APPLICATION OF PRODRUGS FOR TRANSDERMAL AND DERMAL DRUG DELIVERY

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ABSTRACT:

In recent times, there has been a lot of interest in developing drug delivery systems to deliver drugs through the skin to the systemic circulation. This interest was further stimulated by reports on the effective treatment of disease states such as motion sickness, hypertension and angina [1,2], via the transdermal route. This has highlighted the possibility of using this route for the therapeutic management of various conditions, including particularly those diseases for which parenteral drug delivery is currently the main method of therapy (e.g diabetes). Other conditions requiring the long term administration of potential gastro-intestinal irritants (e.g. in chronic rhematoid arthritis), are equally receiving attention.

The advantages of the trasdermal route include avoidance of the variable absorption and first-pass metabolism which can occur with oral therapy, continuous drug input, allowance of the use of drugs with short elimination half-lives, ability to terminate drug action rapidly, improved patient compliance and a reduction in systemic toxicity.

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.

Prodrug for Transdermal and Dermal Delivery

The skin is a highly active metabolic organ[3]. It contains a multitude of different enzymes which can metabolize a wide range of synthetic and naturally occuring xenobiotics[4]. 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 prodrug [1]. Most drugs diffuse poorly through the skin. Manipulation of the physico-chemical 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 some examples are listed in Table 1. In considering dermal delivery, it is important to identify the two distinct alternative objectives. First is the optimization of systemic delivery (e.g. anti-hypertensive agents and oestrogens, in transdermal or percutaneus drug delivery). The second involves optimization of delivery to the dermis (e.g topical corticosteroids and agents for the treatment of skin disease such as eczema and coetaneous tumors). It is important to note that the physicochemical attributes necessary for the prodrug to meet this distinct requirement will be different.

Skin metabolism of prodrugs

In order to maintain the activity profile of the parent drug, there must be reversion of the prodrug to the active agent by enzymatic or non-enzymatic reactions. Many prodrugs possess an ester linkage[5] capable of undergoing enzyme-catalysed cleavage to the parent drug. It is well documented that dermal enzymes are effective in promoting such metabolism[6].

In their work, the cutaneous stereoselective hydrolyses often ester prodrugs of propranolol in hairless mouse were compared to those in liver and plasma. The skin was shown to be rich in both caboxylesterases and cholinesterases, and it also showed the highest stereoselectivity. Johansen et al,[7] investigated the transport and bioconversion of a series of aliphatic esters of metronidazole in the skin.

Table 1: Prodrugs for transdermal and dermal drug delivery

S/No.	Parent drug	Bioreversible modification	Improvement	Tissue studied
1.	Aspirin and salicylic acid	Methylthiomethyl and methylsulfinylmethyl esters	Absorption	Full thickness mouse skin
2.	Betamethasone	17 - valerate	Prolonged action	Whole human skin
3.	Ephedrine	3,4-Dimethyl-5-phenyl oxazolidine	Absorption	Full thickness human skin
4.	5-fluorouracil	1-alkylcarbonyl	Absorption	Full thickness mouse skin
5.	Hydrocortisone	Butyrate propionate, diester	Absorption	Dog skin & enzyme extract of dog & rat skin
6.	Metronidazole	Accetate, propionate, butyrate, valerate, caproate esters	Absorption	Whole human skin and skin homogerate
7.	Propranolol	Esters	Absorption	Hairless mouse
8.	Propranolol	Esters	Absorption	
9.	Propanolol	Isovaleryl and cyclopropanoyl ethers	Absorption	

Besides the presence of esterases in the skin, other cutaneous enzymatic activities have also been identified [12, 13, 14]. Therefore, it is important to understand how such enzyme system might modulate the activity of topically applied drugs and then to optimize the design of the prodrugs accordingly [15, 16]. Table 2 is a summary of the mechanism of bioactivation of prodrugs upon dermal absorption.

