medium layer at the surface of the solid, where the drug concentration reaches C_s at steady-state dissolution. Indeed, it is preferable to consider C_s to be the solubility of the drug in the diffusion layer, since it is the maximum concentration possible in that layer that controls the dissolution rate. Nevertheless, on the basis of this equation, it can still be seen that if the solubility in the dissolution medium was increased, the dissolution rate would also increase.

It is also acknowledged that the dissolving solid might act as its own buffer in this stagnant medium (Benet, 1973). This is likely to be the case when the salt is formed by the reaction of a weak acid with a weak base. The cation and anion employed in salt formation can often modify the dissolution rate by acting as buffer components in the stagnant layer found at the solid surface, establishing a pH different from that found in the bulk dissolution medium, which in turn effectively increases or decreases C_s found in Equation 15.39 (Berge et al., 1977). This was believed to be the underlying cause of differences in dissolution rates seen with salts of nonsteroidal anti-inflammatory drugs, including alclofenac, diclofenac, fenbufen, ibuprofen, and naproxen (Fini et al., 1985). In each case, the salt form was able to improve the dissolution rate, and for each drug, the effect of the cation in promoting dissolution was sodium > *N*-(2-hydroxyethyl)piperazinium > *N*-methylglucosammonium > argininium. In the case of the weak base salts, dissolution depends on the acidity of the counterion that can influence the pH of the microenvironment at the solid surface.

A drug dissolution rate effect as a result of deposition of insoluble particles or a film on the solid surface of a tablet has been observed in at least three cases, aluminum acetylsalicylate (Levy and Sahli, 1962), benzphetamine pamoate (Higuchi and Hamlin, 1963), and tolazamide (Higuchi et al., 1965). As a representative example to explain this phenomenon, the precipitation of the weak acid, pamoic acid, employed as the source of the counterion, slowed the release rate of benzphetamine in acidic media from a bead containing the weak acid salt of the drug (Higuchi and Hamlin, 1963). A mathematical analysis was presented and applied to release of drug from benzphetamine pamoate pellets. When the acid coat forms, the dissolution rate can be reduced essentially to that of the poorly soluble acid (Higuchi et al., 1965).

The improved thermal stability of naproxen and tolmetin as a result of formation of the choline salt has already been noted. Stability studies of lincomycin as its hydrochloride or cyclamate salt revealed that the cyclamate counterion provided an enhanced thermal stability to the antibiotic without compromising the aqueous solubility (Neville and Ethier, 1971; Neville et al., 1971).

CONCLUSIONS

In conclusion, then, the aqueous solubility of a poorly soluble drug can be improved by the selection and preparation of an appropriate salt. The formulation scientist must then determine the resulting physicochemical properties and assess the sensitivity of the product to the environmental and chemical conditions likely to be encountered in handling and storage. In addition, formation of the salt may also reduce the toxicity and modify the pharmacological activity of the drug. Therefore, it is recommended that salt forms be screened early in the preformulation investigations to allow clinical evaluation of those candidates deemed suitable by virtue of their physicochemical properties. The reader is directed to reviews and discussions regarding various salt forms currently in use in pharmaceutical products, including parenterals (Berge et al., 1977; Motola and Agharkar, 1984; Fiese and Hagen, 1986; Bighley et al., 1995; Wermuth and Stahl, 2002; Paulekuhn et al., 2007; Serajuddin, 2007; Guerrieri et al., 2010; Thackaberry, 2012).

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