REVIEW ARTICLE

PERCUTANEOUS ABSORPTION

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The application of preparations to the skin for cosmetic and medical purposes is as old as the history of medicine itself and references to the use of ointments, salves and pomades may be found in the early records of Babylonian and Egyptian medicine. In Roman times, drugs were sold by the "ungentarii" who were the compounders of ointments. Galen's formula for cold cream has persisted through the ages and, with some modification, it is still in use to-day.

Although the use of ointments goes back to antiquity, their use has, until recently, been largely empirical. It is only with the advances in dermatology that there has been an appreciation of the requirements of different ointment bases for different skin conditions. Before 1948, with the exception of hydrous ointment, official ointments were made with fatty materials such as soft paraffin, anhydrous wool fat, or beeswax or combinations of these substances. It was hardly appreciated that the therapeutic usefulness of an ointment depends as much on the kind of base used as on the active medicament. To-day, there are available many different synthetic substances allowing the formulation of a wide variety of preparations for application to the skin. The clinician has, therefore, a considerable choice of bases in the prescribing of dermatological preparations and the pharmacist needs to have an expert knowledge of the properties of the different preparations. Both should understand the main principles concerned in percutaneous absorption.

The percutaneous route has been used as a method of drug administration and, although of strictly limited value, may be useful in particular circumstances. With the introduction of toxic synthetic chemicals such as plasticisers in industry, and the use of highly potent insecticides in agriculture, hazards from the toxic effects after percutaneous absorption have become very real ones. The study of percutaneous absorption is of importance also in the elucidation of the normal functioning of the skin.

This review describes the main factors affecting percutaneous absorption, their assessment and application in preparations used in dermatology and drug administration.

Structure and Physical Properties of the Skin

Structure

The skin consists of an outer layer, the epidermis, and an inner layer, the dermis. The epidermis is a horny layer of keratinised epithelial cells, rich in lipoids and cholesterol. The thickness of this layer depends much on the position on the body and is largely determined by the amount

of wear and tear. Thus it is thickest on the palms of the hands and soles of the feet. The outer layers are being continuously shed and are renewed from the inner Malpighian layer, where transformation of protoplasm into keratin takes place. The layer of epidermis next to the Malpighian layer (or rete mucosum, prickle cell layer) is the stratum granulosum. Directly outside this is the stratum lucidum and the outermost layer is the stratum corneum. The cells of the Malpighian layer contain granules of the pigment, melanin, which are particularly abundant in the dark skinned races.

Beneath the epidermis is the cutis vera or true skin, a thick highly vascular layer consisting of connective and elastic tissue and containing many blood capillaries. The outer layer is folded into minute papillæ, over which the epidermis is moulded to form ridges. The papillæ may contain sensory nerve cells, or tactile corpuscles. The inner layer of the cutis vera passes into the sebaceous tissue.

The skin has a number of appendages—the hair follicles, sebaceous glands and the sweat glands. Each hair grows from a recess, or follicle, formed by the epidermal epithelium dipping into the subcutaneous tissue. The number of epithelial cells is much reduced in the follicle and at the base it thins out into a single layer of non-keratinised cells. The hairs arise from the base of the follicles and each hair consists of an external shaft and a root, called the hair bulb, implanted in the skin. The hair follicles are filled with sebum, a secretion from the sebaceous glands the ducts of which open into the upper portion of the hair follicle.

The sweat glands cover the whole of the human skin and each consists of a coiled tube in the dermis with a duct passing through the epidermis to the skin surface. The sweat glands are under vasomotor control and secrete sweat which helps to control the body temperature.

Physical Properties

The skin forms a relatively tough and impervious coating over the body. It has an important protective function and also plays an important part in the maintenance of a constant internal environment. It is not surprising that most substances penetrate the skin with difficulty and that the skin is highly selective in allowing substances to pass through it to the underlying tissues.

Externally, the skin is covered by a greasy secretion from the sebaceous glands consisting of waxes and cholesterol[1]. While this layer delays the penetration of water, prolonged immersion allows the waxes and cholesterol to be emulsified and water then penetrates into the horny epidermis. The keratin swells and the skin becomes white and wrinkled.

