formulations and therefore derivatizing agents containing low pK_a amines may also improve the ability of the carboxylic acids to penetrate biological membranes. The potential advantages of such derivatizing agents are firstly, that the amine group generally confers to the molecule a greater ability to partition from an aqueous environment into lipids than does a carboxylic acid group; and secondly, the low pK_a amine is present in its unprotonated form (99% at pH 7.4) which is the form that undergoes partitioning. Concerns about the mutagenicity of topically applied amino compounds may, however, be a distinct handicap to wider use of these amino products.

To determine if the substitution of a carboxylic acid group by a low basicity amino group had an effect on the ability of the parent compound to penetrate biological membranes, the diethylhydroxylamine derivative of indomethacin was compared with indomethacin in diffusion cell tests with mouse skin using isopropyl myristate as vehicle (Sloan et al., 1984b). Almost five times as much indomethacin was delivered by the derivative than by indomethacin itself. It is also more effective than indomethacin in inhibiting thermal inflammation in animal models, but only as effective as indomethacin in inhibiting UVB radiation erythema in human volunteers.

Oxazolidines

Oxazolidines are another group of prodrugs which undergo rapid hydrolysis in water to give formaldehyde, as illustrated in Fig. 6 (Young-Harvey et al., 1986). The oxazolidines formed by condensation of benzaldehyde and salicylaldehyde with ephedrine have significantly lower pK_a values than ephedrine. Thus it was anticipated that the oxazolidines would exist as a neutral molecule to a greater extent than ephedrine, in the pH range 3–8, compatible with that of the human skin, and

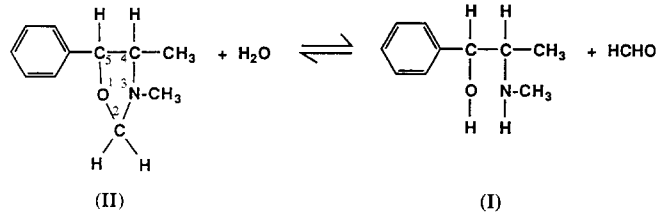


Fig. 6. The 3,4-dimethyl-5-phenyloxazolidine prodrug (II) is hydrolysed to ephedrine (I) and formaldehyde.

that oxazolidines would penetrate the skin more rapidly than ephedrine from aqueous solutions with pH values in the same range. Once the prodrugs have passed through the rate-determining barrier, appreciable hydrolysis of oxazolidines to ephedrine occurs within the skin. Young-Harvey et al. (1986) went on to suggest that perhaps other aldehydes which are less toxic than formaldehyde could be used with β-amino-alcohols to develop other prodrug derivatives.

Prodrugs regenerated by enzymatic reactions

Hydrolysis

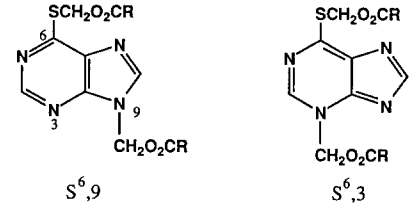
S-acylheteroalkyl derivatives of thiopurines

The thiopurines have poor biphasic solubilities and are also poorly absorbed through biological membranes. Sloan et al. (1983) prepared prodrugs of the thiopurines to increase the solubilities, while at the same time ensuring delivery of only the parent compounds by the alkylation of the thiopurines with acylheteroalkyl halides under neutral or basic conditions.

6-Mercaptopurine is one of the thiopurines studied by the investigators. Although 6-mercaptopurine is a well-known anti-proliferative agent for the systemic treatment of psoriasis, it is inactive when given topically. The reason for its lack of topical activity is that not enough 6-mercaptopurine is delivered through the stratum corneum into the epidermis for it to be effective. Because of its polarity, 6-mercaptopurine is a good candidate for conversion to a prodrug which transiently masks the polar functional groups and introduces non-polar or less polar functional groups into the molecule to decrease the melting point and increase the solubility of the parent drug. 6-Mercaptopurine contains two functional groups that are potential sites for transient chemical modifications.

Waranis and Sloan (1987) described the application of a combination of formulation and prodrug approaches to solving the topical delivery problem posed by 6-mercaptopurine. A homologous series of 6,9-bisacyloxymethyl prodrug derivatives of 6-mercaptopurine was synthesized and characterised, as shown in Fig. 7. The relative rates at which the prodrugs deliver 6-mercaptopurine through hairless mouse skin from various vehicles were measured. The effect of the length of the acyl chain on the amount of intact prodrug delivered through the skin was also determined. Not surprisingly, the best solvent for optimising delivery was found to be dependent on the prodrug concerned.