Table 2 : Bioreversion mechanisms of prodrugs

Mechanism	Prodrug derivative	Parent drug
Chemical hydrolysis	a) N-Mannich bases	5-fluorocytosine 5-fluorouracil
	b) N-N- dialkylhydroxyl	Indomethacin
	c) Oxazoli 11 dines	Ephedrine
Enzymatic reactions Hydrolysis	a) S-Acylhetero-alkyl derivatives	Thiopurines e.g. 60mecatopurine
	b) N-I-alkyl carbonyl Derivatives	5-fluorouracil
	c) Esters	Corticosteroids metronidazole
Oxidation	7-Acyloxymethyl derivatives ester	Theophylline
Reduction	Pivalyloxymethyl nitrate ester	Cromolyn

Prodrugs regenerated by chemical hydrolysis

a. Mannich base prodrugs:

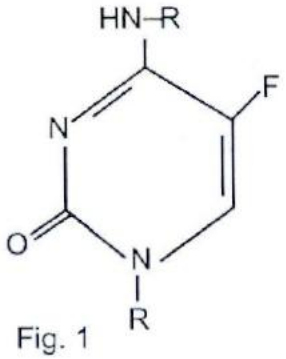

Fig. 1

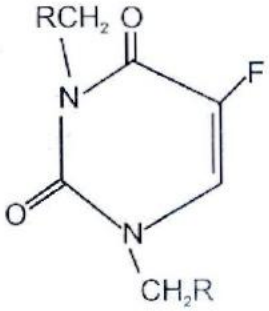

Fig. 3

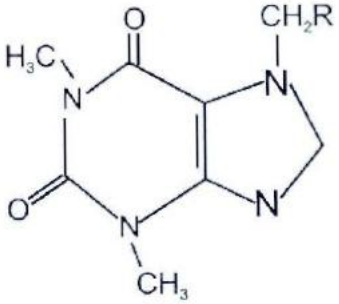

Fig. 2

The mannich base prodrugs of

Fig. 1: 5-fluorocytosine

I : R = -H

II : R = $-CH_2NC_2H_5$

III : R = $-CH_2N(C_2H_5)_2$

IV : R = $-CH_2-N(CH_3)_2$

Fig. 3 : 5-fluorouracil

I : R = -H

II : R = $N(CH_2)_5$

III : R = $-N(CH_2CH_2)_2O$

Fig. 2: 6-mecaptopurine

I : R = $CH_2N(C_4H_9)_2$

II : R = $CH_2N(CH_2)_5$

III : R = $CH_2N(CH_2)_4$

Bundgard et al [2]; Koch et al[17] and Beall and Sloan[21] derived and studied the mannich base prodrugs of 5-fluorocytosine, 6-mecaptopurine and 5-fluorouracil (Fig. 1-3). They found that these derivatives enhanced the delivery of their parent drugs through the skin because of enhanced water and lipid solubility. Therefore, 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 appears 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. However, formaldehyde is liberated upon hydrolysis of these prodrugs, and there is concern about its acceptability and possible toxicity to the skin. Instability of the prodrugs during storage may also be a problem.