The main resistance to penetration of water and aqueous solutions through the epidermis is the presence of a polarised layer, or "electrophysiological barrier"[2], between the horny layer and the basal cell layer. This is situated between the acid stratum corneum (pH 5) and the slightly alkaline Malpighian layer, and represents an electrical double layer with positive H^+ ions on the one side and negative OH^- ions on the other. Substances applied to the skin penetrate mainly down the hair follicles[3–6].

Abnormal Skin

The normal condition of the skin can be altered by physical and pathological changes. These will affect percutaneous absorption. Removal of the epidermal layers by abrasion or cutaneous lesions allows medicaments to penetrate directly into the subcutaneous tissues and the circulation. With broken skin there is a definite danger of topically applied medicaments causing toxic effects when applied to large areas[7]. Degreasing the skin with solvents, such as benzene, chloroform, ether or acetone will remove the sebum from the skin and hair follicles, thus considerably facilitating percutaneous absorption[8]. Their main action is to dissolve the lipoid compounds in the living cells themselves[9]. Detergents also degrease the skin and are capable of bursting lipoid from the epidermal cells, thus creating conditions for percutaneous absorption. Astringents and caustic substances, for example, phenol, by precipitating cellular protein, may actually decrease absorption[10–12]. In lower concentrations, however, phenol may be absorbed with dangerous toxic effects.

In pathological conditions, functional changes alter the electrical behaviour and diminish skin resistance[9]. Changes in the skin membrane cause increased permeability and decreased polarisation currents, which can be demonstrated in inflammatory lesions. The normal acidity of the external skin may be changed to an alkaline reaction[13], as in seborrhœic dermatitis and eczema. Keratin is an amphoteric protein with an isoelectric point at pH 5·6. At the normal hydrogen ion concentration of the skin, there is a high resistance to hydrolytic agents, but in the presence of alkali the keratin becomes hydrated and behaves as a colloid gel[14]. At very alkaline values, hydrolysis occurs irreversibly with destructive effect. Increase in pH, therefore, will render the skin more permeable to external irritants.

Factors Affecting Percutaneous Absorption

The main factors affecting percutaneous absorption are (*a*) penetration and mode of absorption, (*b*) the temperature of the skin, (*c*) the properties of the medicament, (*d*) the influence of the vehicle and (*e*) the mode and duration of application.

Penetration and Mode of Absorption

Before a medicament can be absorbed it must first penetrate the skin. The main route of penetration is through the hair follicles[3–6] and sebaceous glands, but some penetration may occur through the sweat glands[16]. Except in special circumstances, absorption does not take place through the horny layer. The inuncted material passes through the follicle opening, along the hair and root sheaths and is absorbed through the sebaceous glands and the epidermal cells at the base of the hair follicles[9,15]. Here the epidermis thins out to a single layer of non-keratinised cells so that conditions are favourable for absorption, after which the medicament diffuses downwards into the highly vascular cutis vera, also horizontally and upwards into the epidermis[17].

Skin Temperature

It is well known that elevation of the skin temperature enhances percutaneous absorption. This may be due to a lowering of the viscosity of the sebum and facilitating its mixing with the inuncted preparation. A rise in skin temperature also increases the cutaneous circulation through vasomotor dilatation of the skin vessels. The skin temperature may be raised by the application of heat, irritant substances, or by covering with an air-tight dressing.

Properties of the Medicament

A major factor in skin penetration is lipoid solubility of the medicament[9,18]. It has been proved that lipoid soluble substances penetrate the skin, while lipoid insoluble substances do not. Salicylic acid, which is lipoid soluble, penetrates with ease; but sodium salicylate, which ionises in solution and is not lipoid soluble, does not penetrate the skin[9,19]. There are some substances, particularly the heavy metals, which are not lipoid soluble but undergo a chemical reaction with fatty acids in the sebum and are slowly absorbed[9]. The beneficial effects of ammoniated mercury have been stated to be due to the slow dissociation of mercuric ions under the influence of the acid reaction of the horny layer and sweat[20], which are then adsorbed on to the epidermal cell walls. Absorption into the general circulation does not take place[20–23].