In a more recent study, homologous series of S^6-acyloxymethyl-6-mercaptopurine and two 9-



S^6,9 S^6,3

Fig. 7. The S^6,9- and S^6,3-bisacyloxymethyl-6-mercaptopurine derivatives.

	Substitution		Substitution
I : R = $-CH_3$	6,3	VII : R = $-C_5H_{11}$	6,9
II : R = $-CH_3$	6,9	VIII: R = $-C_7H_{15}$	6,3
III: R = $-C_2H_5$	6,9	IX : R = $-C_7H_{15}$	6,9
IV: R = $-C_3H_7$	6,9	X : R = $-C(CH_3)_3$	6,3
V : R = $-C_4H_9$	6,9	XI : R = $-C(CH_3)_3$	6,9
VI: R = $-C_5H_{11}$	6,3		

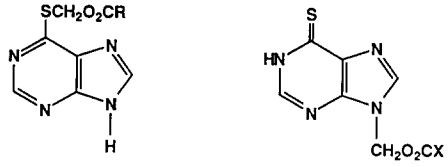


Fig. 8. The S^6-acyloxymethyl- and 9-acyloxymethyl-6-mercaptopurine derivatives.

I : R = $-CH_3$ VI : R = $-C_7H_{15}$
II : R = $-C_2H_5$ VII : R = $-C(CH_3)_3$
III: R = $-C_3H_7$ VIII: X = $-C(CH_3)_3$
IV: R = $-C_4H_9$ IX : X = $-CH_3$
V : R = $-C_5H_{11}$

acyloxymethylmercaptopurine prodrugs were synthesized by Waranis and Sloan (1988) (see Fig. 8 for the chemical structures). From evaluation of the rates of delivery of these prodrugs, it was found that it was much less important to mask the imidazole than the thionamide functional group in 6-mercaptopurine to enhance the topical delivery of 6-mercaptopurine. One interesting conclusion drawn from the results was that the S^6-acyloxymethyl derivatives that are best at delivering 6-mercaptopurine have greater water solubility as well as lipid solubility than 6-mercaptopurine.

N-1-acyloxymethyl derivatives of 5-fluorouracil

Topical application of 5-fluorouracil has been useful in the treatment of various diseases, such as actinic keratoses, epithelial neoplasms and psoriasis. Although 5-fluorouracil is useful, it does not penetrate the skin well because of its low lipophilicity. Møllgaard et al. (1982) and Bundgaard et al. (1983) designed and synthesized *N*-1-acyloxymethyl prodrugs of 5-fluorouracil, as shown in Fig. 9, and reported that 1-butyryloxymethyl-5-fluorouracil penetrated 5 times more readily through the human skin than 5-fluorouracil and at the same time was fully bioavailable in the form of the parent drug due to an extensive cutaneous metabolism. Enzymatic cleavage of the ester group results in the formation of 1-hydroxymethyl-5-fluorouracil which is decomposed instantaneously into formaldehyde and 5-fluorouracil. The authors suggested that *N*-acyloxymethyl derivatives of 5-fluorouracil may be promising

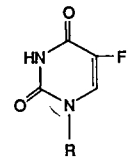


Fig. 9. The *N*-1-acyloxymethyl prodrugs of 5-fluorouracil.

I : R = H
II : R = $CH_2CO_2CH_2CH_2CH_3$
III: R = $CH_2CO_2C(CH_3)_3$

prodrug candidates for the enhanced delivery of 5-fluorouracil.

1a-N-substituted derivatives of mitomycin C

Two of the lipophilic 1a-*N*-substituted derivatives of mitomycin C (benzyloxycarbonyl and pentyloxycarbonyl) which exhibited low melting points, high biphasic solubilities and complete metabolic conversion to the parent drug, were effective in enhancing the transdermal delivery of mitomycin C (Mukai et al., 1985) (see Fig. 10, for the list of possible prodrugs of mitomycin C). The benzyloxycarbonyl derivative is probably converted to mitomycin C by metabolic cleavage of the carbamate linkage in the skin. However, saturation of the metabolic conversion was observed in the hairless mouse skin, but not in the rat skin, probably because of the relatively low enzymatic activity in the mouse skin (Hashida et al., 1985).