b) N,N-dialkylhydroxylamines

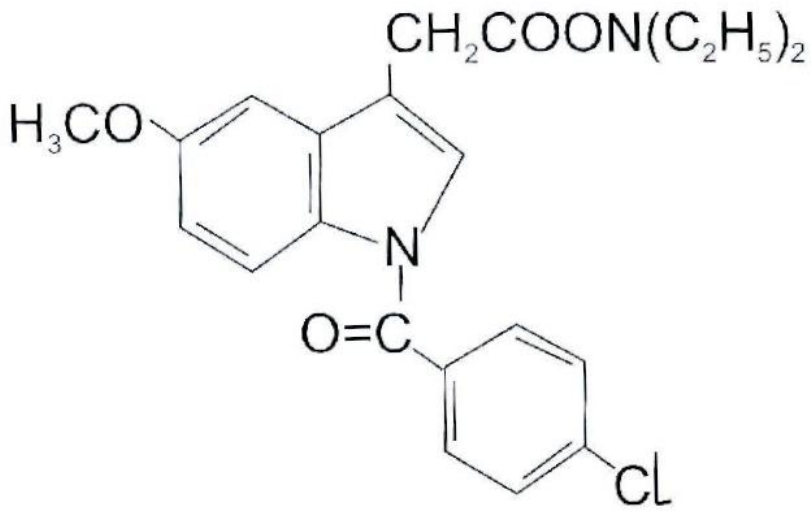

Fig. 4: N, N-diethylhydroxylamine derivative Indomethacin

This derivative (Fig. 4) appears to be attractive candidate as derivative agents for carboxylic acids. They are relatively stable and yet sufficiently liable to serve as activated esters in amination reactions where the reaction is catalysed by a weak acid [18]. They are stable as long as they are not in contact with protic solvents. In addition, the derivative agents exhibit a low order of toxicity. Amines have been used as penetration enhancers in formulations and therefore derivative agents containing low pKa amines may also improve the ability of the carboxylic acids to penetrate biological membranes. Concerns about the mutagenicity of topically applied amino compounds may, however, be a distinct handicap to wider use of these amino products.

In order to determine if substitution of the derivative has 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 isoprophylmyristate as vehicle [18]. Almost five times as much indomethacin was delivered by the derivative than by indomethacin itself. It was also found to be more effective than indomethacin in inhibiting thermal inflammation in animal models.

c) Oxazolidines

Oxazolidines are another group of prodrugs which undergo rapid hydrolysis in water to give formaldehyde, as illustrated in Fig. 5 (9)

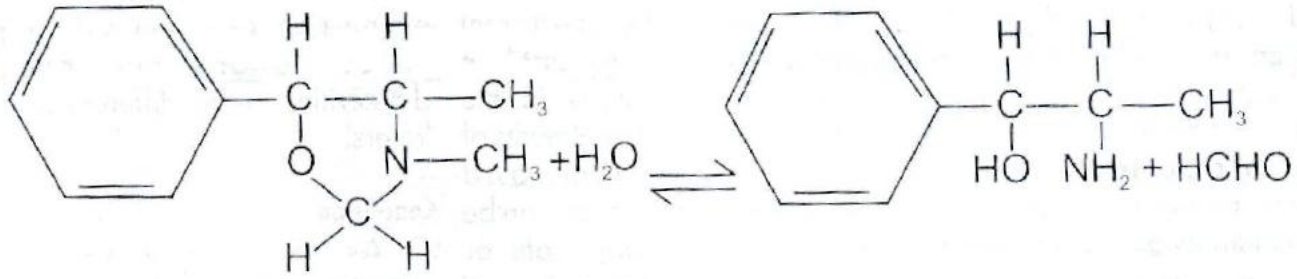

Fig. 5: The 3,4-dimethyl-5-phenyloxazolidine prodrug II is hydrolysed to ephedrine (I) and formaldehyde.

The oxazolidines formed by condensation of benzaldehyde and salicylaldehyde with ephedrine have significantly lower pKa values than ephedrine. Thus, it was anticipated that the oxazolidines would exist as a neutral molecule to a greater extent. Then ephedrine, in the pH range 3-8, compatible with that of the human skin, and 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 ephedine occurs within the skin. Young-Harvey et al [9] went on to suggest that perhaps other aldehydes which are less toxic than formaldehyde could be used with p-amino alcoholic to develop other prodrug derivate.

Prodrugs regenerated by enzymatic reactions hydrolysis:

1. s-acylheteroalkyl derivatives of thiopurines.