Maximal percutaneous absorption occurs when the medicament combines lipoid solubility with a moderate solubility in water. These substances are soluble in the sebum, readily penetrate into the skin and then dissolve in the tissue fluids. The organophosphorus insecticides are particularly dangerous in this respect and it is difficult to oppose their absorption by the use of barrier creams. Progesterone has a similar chemical structure to œstradiol and the same lipoid solubility, but it is not so well absorbed because it is less soluble in water[24].

Influence of the Vehicle

The function of the vehicle in percutaneous absorption is to facilitate contact between the medicament and the absorbing cells in the sebaceous glands and at the base of the hair follicles. The vehicle itself cannot promote percutaneous absorption of a lipoid insoluble substance, nor can it transport the substance through the cell membrane. It can, however, retard penetration and absorption, for an ointment base which is not miscible with the sebum will hinder the penetration of the medicament into the hair follicle.

Absorption is best from vehicles which spread easily over the skin surface, readily mix with the sebum and so bring the medicament into contact with the absorption cell areas. It has long been known that absorption is better from animal and vegetable oils than from mineral oils, because they more readily penetrate the skin[3,5,25]. Organic solvents, like ether, chloroform, benzene and acetone penetrate the skin with ease[26], and enhance the percutaneous absorption of a medicament to such an extent that toxic effects can occur. Surface active agents, because of their

high wetting and detergent properties, should increase percutaneous absorption, but when they are incorporated in ointment bases there is little evidence that this occurs. It has been reported that deeper and more rapid penetration of ammoniated mercury is obtained by the addition of a wetting agent to a paraffin ointment base[27], but the addition of sodium laurylsulphate to a polyethylene glycol base fails to increase the absorption of phenolsulphonphthalein or potassium iodide[28]. In other experiments, the penetration of iron, bismuth and sulphonamides was promoted by the addition of alkylbenzene sulphonate to aqueous vehicles containing propylene glycol[15].

The addition of lipoids, such as cholesterol, increases the penetrating properties of liquid paraffin[5], but the application of cholesterol to the skin reduces permeability to water soluble salts by reinforcing the resistance of the fatty substances normally present in the skin[29].

The absorption of a medicament from an ointment will depend on its rate of liberation from the base, and this will depend upon the partition coefficient of the medicament between the base and the sebum. The inunction of a solution of phenol in oil will not have a toxic effect because the amount of phenol liberated is negligible, while aqueous solutions can have a caustic effect.

Incorporation of the medicament in an emulsified base affects absorption. It has been found that the absorption of diiodofluorescein ^{131}I is poor from an oil-in-water base, because the continuous aqueous phase probably retards penetration[30]. Absorption is better from water-in-oil emulsions, where the external phase is readily miscible with the sebum, and from cetomacrogol which possesses both lipophilic and hydrophilic properties.

Mode and Duration of Application

The mode of application affects percutaneous absorption. Friction and massage cause a local vasodilatation of the skin vessels, so increasing the skin temperature and promoting absorption. Mechanical pressure forces the ointment and the medicament into the hair follicles, mixes them with the sebum and displaces entrapped air[9,25].

The duration of application also affects absorption. With diiodofluorescein ^{131}I it has been shown that there is an increase in absorption with time[30]. After inunction, urinary excretion of mercury continues at a high level for at least a week after cessation of application. This is due to a store of accumulated mercury in the follicles[31].

Assessment of Percutaneous Absorption

The assessment of percutaneous absorption presents a number of fundamental problems. It is necessary to differentiate clearly between skin penetration and absorption.

The methods can be divided into two main groups (*a*) those which measure skin penetration and (*b*) those which measure systemic absorption. In all *in vivo* methods allowance must be made for an inherent variability between the test objects. Ideally, any scheme of quantitative

assessment should follow the general basic principles for biological assays defined by Dale[32] and enumerated by Emmens[33]. Simultaneous comparisons should always be made with a standard preparation under the same experimental conditions. However, strictly valid numerical assessments can rarely be made, for, in comparing absorption from different vehicles, the standard and test differ in composition and so do not comply with the biological assay principles. It is usually necessary to be content with generalised statements, such as "absorption is better from one vehicle than from another". Finally, the importance of species differences must be considered in transferring results obtained in experimental animals to man.