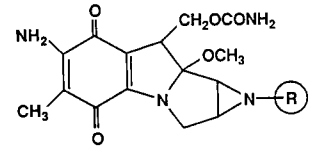


Fig. 10. The mitomycin C prodrugs.

I	Mitomycin C (MMC)	R = $-H$
II	Benzyl-MMC	R = $-CH_2C_6H_5$
III	Benzoyl-MMC	R = $-CO-C_6H_5$
IV	Benzylcarbonyl-MMC	R = $-COCH_2-C_6H_5$
V	Benzyloxycarbonyl-MMC	R = $-COOCH_2-C_6H_5$
VI	Propyloxycarbonyl-MMC	R = $-COOC_3H_7$
VII	Pentyloxycarbonyl-MMC	R = $-COOC_5H_{11}$
VIII	Nonyloxycarbonyl-MMC	R = $-COOC_9H_{19}$

Prodrugs of corticosteroids, hormones and prostaglandin

Many endogenous substances, for example, steroid hormones such as hydrocortisone, testosterone, oestradiol and prostaglandins, can be considered as soft drugs since they are readily metabolized by the body when their concentrations are close to their natural levels. At physiological levels, there are essentially no toxicities associated with their use; however, the cutaneous metabolism of these endogeneous compounds is so fast and efficient that this level cannot be used clinically. The solution to this problem is the design of specific chemical protecting techniques for their sustained release, or a prodrug-soft drug combination. Methods of slowing the hydrolysis rate of steroid hormone derivatives include the preparation of long chain fatty acid esters and derivatives sterically hindered at or near the site of hydrolysis. There are numerous pro/soft drugs of this nature and only a few will be mentioned here.

Corticosteroids have been frequently used in topical dosage forms for cutaneous diseases. In recent years, separation of the drug effect from side effects has been an important area of investigation. Many studies have been made of the effects of esterification at the 17 and 21 positions (Fig. 11) and their biotransformation by enzymatic hydrolysis. It was found that the 17-ester derivatives were more slowly hydrolysed than their 21-isomers, as were the 17, 21-diesters (Rawlins et al., 1979; O'Neill and Carless, 1980). Further investigations by Cheung et al. (1985a, b) revealed that the corticosteroid-17-esters were resistant to hog liver and mouse skin esterases while the 21-esters were highly susceptible. This difference could account for the reported differences in the topical activity and toxicities of the isomers.

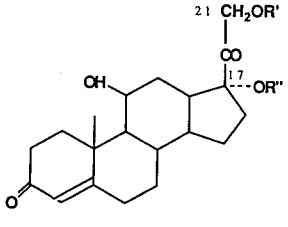


Fig. 11. Hydrocortisone esters.

R = Acyl group
R′ = 21-ester
R″ = 17-ester

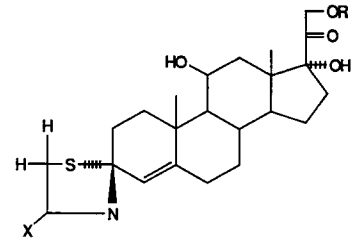


Fig. 12. Examples of 3-spirothiazolidines of hydrocortisone.

I : R = $COCH_3$, X = $CO_2C_2H_5$
II: R = $COCH_3$, X = H

In animal experiments, the anti-inflammatory effect of topically applied hydrocortisone was found to be increased and the systemic effects decreased by the use of the spirothiazolidine prodrugs (Smith, 1988), as in Fig. 12. These beneficial effects are due to restriction of the action of hydrocortisone within the skin. During or after absorption, the prodrug is hydrolysed in a stepwise manner with the eventual release of hydrocortisone, the active agent. There is a sustained release of hydrocortisone within the skin from the accumulated prodrug, accounting for the more intense anti-inflammatory effect and a decrease in its rate of leaching into the blood stream to produce systemic effects. The sustained release of hydrocortisone is due to the retardation of the intermediate hydrolytic product by disulphide formation between its thiol group and a thiol group of the skin, followed by a slow breakdown of the complex to give hydrocortisone.

