HEALTH SCIENCES, PHARMACY

PREPARATION AND PHARMACOLOGICAL INVESTIGATION OF DIETHYLAMINE SALICYLATE AND THE DETERMINATION OF THE PHYSICOCHEMICAL PROPERTIES OF FIVE SALICYLATE DERIVATIVES. I. A STUDY TO EVALUATE THEIR: (A) IN-VITRO AND IN-VIVO TRANSDERMAL PENETRATION, (B) PHARMACOKINETICS, AND (C) ANTI-INFLAMMATORY EFFICACY IN RABBITS. II. DEVELOPMENT AND BIOAVAILABILITY EVALUATION OF TOPICAL DOSAGE FORMS OF DIETHYLAMINE SALICYLATE FOR POTENTIAL USE IN RHEUMATOID ARTHRITIS

Order No. DA8408595

AREH, OKECHUKWU MICHAEL NNAKA, PH.D. *Massachusetts College of Pharmacy and Allied Health Sciences*, 1983. 246pp.

Diethylamine salicylate was prepared and evaluated with other salicylate derivatives. The aqueous solubilities, isooctane-water and isooctane-PEG 400-water partition coefficients of the salicylates were determined. It was noted that the addition of PEG 400 up to 20% w/w conc. in water increased the partition coefficients of the salicylate salts while that of the salicylate esters and salicylic acid were reduced.

A study was conducted on the in-vitro transdermal penetration of the sallcylates from PEG 400 using excised rabbit skins. The observed in-vitro pharmacokinetic parameters were found to correlate with the determined physicochemical properties of the salicylates. This work suggests that the in-vitro permeability of highly lipophilic drug substances is controlled primarily by the dermis.

The effect of storage of isolated skin on transdermal penetration of salicylates was studied; no appreciable differences were found in permeability between fresh skin segments and those frozen and stored at −20°C for three and six months.

A study was conducted to investigate the in-vivo transdermal or percutaneous penetration from PEG 400 vehicle, and pharmacokinetics of the salicylates in rabbits. The pharmacokinetic parameters were established for methyl salicylate and glycol monosalicylate. The skin permeability was noted to be significantly altered as the salicylate salts permeated. Positive and quantitative correlation was observed between the in-vivo permeation of the stratum corneum and the partition coefficients of the salicylate esters. The in-vivo data suggest that the viable epidermal and the dermal layers may be precluded as the major rate controlling strata in the percutaneous absorption of the compounds as they are absorbed directly into the microcirculation of the upper part of the dermis. The elimination process for the salicylates was established to follow first-order kinetics.

Evaluation of the salicylates in an experimental model of dermatitis induced in the rabbit ear using croton oil revealed clearly differentiable inhibitory effects on both the rise in skin temperature and edema.

Topical dosage forms of diethylamine salicylate were prepared and the physicochemical properties were evaluated. Salicylic acid levels in blood, muscle and skin following application of the topical dosage forms of diethylamine salicylate were determined. . . . (Author's abstract exceeds stipulated maximum length. Discontinued here with permission of author.) UMI

INFLUENCE OF SMOKING, OBESITY AND UREMIA ON DRUG-SERUM PROTEIN BINDING

Order No. DA8416121

BENEDEK, IRMA HELENE, PH.D. *University of Kentucky*, 1984. 149pp. Co-Directors: Dr. H. B. Kostenbauder, Dr. P. J. McNamara

The extent of binding to serum proteins influences a drug's disposition. Serum protein binding can be affected greatly by changes in serum constituents as a result of altered physiological or disease state.

The protein binding of phenytoin and propranolol was determined in smokers and nonsmokers. The smokers had increased alpha-1-acid glycoprotein (AAG) concentration, a trend toward lower serum albumin concentration and lower free fraction of propranolol. No difference was observed in phenytoin free fractions.

The influence of obesity on protein binding of phenytoin, propranolol and diazepam was evaluated in male and female subjects with various degrees of obesity and in an obese rat (Zucker) model. AAG concentrations were dramatically increased in the human obese state, resulting in increased binding of propranolol in the obese subjects. Diazepam binding was slightly decreased in the obese state due to lowered serum albumin concentrations and elevated free fatty acids. Obesity had no influence on phenytoin binding.

There were significant intrastrain (lean *vs.* obese Zucker rat) and interstrain (female lean Zucker *vs.* female Sprague-Dawley) differences in the serum protein binding of phenytoin, diazepam and propranolol. The obese Zucker rats had different serum component concentrations than their lean littermates. There was a significant difference between male and female Sprague-Dawley rat groups in the binding of phenytoin and diazepam but not propranolol.

Serum hippuric acid (HA) concentrations and phenytoin binding were evaluated in uremic patients. An HPLC assay was developed to determine serum HA concentrations. Elevated HA levels in uremics did not correlate with decreased phenytoin binding. HA and serum creatinine levels did significantly correlate. HA was not as important in the role of an endogeneous binding inhibitor in uremia as initially expected.

EVALUATION OF RENAL FUNCTION IN A GENETICALLY OBESE RODENT MODEL

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FISKE, WILLIAM DAVID, III, PH.D. *University of Kentucky*, 1984. 145pp. Co-Directors: Dr. H. B. Kostenbauder, Dr. P. J. McNamara

An obese animal model, the Zucker rat, was evaluated as a potential model of obesity for drug disposition studies involving renal function. Comparisons were made in 5 and 10 month old rats between lean (LZ) and obese Zuckers (OZ) and between 5 month old LZ and Sprague-Dawley (S-D) rats.

The renal function evaluation in the 10 month old rats showed the obese rats had significantly decreased glomerular filtration rates (GFR) as measured by inulin clearance. The effective renal plasma flow (ERPF) was lower but not significantly decreased in the obese as measured by p-aminohippurate (PAH) clearance. The transport maximum (Tm) for PAH was also lower but not significantly lower in the obese group as compared to the lean. When normalized on a kidney weight or body weight basis the GFR, ERPF and Tm were all significantly lower in the obese group. The decreased function was accompanied by pathological changes in the renal tissue of the OZ rat group.

The 5 month old OZ rats showed marked improvement in inulin clearance. No significant differences were seen in the unadjusted inulin clearances between S-D and LZ rat groups or OZ and LZ rat groups. Unadjusted PAH clearances between the S-D and lean, or between the obese and lean rat groups were not significantly different. When normalized the clearances of the obese group were significantly lower than the lean group. The Tm of PAH was significantly higher in the S-D versus LZ rat group on an unadjusted and on a per gram of kidney weight basis. The lean versus obese comparison was only significant when normalized.

Results from these studies indicate the obese rat has a decreased renal clearance. Studies in younger obese animals show the renal clearance is greatly improved and pathological changes less pronounced. The use of the OZ rat for drug disposition studies involving renal function should be limited to animals 5 months old and younger in order to avoid the complications of functional and pathological changes associated with the older animals.

EFFECT OF CRYSTALLIZATION KINETIC PARAMETERS ON THE PARTICLE SIZE DISTRIBUTION OF OXALIC ACID DIHYDRATE

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RODRIGUEZ HORNEDO, NAIR, PH.D. *The University of Wisconsin - Madison*, 1984. 309pp. Supervisor: Professor Jens T. Carstensen

The external properties of solid drug substances are exceedingly important in the processes by which they are converted into solid dosage forms (e.g., tablets). Such properties as flow, blending efficiency and dissolution rate are but three examples of properties that are affected by the crystal size and shape of the drug substance. It is therefore important to understand the factors during crystallization, which affect the magnitude of the mean particle size and shape of the distribution.