For the study of skin penetration medicaments are used which can be easily detected microscopically. Sections of the skin are prepared under carefully controlled conditions to prevent the movement of the medicament. The skin used may be animal or human skin removed in biopsies. Among the substances which have been employed in such investigations are oil soluble dyes[5], sulphonamides and iron and bismuth compounds[15]. Radioactive tracer materials may also be used where autoradiographs are prepared on photographic emulsions for comparison with normal sections[34]. A useful method for assessing skin penetration is to apply the medicament in solution to the skin under a bell jar. Changes in the concentration of the compound in the solution are measured at increasing time intervals[35,36]. This method is most suitable for solutions in volatile liquids and it gives valuable information on changes in penetration with both time and concentration.

For the study of skin absorption both *in vitro* and *in vivo* methods are used. *In vitro* methods are of a limited value only, for they bear little relation to the conditions occurring in normal skin. They do give useful information on the release of the drug from the base. The most commonly used methods are based on the diffusion of the medicament from cups in an inoculated agar plate. The zones of inhibition are measured, as in microbiological assay techniques[37,38]. Their main value is in determining the antiseptic activity of medicaments in ointment bases. Attempts have been made to simulate skin conditions by using natural and artificial membranes. Measurements have been made of the release of sodium chloride from various ointment bases through cellophane bags[39], and sodium iodide through sheep bladders[40].

For the assessment of skin absorption *in vivo*, the medicament is applied to the skin in the vehicle being tested. The amount absorbed is measured in the blood, urine, fæces or some particular organ by suitable chemical or physical methods. Substances used have included methyl salicylate[41] and iodine[42]. The availability of radioactive tracer substances has increased the sensitivity of such methods[30,43–45].

Alternatively, substances are applied to the skin which cause characteristic pharmacological actions when absorbed, such as local anæsthesia, inhibition of cholinesterase, growth of a particular organ or even death. Substances used have included the alkaloids[46,47], hormones[48,49], vitamins[50] and chemotherapeutic substances[51]. Some of these methods have been used for clinical assessment in man[41,52].

PERCUTANEOUS ABSORPTION

Radioactive tracer techniques provide new and sensitive methods for the assessment of percutaneous absorption, but they have some disadvantages when used in animal tests. Variations in absorption in different animals can be great, and it is difficult to use large numbers in a single test, because of increased radiation hazards and difficulties in the disposal of contaminated materials[30].

Dermatological Requirements

The determatological requirements of an ointment base differ according to the skin condition under treatment[53]. When the horny external layer of the skin has been damaged, or exfoliated, an ointment may be needed as a protective. Such ointments are usually inert, bland preparations, which are largely unabsorbed by the skin. They include the paraffins, which are particularly valuable in xerodermia and ichthyosis. They may include medicaments which are usually poorly absorbed and exert only a local action, e.g., ammoniated mercury, sulphur and zinc oxide.

Barrier creams are protective preparations, which are applied to the skin before exposure to irritant and other noxious substances. Their formulation will depend to a large extent on the type of substance which they are intended to guard against.

When it is desired to soften the skin an emollient ointment is used. Preparations of this type must penetrate the hair follicles. They usually contain an animal or vegetable oil, which is intended to replace a deficiency of the natural fats in the skin, as in xerodermia, ichthyosis and senile skin.

Ointments applied to the skin surface to convey a medicament to a localised area are used in the treatment of superficial lesions. In such preparations, it is important that the medicament should be released from the base but should not be absorbed systemically. Antiseptic ointments are best formulated in emulsified bases[54], such as hydrous emulsifying ointment, and it is important that the base chosen should have no adverse effect on the activity of the medicament.

In some conditions the medicament must penetrate through the skin to permeate the lower layers. In ringworm of the scalp, for example, fungal spores and mycelia become embedded deep in the hair follicles and are not reached by fungicides in the usual type of base. By the use of polyethylene glycols, ointments have been formulated, containing phenylmercuric nitrate or salicylanilide, which will destroy the mycelia and spores without the need for previous epilation[55,56]. Penetrating vehicles have also been used for the application of sulphur in acne vulgaris[57], and tyrothricin in the treatment of pyodermas[58].