The thiopurines have poor aphasic solubilities and are also poorly absorbed through biological membranes. Sloan et al[19] prepared prodrugs of the thiopurines to increase the solubilities, while ensuring at the same time delivery of only the parent compounds by the alkylation of the thiopurines with acylheteroalkyl halides under neutral or basic condition. 6-mercaptopurine, a well-known antiproliferative agent for the systemic treatment of psoriasis is inactive when administered topically[18]. This is because, not enough of it is delivered through the stratum corneum into the epidermis for it to be effective.

b. N-l-alkylcarbonyl derivatives of 5-fluorouracil

Topical application of 5-flouorouracil has been useful in the treatment of various diseases, such as actinic keratoses, but it does not penetrate the skin well because of its low lipophilicity. Beall and Sloan[2] synthesized l-alkyl carbonyl derivatives that penetrated five times more readily through the human skin than 5-fluorouracil and at the same time was fully bio-available in the form of the parent drug due to extensive cutaneous metabolism[2].

c. Prodrugs of corticosteroids, hormones and prostaglandins

Many endogenous substances, for example, steroid homones such as hydrocortisine 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 endogenous 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. Examples; it has been reported that the 17, 21-diesters[20]. Also it was shown that the corticosteroid - 17-esters were resistent 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 isomers.

It has also been shown that the anti-inflammatory effect of topically applied hydrocortisone increased and the systemic effects decreased by the use of the spirothiazolidine prodrugs (Smith 1988)[23].

Bodor et al[24] have designed and synthesized ethyl ester thiazolidine derivatives of progesterone. They yielded more than twice the radiolabelled steroid concentration in the skin after topical application compared to topical application of progresterone itself.

d. Esters of acetylsalicylic acid

Several prodrugs have been developed by Loftson et al[8]. They are freely penetrable compounds and easily hydrolysed to acetylsalicylic acid by skin esterases[5].

Esters of cromolyn, dithranol, hexachlorophene and many others have been made as prodrugs to improve absorption and/or reduce toxicity.

Oxidation and reduction

Prodrugs like 7-alkyltheophilline undergo oxidation to liberate the parent drug. Nitrate ester of cromolyn undergoes both esterase hydrolytic reaction and reductive cleavage to liberate parent drug.

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. Methematical treatments of skin metabolism and percutaneous absorption can be classified into steady state or non-steady state models[25].

The steady state model was adopted by Ando et al[26], Higuchi et al[27] and others 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 the linear concentration gradient does not exist across the skin, the non steady state model is applicable. 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 state. Therefore, whether a steady state model is adequate for producing 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.

Conclusion

As the full metabolic potential of the skin is gradually being unravelled along with the physiochemical process, it should be anticipated that more prodrugs would be designed for dermal delivery to optimize the bio-availability of each drug delivery 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 This could be refined and expanded further 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 could increase this low percentage many fold.

