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Skin Permeability

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Contents

1. Pharmaceutical Problems of Externally Applied Drugs

A pharmacologically active drug can only in special cases be applied therapically without prior preparation with auxiliary and carrier substances necessto constitute a compound. This holds true for drugs irrespective of the ined route of administration. Bioavailability of a systemic preparation is defined he amount of substance available in the inner compartment within a definite after application. It depends on the release of active ingredient from the ve-. The influence of the pharmaceutical carrier on both in vitro release and in availability of active ingredient is thereby investigated. Such investigations become mandatory, since marked pharmacological and pharmacokinetic difnces have been noted after administration of identical amounts of active ingret in different preparations.

2. Availability of Topically Applied Drugs

Difficulties are encountered in attempts to apply the generally accepted princiof pharmacology and pharmacokinetics to the field of external therapy, since e are defined primarily for the systemic application and subsequent distribuof drugs. Thus, modern terms, such as bioavailability of drugs which describes presence of active ingredient in central compartments, cannot be applied in the of external therapy, where the sites of application and action are identical. s is particularly true for DOST's definitions of modern pharmacokinetics (DOST, 8) and the recently introduced modifications which apply to measurements le in flowing blood. Such kinetics are, at the most, applicable to local therapy in a completely altered form. On the other hand, the tissue concentration of skin, i.e., the compartment of the target organ itself, can be determined directly not just the compartment bordering on the target organ as is the case in these od measurements. When investigating penetration kinetics, we are in the favorposition that, in the particular case of topical treatment, the clinical effectives can be estimated by comparison of the course of the disease, so that the menled extensions theoretically investigated are superfluous. Problems of side-efs can be seemingly solved by absorption studies, whereby a yes or nor answer n suffices.

It must, however, be remembered that drug penetration into the skin is usually latively slow process with only a low uptake of substance, in comparison to oral ake. Dermal side-effects in topical treatment could for a long time generally be lected or have remained unrecognized by the physician. Since the introduction owerfully active drugs such as fluorinated prednisone derivatives in local thera- however, reports of side-effects have become more frequent. These side-effects ome evident in long-term clinical studies. However, specific pharmacokinetic lies on the half-life, and further transport of a drug within the tissue yield quantive data, which enable one to judge the relationship between local side-effects therapeutic efficacy (HSIA et al., 1964).

The availability of methods to investigate the quantitative distribution of loy applied drugs at their site of action, as well as their penetration rates and ount and time necessary for further transport via vessels and lymph system in corium, help to ascertain both the correct dosage and optimal vehicle for a givdrug (FELDMANN and MAIBACH, 1968c). Furthermore, the tissue concentration drug, i.e., the amount which effects a particular pharmacological reaction at target organ, can be determined. Kinetic investigations on blood level curves excretion rates often yield surprising data for substances whose therapeutic

properties are well-known. Similar investigations on local pharmacokinetics may yield new treatment methods. It is well-known that alterations of the inert contents of tablets cause considerable variations in the blood levels of drugs. This is true also for topically applied drugs. Thus, in contrast to drugs administered orally, which in general exhibit uniformity in preparations by individual manufacturing companies, externally applied drugs have a range of preparations for different therapeutic requirements. Ointments, creams, lotions, powders, pastes, and suspensions containing the same drug, lead to considerable variations in dosage requirements. Since it is comparatively simple to determine the clinical effectiveness attained in the skin by a definite drug preparation in comparison to other preparations, any disadvantages of a particular carrier may be compensated for by a corresponding increase in dosage. However, in most cases, the optimal vehicle to drug relations are not realized, meaning that different preparations with identical concentrations of a drug are encountered. Only in the search for the minimal dosage necessary for topical application of powerfully active corticosteroids is importance attached to the penetration-promoting or inhibiting properties of carriers. These latter studies illustrated the fundamental problem encountered in the external application of drugs: the carrier in this case is not purely auxiliary but has intrinsic essential therapeutic activities.

The more acute a dermatosis, the higher the therapeutic effect of the carrier is in relation to that of the drug. The choice of ointment base is of importance in the therapeutic success of every course of topical therapy. It appears expedient, therefore, to discuss the fundamental features of topically applied drug forms.