Ozawa et al. (1985) studied the percutaneous absorption and skin metabolism of [^{3}H]hydrocortisone butyrate propionate, as a diester derivative of hydrocortisone in vivo. The derivative was dissolved in saline and applied to the shaved abdominal skin of dogs. Most of the absorbed diester was present in an unmetabolized form in the stratum corneum. Sampling of the underlying skin showed that 80% of the corticosteroid in rats and about 50% in dogs were found as metabolites. This is not surprising since the esterase activity in this layer is stronger than in the stratum corneum, and rats

have greater esterase activity than dogs (Ozawa et al., 1985). It appears that skin metabolism significantly affects the biological activity of esterified corticosteroid.

McKenzie and Atkinson (1964) assayed the topical potency of betamethasone and 23 of its esters, using a vasoconstriction assay. It was found that ester derivatives, such as betamethasone dipropionate and hydrocortisone butyrate propionate, are more active than the parent compound in the clinical management of psoriasis, because an increase in lipophilicity improves transfer across the stratum corneum.

Tauber and Toda (1976) examined the metabolism of diflucortolone valerate and reported that the rate of hydrolysis in man was considerably lower than that in rats and guinea pigs. There appears to be species variation in esterase activity. However, despite the extremely low absorption rate, the slow hydrolysis of the valerate derivative in human skin ensures an adequate level of active ingredient in the skin over a long period.

Bodor et al. (1982) have designed and synthesized ethyl ester thiazolidine derivatives of progesterone that yielded more than twice the radiolabelled steroid concentration in the skin after topical application compared to topical application of progesterone itself.

Tojo et al. (1986) incorporated 5 oestradiol prodrugs into a transdermal delivery system and studied the enzymatic conversion of the various estradiol esters to oestradiol. The rate of appearance of oestradiol from the bioconversion of its prodrugs was found to be dependent upon the enzyme activity in the skin.

Methyl (±)-(11a,5Z) {and 5E}, 13E, 16R {and 16S})-16-ethenyl-11,16-dihydroxy-9-oxoprosta-5,13-dien-1-oate (viprostol), a prostaglandin analogue is a topical effective antihypertensive agent (Sinkula and Yalkowski, 1975). In the blood, it apparently undergoes instantaneous and complete ester hydrolysis to give an equally effective compound, (±)-(11a,5Z {and 5E}, 13E,16R {16S})-16-ethenyl-11,16-dihydroxy-9-oxoprosta-5,13-dien-1-oic acid. It was found that about two-thirds of the dose underwent metabolism during absorption from the topical application site and/or during transit to the point of blood sampling in the same skin.

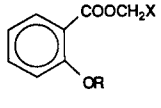


Fig. 13. The 2-acetoxybenzoate esters of aspirin.

I : R = CH_3CO, X = CH_3S– Methylthiomethyl-ester
II: R = CH_3CO, X = CH_3SO– Methylsulfinylmethyl-ester

Esters of acetylsalicylic acid

Salicylic acid and acetyl salicylic acid are useful in topical drug therapy. Several prodrugs of these drugs have been developed by Loftsson et al. (1981), (Fig. 13). In vivo studies of the methylthiomethyl and methylsulfinylmethyl 2-acetoxybenzoate ester prodrugs of acetylsalicylic acid have shown these compounds to be freely penetrable compounds and easily hydrolysed to acetylsalicylic acid by the skin esterases (Loftsson and Bodor, 1981). Significant metabolism of all the salicylic acid derivatives occurs in the skin. However, further investigations are required to determine whether levels sufficient for a keratolytic, anti-inflammatory or analgesic activity can be reached by these prodrugs in vivo.

Esters of cromolyn

Bodor et al. (1980) postulated that cromolyn would have anti-pruritic activity as well as anti-inflammatory activity based on its mechanism of action and its structure. However, because of its polar character and short biological half-life, it would not be effectively delivered to the sites of action. Enhanced penetration was accomplished by the development of more lipophilic prodrugs of cromolyn as shown in Fig. 14. The carboxy groups were esterified. The resulting prodrugs, the hexanoyloxyethylidene, hexanoyloxymethyl and pivalyloxymethyl nitrate esters showed improved delivery of cromoglycic acid, thus indicating that significant metabolism of the prodrugs must have taken place in the skin. These metabolic pathways included not only esterase hydrolysis, but reductive cleavage as well, since the nitrate ester must cleave by a reductive process. The hexanoyloxy-

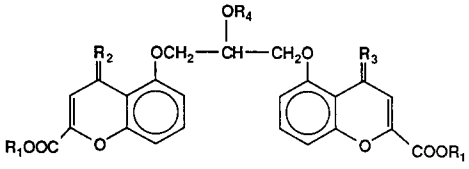


Fig. 14. Selected prodrugs of cromoglycic acid.