Percutaneous Administration

The percutaneous route has only a limited sphere of usefulness in the administration of drugs. It has the advantage of enabling a high concentration of the drug to be built up in a certain region of the body for an intense localised action[59,60] with limited side effects. In addition, it offers an alternative route of administration for substances which are inactivated in, or irritate the gastro-intestinal tract, and would normally have to be given by parenteral injection. The main difficulty with percutaneous

administration is the control of doses. It is particularly useful when it is desired to build up the concentration of a drug slowly in the body and then to maintain it at a constant level. This was the basis of the use of mercurial ointments in the treatment of syphilis, where a depot of mercury was retained and slowly absorbed from the hair follicle[31].

A few of the more important drugs which have been administered percutaneously will now be discussed.

Vitamins and Hormones

The absorption of vitamins and hormones through the skin depends on their lipoid solubility. Oil soluble vitamins and hormones are well absorbed while, the water soluble ones are not.

Sex Hormones. The natural œstrogens are better absorbed through the skin than the synthetic ones, and the gradual and maintained concentration obtained in the body provides the optimal conditions for their action[61]. An intense local action is the basis of the application of œstradiol to promote development of the breast in the hypogonadal female[62]. Experience in the treatment of acne and various dermatoses, has shown that beneficial local effects can be obtained by the topical application of œstrogens in alcoholic solution, or in a vanishing cream base, without systemic effects[63].

The inclusion of œstrogens in cosmetic preparations for the improvement of senile skin has recently caused some controversy[64]. Provided they are used in moderation the amount of œstrogen absorbed does not appear to be significant. The indiscriminate use of œstrogens in cosmetic creams, however, is not to be encouraged, for systemic effects have been observed[65] and a possible carcinogenic action has not been disproved. Progesterone is not so well absorbed as the œstrogens[24,49,66] and the tissues are less sensitive to it. It has been used as a constituent of cosmetic creams.

Both testosterone and its propionate are absorbed through the skin, the free alcohol being more effectively absorbed than the ester[61,67]. Methyltestosterone is also absorbed, but to a less extent[68]. Percutaneous administration of testosterone propionate in sesame oil solution has been used in the treatment of dysmenorrhœa[69]. In other clinical conditions, both in the male and the female, percutaneous administration has been valuable for obtaining a localised effect[70,71].

Cortical Hormones. Cortisone and hydrocortisone can only be absorbed through the skin to a small extent. Systemic effects have not been observed, even when large doses have been applied over extensive areas of the skin. The application of a total dose of 750 mg. of hydrocortisone, over a 3 day period in a washable ointment, failed to increase the blood and urine concentrations of 17:21-dihydroxy-20-ketosteroids[72]. It has also been shown that the topical application of hydrocortisone does not increase the circulating eosinophils[73].

Deoxycortone is absorbed through the skin, and it has been reported that percutaneous absorption from a solution in eucalyptol is as effective as a subcutaneous injection in oil[25].

Vitamins. The fat soluble vitamins can be absorbed through the skin and vitamin A deficiency in animals has been cured by the percutaneous administration of the vitamin[74]. Absorption is better from organic solvents than from oily solutions or ointment bases[75]. Any beneficial effects from the application of vitamin A ointment in the treatment of ichthyosis, however, may be attributed to a non-specific effect on the epidermis, and even the administration of excessive doses does not significantly increase the total vitamin A plasma levels[76].

Vitamin K and its analogues are absorbed through the skin and percutaneous administration in light liquid paraffin and kerosene has been described as a convenient way of administering menaphthone to new-born infants[77].

Toxicity Hazards following Percutaneous Absorption

A brief mention must be made of the dangers following the absorption of toxic substances through the intact skin. Skin absorption is an industrial hazard in the use of some solvents, plasticisers, detergents and, more recently, in the handling of radioactive materials. The introduction of new and potent pesticides, particularly the organo-phosphorus compounds, raises a very definite occupational risk in agriculture. These compounds are found to penetrate the waxy cuticle of the insect so it is not surprising that they penetrate human skin with ease. Protection is afforded by special clothing and suitable barrier creams as a second line of defence.

In medicine there must always be a danger of toxic effects when potent medicaments are applied to large areas of broken skin. Attention has recently been drawn to an increasing number of instances of boric acid and borax poisoning in babies, many of which have been fatal[7]. The two most important factors involved are the concentration of the drug in the preparation and the area of broken skin to which it is applied.

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