3. Drug Release Into the Stratum Corneum and Optimal Vehicle Properties

In the development of new topical fluorinated steroids, the inadequacies of a vehicle are often concealed by increasing concentration in the vehicle, which may lead to intensification of cutaneous side-effects. Steroid still detectable in the horny layer reservoir days after application can reduce the physiologic regeneration processes. So-called "top corticoids," preferably prepared in an optimal ointment base, are valuable drugs in short-term therapy, but in the hands of "cosmetic-conscious" patients can be hazardous. "Super-optimal" vehicles can effect rapid transport of large quantities of drug into the skin; the concentration attained, however, may just as rapidly decrease via resorption. This kinetic behavior may not be recognized using the vasoconstrictor test, since a highly potent drug may effect long-term vasoconstriction. The initial unnecessarily high concentration maximum of a steroid may lead to disproportionately high transport to the whole organism under pathological conditions involving, for instance, damaged horny layer.

In general, uncontrolled, high absorption may occur in all local therapy if the horny layer exhibits damage. For this reason, the concentrations of the active substance in a topical preparation should be as low as feasible in order to obtain as broad a therapeutic range as possible. This necessitates finding the optimal vehicle which allows uniform release of substance to the epidermis and corium over longer periods in intact and slightly damaged horny layer. It is practically impossible to obtain equally effective activity of drugs made up as lotions, tinctures, creams, ointments, or powders, as only one of two preparations are optimal for a given substance with respect to permeation and wide therapeutic range.

General statements concerning the optimal vehicle for a substance (e.g., a polar drug in a lipophilic vehicle) necessitate prior biopharmaceutic investigations. Thus,

hranol penetrates particularly well from water-free vehicles. Using vaseline, ere is practically no stratum corneum reservoir formation, the highest concen- tions being found in vivo in the epidermis. Although the reservoir and barrier nction remain intact using hydrophilic emulsions or polyethylene glycol oint- nt, the penetration from these bases is pratically insignificant compared to that m lipophilic vehicles (KAMMERAU et al., 1975).

Skin permeability and drug release from the vehicle determine the essential dif- sion processes. These are a product of the physicochemical properties of drugs d of the vehicles. This naturally excludes the possibility of a universal vehicle. herefore, a theoretic and experimentally corroborated design for the composition choice of vehicles is necessary for efficient local therapeutic agents. "Taylored" hicles have been sought for some steroids, notably in the extensive experimental d clinical studies of fluocinolone acetonide and its ester. The solubility, release substance from the vehicle to isopropyl myristate (OSTRENGA et al., 1971 c), and e partition coefficient were investigated using model systems. The vehicle compo- ions under consideration were compared using the vasoconstrictor test. Thus, e optimal base (i.e., the "appropriate" vehicle, see p. 666) was determined from hich the most powerful and long-lasting vasoconstrictive activity of fluocinolone etonide acetate could be obtained (KATZ and NEIMAN, 1971).

As a result of such investigations the following aspects should be observed in e choice of vehicle for substances to be applied locally:

1. The substance should be dissolved at near saturation levels in a phase of an ulsion or in a minimal quantitiy of a solvent (e.g., propylene glycol for fluocino- he acetonide acetate) added to a single-phase ointment (see also p. 658).
2. At higher drug concentrations, the substance need only be adequately solub- in one phase of the vehicle or in the single-phase vehicle, since further substance n become dissolved during the penetration process.

These considerations were substantiated by the comparatively high penetration tes of various 1% hydrocortisone ointments (ZESCH and SCHAEFER, 1973), hereby the penetration is not as strictly vehicle-dependent as in the case with orinated steroids, which are usually applied at one-tenth of the hydrocortisone se (HOFFMANN et al., 1974; POLANO et al., 1976; ZESCH and SCHAEFER, 1973 a, 75 a).