	R_1	R_2	R_3	R_4	
I	$-CH_2CO_2(CH_2)_4CH_3$	O	O	H	Hexanoyloxy-methyl ester
II	$-CH_3-CHCO_2(CH_2)_4CH_3$	O	O	H	Hexanoyloxy-ethylidiene ester
III	$-CH_2CO_2C(CH_3)_3$	O	O	NO_2	Pivalyloxy-methyl-nitrate ester

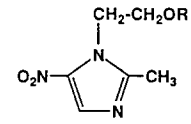


Fig. 16. Metronidazole and its esters.

I	R = –H	Metronidazole
II	R = $-CO-CH_3$	Metronidazole acetate
III	R = $-CO-CH_2CH_3$	Metronidazole propionate
IV	R = $-CO-CH_2CH_2CH_3$	Metronidazole butyrate
V	R = $-CO-CH_2CH_2CH_2CH_3$	Metronidazole valerate
VI	R = $-CO-CH_2CH_2CH_2CH_2CH_3$	Metronidazole caproate

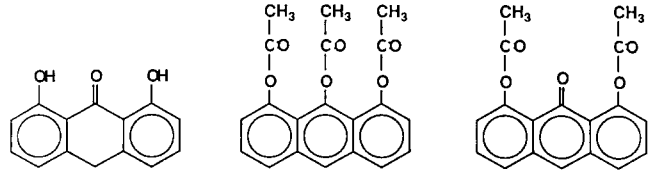
methyl ester was found to be a promising therapeutic agent.

Ester of dithranol

Dithranol is an antipsoriatic drug, but when applied topically, it causes irritation and discolouration of the skin. Dithranol triacetate, which is colourless and less irritating, is used as the prodrug (Fig. 15). Arylesterases present in the skin hydrolyse the triacetate to give dithranol diacetate (Wiegrebe et al., 1984). The central acetoxy group in the dithranol triacetate molecule is found to be preferentially hydrolyzed by the action of enzymes. The dithranol diacetate, resulting from the hydrolysis, is further oxidized non-enzymatically to dithranol. However, the triacetate acts more slowly and more weakly than dithranol itself.

Ester, ether and hemiester of hexachlorophene

If little or no skin metabolism occurs, the chemical that penetrates the skin barrier is introduced directly into the systemic circulation. The implication is that some chemicals may be more toxic after topical application than when administered orally. For example, topically applied hexachlorophene does not appear to be metabolised to any extent. It passes into the bloodstream unchanged. In contrast, orally ingested hexachlorophene quickly reaches the liver through the enterohepatic shunt system and is metabolized. The first-pass metabolic detoxification that occurs after oral absorption is not present after topical application. Various ester, ether and hemiester derivatives of hexachlorophene have been synthesized and evaluated as prodrugs for dermal delivery. These prodrugs could be easily transported across the skin barrier but have to be cleaved hydrolytically into hexachlorophene before it exerts any systemic effects (Sinkula and Yalkowsky, 1975). The toxicity of the parent drug upon application to the skin is reduced with the introduction of the prodrugs.



Dithranol | Dithranol triacetate | Dithranol diacetate

Fig. 15. Dithranol and its esters.

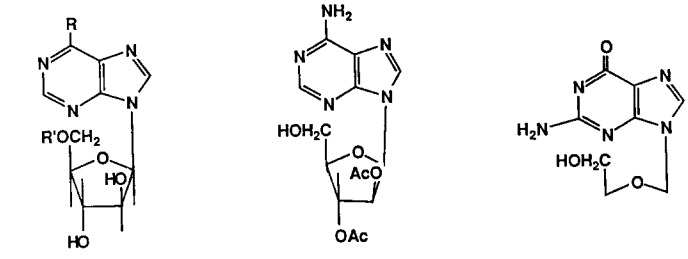


Fig. 17. Vidarabine esters and acyclovir.