REFERENCES

1. Bucks DAW, (19840 Skin structure and metabolism. Relevance to the design of cutaeneous therapeutics. Pharm. REs., 1:148-153.
2. Beall HD and Sloan KB (1996) Transdermal delivery of 5-fluorouracil (5-Fu) by l-alkyl carbonyl-5u prodrugs. Int. J. Pharm. 129, 203-210.
3. Bickers DR, and Kappas A (1980) The skin as a site of chemical metabolism. In Gram TE (Ed), Extrahepatic metabolism of drugs an dother foreign compounds, MTP< 1980, 295-318.
4. Noonan PK and Wester RC (1985) Cutaneous metabolism of xenobiotics, in Bronaugh RL and Maibach IH (Eds), percutaneous absorption mechanisms - methodology - Drug Delivery, Dekker, New York, 65-85.
5. Bundgarr H and Nielsen NM (1988) Prodrug derivatives of carboxylic acid drugs. Int. Patent, PCT W088/06151, March 1988.
6. Ahmed S, Imai T, Yoshigae Y and Otagiri M, (1997). Stereospecific activity and nature of metabolizing esterases for propranolol prodrug in hairless mouse skin, liver and plasma.
7. Johansen M, Mollgarrd B, Wolton PK, Larsen C and Hoelgaard A (1986). In vitro evaluation of dermal prodrug delivery - transport and bioconversion of a series of aliphatic esters of metronidazole. Int. J. Pharm. 32, 199-206.
8. Loftsson T, Kaminski JJ and Bodor N (1981). Improved delivery throug biological membranes. VIII J. Pharm. Sci. 70:743-749.
9. Young-Harvey JH, Rae ID and Pitman IH (1986). Oxazolidines: Prodrugs for the delivery of B-aminoalcohols through human skin from aqueous solution. Int. J. Pharm. 30:151-160.
10. Ahmed S, Imai T and Otagiri M (1996) Evaluation of stereoselective transdermal transport and concurrent cutaneous hydrolysis of several ester prodrugs of propranolol: mechanism of stereoselective permeation.
11. Ahmed S, Imai T and Otagiri M (1995). Steroselective hydrolysis and penetration of propranolol prodrugs - invitro, evaluation using hairless mouse skin.
12. Wester RC and Maibach HI (1986). Dermatopharmacokinetics: a dead membrane or a complex multifunctional viable process. Progr. Drug metab. 9:95-109.
13. Guy RH, Hadgraft J and Bucks DAW (1987) Transdermal drug delivery and cutaneous metabolism. Xenobiotica, 17, 3250343.
14. Martin RJ, Denyer SP and Hadgraft J. (1987) Skin metabolism of topically applied compounds. Int. J. Pharm. 39:23-32.
15. Higuch T (1977) Prodrug molecular structure and percuteneous delivery, in Roche, E. B. (Ed.) Design of Biopharmaceutical propreties through Prodrugs and Analogs, Am. Pharm. Assoc., Washington, 409-421.
16. Higuchi WI and Yu CD (1987) Prodrugs in Transdermal delivery in kydonieus AF and Berner B (Eds), Transdermal Delivery of Drugs, CRC Series Vol. III< 43-83.
17. Koch SAM ad Sloan KB (187) N-mannich base derivatives of 5-fluorocytosine - a prodrug approach to improve topical delivery. Int. J. Pharm., 35:243-252.
18. Sloan KB, Selk S, Haslam J, Caldwell L and Shaffer R (1984b) Acyloxyamines as prodrugs of anti-inflammatory carboxylic acids for improved delivery thorugh skin J. Pharm. Sci. 73:1734-1737.
19. Sloan KB, Hashida M, Alexander J, Bodor N, and Higuchi T (1983) Prodrugs of 6-thiopurines. Enchanced delivery through the skin J. Pharm. Sci. 72:372-378
20. O'Neill RC and Carless, JE (180) Influence of side chain on the hydrolysis of some hydrocortisone esters. J. Pharmacol. 32:19P
21. Bundgaard H, Hoelgaard A and Mollgard B (1983) Leaching of hydrolytic enzymes from bunman skin in cutaeneous permeation studies as determined wtihmetronidazole and 5-fluorouracil prodrugs. Int. J. Pharm. 15:285-292.
22. Sloan KB and Bodor WC (1982) Hydroxymethyl and acyloxymethyl prodrugs of theophylline: enhanced delivery of polar drugs through skin, Int. J. Pharm., 12:299-313.
23. Smith HJ (1988) Relationship of drug metabolism to drug design, in Smith J and Williams H (Eds) INtroduction to the Principles of Drug Design, Wraith, London, pp. 222-239.
24. Bodor N, Sloan KH, Little RJ, Selk SH and Caldwell (1982) Soft drugs 4. 3-spirothiazolidines of hydrocortisone and its derivatives. Int. J. Pharm. 10:307-321.
25. Guy RH and Hadgraft J (1982) Percutaneous metabolism with saturable enzyme kinetics, Int. J. Pharm. 11:187-197.
26. Ando, HY, Ho NFH, and Higuchi WI (1977), Skin as an active metabolizing barrier. I. Theroretical analysis of topical bioavailability. J. Pharm Sci. 66, 1525-1528.
27. Highuchi WI, Kusia A, Fox JL, Gordon NA, Ho NFH, Hsu CC, Park YY, Baker DC and Shannon WM (1983a) Controlled release of drugs - prodrug performance in target tissues. In Roseman, TJ and Mansdorf SZ (Eds), controlled Release Delivery Systems, Dekker, New York, 43-76.