In vitro investigations of drug availability or liberation from ointment base (see 660) are considered today to be prerequisites for adequate diffusion to the oint- ent-skin interface. If a drug is poorly soluble, the higher the ratio of drug dis- lved in the vehicle to the amount suspended, the greater the liberation attained. he drug concentration present should, however, not be lower than the theoretical turation concentration, i.e., the amount that is soluble in the vehicle, because herwise an unsuitable partition coefficient between the ointment and membrane horny layer might be attained. This coefficient is ideally unity. Therefore, if the ug concentration equals or is slightly higher than the saturation concentration the ointment (HORSCH et al., 1975), diffusion alone is rate-limiting for its liber- ion.

4. Vehicle Systems

A drug may be applied as such (single component system) or, as is usually the se, prepared as an ointment, tablet, or solution before application. A multicom- nent system exists when more than one chemically defined substance is included a homogeneous or heterogeneous mixture. A disperse system consists of sub-

stances of irrespective form and size distributed evenly in another substance (exter- nal phase), which is termed an embedding or dispersion medium. The substance in the inner phase is the dispersed compound. If the dispersant and the dispersed particles are in association, then a coherent system (gel) exists. Nonassociation of the dispersed particles is found in incoherent systems (emulsions, pastes). Disperse systems occur in all states of aggregation and their intermediary forms. A common- ly encountered form is the semisolid system, which can also be termed "soft and easily deformable."

The semisolid system is more rigid in elastic systems (gels) and more fluid in the flowing, i.e., plastic or viscous systems (fats, vaselines). Gels are, therefore, elas- tic systems containing a coherent three-dimensional network. The framework of gels is stabilized by electrostatic bonds (interaction of two polar groups), polymer- ization to form a network, dipole-dipole interactions, and hydrogen bonds. The classic gel is gelantine (gel-gelantine), which is prepared using bone glue as the elastic element and water and glycerine.

The deformable, plastic system is found both in a coherent and incoherent form (vaseline, fat, wax, polyethyleneglycol ointment, and swelling promoter oint- ments). It is assumed by MÜNZEL (1953) that coherent structures exist in the oint- ment bases of uniform chemical substance classes (vaseline, fatty glycerides, polyethyleneglycols). Such structures would similarly correspond to gel structures. A coarse disperse system of two or more immiscible liquids is termed an emulsion. The dispersed system usually in the form of globules, is the internal phase. The greater the degree of dispersion dependent on the mechanical force of the emulsi- fication, the greater the stability of an emulsion. Every emulsion is unstable and tends to demulsify. This is due to the differing specific weights of the two liquid phases (separating out of a phase) as well as to interfacial tension (energy gain by dispersed particles coming into contact and flowing together).

a) Emulsifying Agents

Emulsifying agents are usually polar substances containing both hydrophilic and lipophilic groups. They belong to the group of substances of surface-active agents (surfactants) and include detergents, dissolving intermediaries, and sus- pending or antifoaming agents. These surfactants form an adsorption film at the surface around the liquid globule in the internal phase. The groups are so orien- tated that the original interfacial tension is eliminated and two new interfaces are formed, whereby the interface tension is reduced due to the hydration of the hydro- philic groups orientated toward the aqueous phase by the interaction with second- ary valencies. This leads to binding of water molecules and solvation in this phase. The lipophilic groups orientate toward the oily phase to become similarly dis- solved. The emulsifier film already mentioned is thus formed at the interface in this orientation. If an emulsifying agent is more soluble in water than oil for instance, then the binding of water molecules by its hydrophilic groups (hydroxyl, carboxyl, sulfate, amino, keto, ether groups) exceeds the binding of oil molecules by lipophil- ic groups (C-chains, rings, carboxyl groups with divalent cations). Therefore, the interface tension of the oil layer is dominant, i.e., the force of the interface molecule inward is stronger, and the lipid globules formed are pushed toward the center to become enveloped by water molecules. An o/w emulsion ensues. Expressed more simply: the phase of an emulsion is the outer phase in which the emulsifying agent dissolves. If an o/w emulsion is displaced with increasing quantities of a w/o emul- sifying agent, then an emulsion inversion occurs from o/w to w/o emulsion. This socalled true emulsifying agent, therefore, stabilizes an emulsion by forming a film