Esters of metronidazole

Johansen et al. (1986) and Bundgaard et al. (1983) employing metronidazole esters (Fig. 16) as delivery systems for metronidazole, showed that no single ester offered optimal properties regarding both skin permeation and enzymatic transformation. As far as enzymic hydrolysis was concerned, the greatest improvement was observed for the derivatives with the longest carbon chains studied, namely the valerate and caproate esters. Enzymatic cleavage was enhanced approximately 2000-fold with increasing chain length, but unfortunately permeation was only marginally improved. The authors concluded that the butyrate ester was the best candidate for improving metronidazole delivery. However, it is unlikely that the derivatives will be sufficiently better than the parent to justify introduction into clinical use.

Esters of vidarabine

Another example of a chemical approach to alter the release rate is the design of controlled release prodrugs of vidarabine (Yu et al., 1979a and b, 1980a–c). Three 5′-monoesters (acetate, valerate and octanoate) of vidarabine were investigated with hairless mouse skin and the mouse vaginal membrane. The *n*-alkyl chain length at the 5′-position were found to affect solubility, lipophilicity, esterase lability and deaminase inhibition and these, in turn, influenced the steady-state vidarabine levels at the target site in topical chemotherapy. Vidarabine valerate, as in Fig. 17, was predicted to be best among all the three prodrugs when the prodrugs were topically applied to whole skin under maximum thermodynamic conditions.

Another prodrug of vidarabine has been designed and synthesized. The compound is vidarabine-2′,3′-diacetate, as in Fig. 17. The increased lipophilicity allows the compound to penetrate the skin, where it is metabolized to the parent drug. In vivo tests indicate that vidarabine-2′,3′-diacetate may be as effective as acyclovir in treating primary lesions (Bucks, 1984).

Oxidation

7-alkyl-theophylline

Prodrugs of theophylline are under development for the treatment of inflammatory condi-

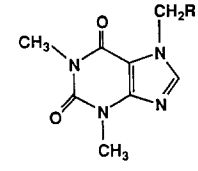


Fig. 18. The derivatives of theophylline.

I : R = H
II : R = HO–
III : R = CH_3CO_2–
IV : R = $C_2H_5CO_2$–
V : R = $C_3H_7CO_2$–
VI : R = $C_5H_{11}CO_2$–
VII : R = $C_7H_{15}CO_2$–
VIII: R = $(CH_3)_3CCO_2$–
IX : R = $(C_2H_5)_2NCOCH_2CH_2CO$–
X : R = $C_2H_5OCO_2$–
XI : R = $(CH_3)_2NCH_2CO_2$–
XII : R = C_2H_5O–

tions and psoriasis. Sloan and Bodor (1982) designed and synthesized 7-hydroxymethyl and 7-acyloxymethyl prodrugs of theophylline which, in vitro, exhibit increased lipid and water solubilities. Such 7-alkyltheophyllines, (refer to Fig. 18) require an oxidative metabolic activation step before they become chemically labile and capable of dissociation into an aldehyde and theophylline. The 7-hydroxyalkyl derivatives that result from the oxidation step are themselves prodrugs. However, their stability in solution is minimal so that they usually are not considered as practical approaches to improving dermal delivery of theophylline. Although the prodrug approach has not been optimized, the available prodrugs showed increased delivery of theophylline into the skin in vivo, and once theophylline was delivered, it was an effective antiproliferative agent.

Ester of dithranol

As mentioned earlier, dithranol triacetate is used as a prodrug of dithranol. In the skin, the triacetate ester is first hydrolysed into the dithranol diacetate, which in turn undergoes oxidation to give the active compound (Wiegrebe et al., 1984). Dithranol diacetate itself is not stable enough to be used as a prodrug.

Reduction

Nitrate ester of cromolyn

As mentioned earlier, the pivalyloxymethyl-nitrate ester of cromolyn required not only esterase hydrolytic reaction, but reductive cleavages as well.

Methods employed in metabolism studies of prodrugs for dermal delivery

Both in vitro and in vivo techniques have been utilized to study skin metabolism. However, there are few reported in vivo skin metabolism studies on prodrugs for dermal delivery (Wiegrebe et al., 1984; Ozawa et al., 1985).

