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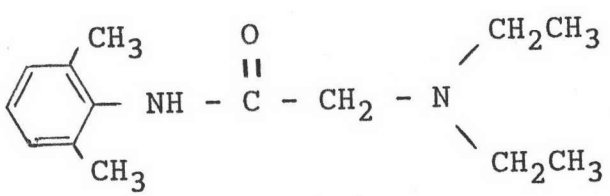
CHAPTER I

INTRODUCTION

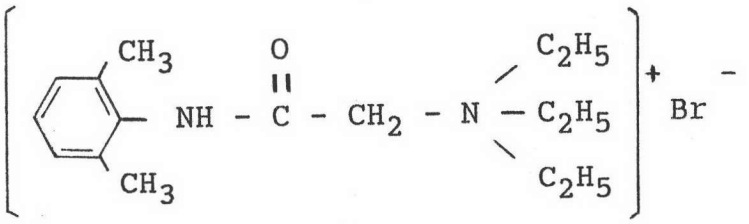
Since the discovery in 1943, lidocaine (I) has been very useful in medication as a local anaesthetic and antiarrhythmic agent. Only two forms of lidocaine, base and hydrochloride, are available for preparation of various dosage forms. Selection of lidocaine form for formulation is usually based on their properties. According to the solubility difference between base and salt, the lipophilic base is chosen in the formulation of cream, ointment and spray. The hydrophilic salt is generally used in preparation of injection and solution.



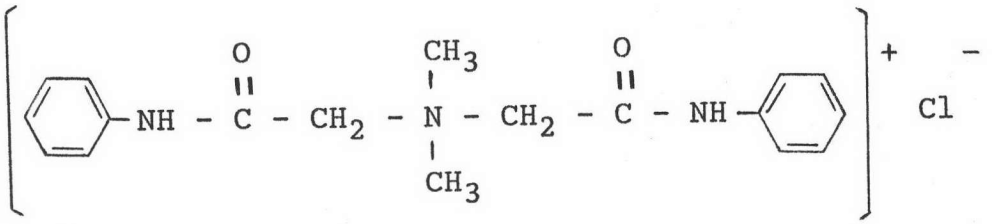
I

The modificatin of chemical structure and formulation in various approaches to improve the efficacy of lidocaine was attempted. Lidocaine analogs with permanent cationic charge were studied by Frazier, Narahashi and Yamada in 1970. QX-314 (II)

and QX-572 (III) were found to have appreciable local anaesthetic action. However, the quarternary ammonium group in II and III which were covalent, not ionic, affected the poor penetration across membrane.



II



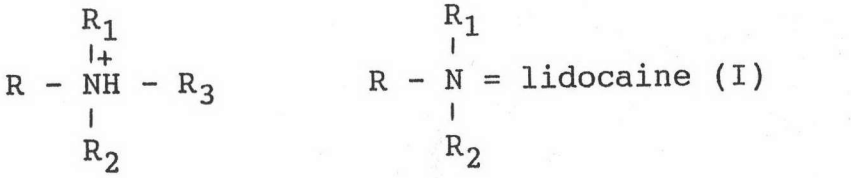
III

Transdermal administration of drug has gained much attention in recent years. Traditional transdermal systems transport drugs through the skin mainly by the laws of passive diffusion. The stratum corneum is considered to be the major barrier for passive transdermal diffusion. For most nonionizable drugs, the relatively high permeability of drug in the skin makes the drugs move across the skin via passive diffusion relatively easily. In contrast, poor permeability of ionized drug in the stratum corneum makes them unable to penetrate by way of passive diffusion. The transfollicular and transappendageal

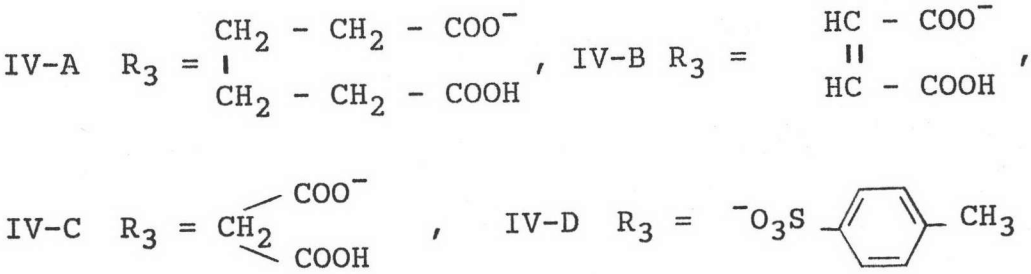
(skin pore) routes are considered to be the main penetration pathways for ionized drugs. Unfortunately, only a small portion of skin surface is occupied by these pathways (Tu and Allen, 1989).

Two mechanisms of transportation, iontophoresis and ion-pair, were proposed to explain the transdermal delivery of ionized drug via entire skin as well as skin pores. Iontophoretic transportation enhanced the penetration of drug across skin by the aid of electrical current. Drug was delivered as ion in this process. Increase in lidocaine delivery through skin by iontophoresis was shown by Siddiqui, Roberist and Polack in 1985. The notion of ion-pair transportation was mentioned by Barker and Hadgraft (1981) besides iontophoretic transportation. Ion-pair between cation of ionized drug and anion of organic acid or fatty acid was formed and skin permeability of the drug was found to be enhanced resulting from higher lipophilicity.

From the stated mechanisms of transdermal delivery, a series of organic salt of lidocaine (IV) was designed to promote skin permeability. The designed compounds (IV-A, IV-B, IV-C and IV-D) which are easily ionized organic salts, are regarded as prodrugs of lidocaine. The skin permeability of IV may be enhanced by ion-pair approach.



IV



The proposed compounds were therefore synthesized in this study. Determination of skin permeability and apparent partition coefficients were also carried out to attest the assumption.