For most in vitro methods used to investigate metabolic regeneration of prodrugs in the skin, either skin fragments or skin homogenates are incubated with the prodrug, and the metabolites formed by the enzymes present are then characterized (Tauber and Toda, 1976; O'Neill and Carless, 1980; Ozaki et al., 1981; Tauber, 1982; Cheung et al., 1985a and b; Ozawa et al., 1985; Johansen et al., 1986). In permeation studies, full thickness skin is usually mounted on a diffusion cell and the receptor phase is monitored for the parent drug, as well as the prodrug (Rawlins et al., 1979; Yu et al., 1979a and b; Bodor et al., 1980; Loftsson et al., 1981a and b; Mollgaard et al., 1982; Sloan et al., 1982, 1983, 1984a and b, 1988; Bundgaard et al., 1983; Hashida et al., 1985; Mukai et al., 1985; Ozawa et al., 1985; Tojo et al., 1986; Johanssen et al., 1986; Young-Harvey et al., 1986; Koch and Sloan 1987; Waranis et al., 1987, 1988). However, Bundgaard et al. (1983) reported the leaching of hydrolytic enzymes from the mounted skin during in vitro percutaneous absorption experiments. It is therefore important to keep in mind the possibility of enzymes leaching into the receptor phase in subsequent studies.

Theoretical models of skin metabolism of prodrugs

There have been many attempts to model mathematically the concurrent penetration and metabolism processes of prodrugs in the skin. Mathematical treatments of skin metabolism and percutaneous absorption can be classified into steady state or non-steady state models (Guy and Hadgraft, 1985).

The steady state model was adopted by Ando et al. (1977), Fox et al. (1979), Yu et al. (1979a and b, 1980a and b), Loftsson (1982), Yacobi et al. (1984) and Higuchi et al. (1983a and b) in order to consider the effect of cutaneous biotransformation and to evaluate rationally topical prodrug delivery. The steady state model assumes a linear concentration gradient of the parent drug across the stratum corneum.

If a linear concentration gradient does not exist across the skin, the non-steady state model is applicable. Of course in any system, the steady state is preceded by a non-steady state model. Following depletion of sufficient drug the steady

state then further decays into a non-steady stage. Therefore, whether a steady state model is adequate for predicting the input behaviour of the applied formulation will depend on a complex series of interacting factors including membrane thickness, enzyme rate constants, prodrug concentrations and drug diffusivities in the different skin layers.

Guy and Hadgraft (1982) applying a non-steady state model to evaluate the amount of unchanged penetrant reaching the dermal vasculature as a function of time found it to be dependent on the kinetics of metabolism of the prodrugs, as well as on the effective partition coefficient of the molecule between the stratum corneum and the viable epidermis. As with all enzymic systems, the possibility of saturation of the system must be considered. With a lack of precise data on enzyme levels and activities in the skin, non-steady state models are at present difficult to test. Guy and Hadgraft (1984) also used a conventional pharmacokinetic model to describe the concurrent skin transport and metabolism processes of the prodrugs. This macro approach may in the short term be practically more useful than concentration on the individual parameters which can currently only be theoreticized, rather than measured.

Tojo et al. (1986) presented a model which takes into consideration the drug binding in the stratum corneum and the decay of enzyme in the viable skin. The model was tested using simultaneous skin permeation and bioconversion of estradiol esters to estradiol in hairless mouse skin. The match was good between the in vitro permeation profiles of these drugs across the skin and predictions made using the mathematical model.

Topically applied compounds may also be subjected to metabolism by micro-organisms found on the skin prior to absorption. Denyer et al. (1985) derived a mathematical predictive model suggesting that microbial degradation of drugs could possibly have an effect on compounds applied to the skin surface. This is especially relevant to drugs incorporated into transdermal delivery systems as these devices may be left on the skin for several days.

Conclusion

As the full metabolic potential of the skin is gradually being unravelled along with the physiochemical processes involved in the transdermal diffusion process, it can be anticipated that more prodrugs will be designed for dermal delivery to optimize the bioavailability of each drug delivered via the percutaneous route, for either local or systemic action. Conferment of controlled release characteristics to the drug may be a further objective. The whole spectrum of in vitro and in vivo work on dermal transport and metabolism of various drug substances could be further refined and expanded to enable the development of analytical models which would, in turn, throw more light on the opportunities promised by the cutaneous prodrug approach. With existing drugs, less than one per cent are suitable for transdermal delivery. The dermal prodrug approach may be able to increase this low percentage manyfold, but over-optimism is not justified. The ground rules are still unclear.

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