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Studies on the adsorption and solubility of nalidixic acid

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Summary

The adsorption of nalidixic acid on certain pharmaceutical additives was investigated and its extent estimated. Also, the effects of various surface-active agents and hydrophilic polymers on the solubility of the drug was determined. The adsorption isotherms have revealed that the degree of adsorption increased in the order; microcrystalline cellulose < ethyl cellulose < silicon dioxide < aluminium magnesium silicate. Studies on the solubility of nalidixic acid at 37 °C using different concentrations of hydrophilic polymers have demonstrated that methyl cellulose, polvinylpyrrolidone and polyethylene glycol 6000 have comparable effects. Polyvinyl alcohol caused only a marginal increase in solubility. The surface-active agents, sodium lauryl sulphate and polysorbate 80, also increased solubility of the drug. The values of the heat of solution and the free energy changes were calculated from the Van't Hoff plots. The values of heat of solution for all systems were comparable, but the free energy changes indicate that sodium lauryl sulphate causes the most marked effect on solubility.

Introduction

Nalidixic acid is a synthetic antibacterial agent frequently used in the treatment of urinary tract infections involving Gram-negative organisms. It is practically insoluble in water and its absorption from the gastrointestinal tract was found to be pH-dependent and faster in the non-ionized form (Takasugi et al., 1968). Nalidixic acid is rapidly metabolized mainly to the hydroxy derivative and about 80% of the dose appears in urine within 8 h (Moore et al., 1965).

The recognition of the importance of bioavailability and compendial dissolution test requirements for oral solid dosage forms stimulated research into drug–excipient interactions resulting in reduced or enhanced dissolution and therefore absorption of the drug substance. Since the process of drug absorption is a dynamic one, it might be influenced by various excipients and surfactants included in the formulation of dosage forms. This is a result of the interaction of active drug substance with additives which may alter the physical properties of the drug. The excipients may thus influence the process of drug delivery from the dosage form.

Drug absorption depends to a great extent on its solubility and one possibility of increasing the solubility is through the incorporation of surface active agents or hydrophilic polymers. Drug solubilization in systems containing surface-active agents is well documented and several comprehen-

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sive reviews on this technique have appeared, particularly by Florence (1981), Swarbrick (1965) and Elworthy et al. (1968). Also, increased solubility of drugs in hydrophilic polymers was reported by Shihab et al. (1970) and Minkove et al. (1980). The effects of some factors, such as the chain length of polyoxyethylene derivatives (El-Sabbagh et al., 1978) and drug–polymer complex formation (Higuchi and Lach, 1954) on the solubility of drugs were also investigated.

This study was undertaken to investigate the adsorption of nalidixic acid onto ethyl cellulose, aluminium magnesium silicate and silicon dioxide at various temperatures and to estimate the extent of such adsorption. Moreover, the effects of various surface-active agents and hydrophilic polymers on the solubility of the drug were also determined.

Materials and Methods

Materials

Products were used as received from the manufacturer or distributor with no further purification. Nalidixic acid complied with the requirements of the United States Pharmacopeia and was purchased from CFS (Switzerland). Silicon dioxide was obtained from Degussa (Frankfurt, F.R.G.), microcrystalline cellulose from FMC (Philadelphia, PA, U.S.A.) and polyvinylpyrrolidone (PVP) from BASF (Ludwigshafen, F.R.G.). Methyl cellulose, ethyl cellulose, aluminium magnesium silicate (veegum), talc, polysorbate 80, polyvinyl alcohol (PVA), polyethylene glycol 6000 (PEG), cetyl alcohol and sodium lauryl sulphate (SLS) were all supplied by E. Merck (Darmstadt, F.R.G.). The water used was double-distilled in glass apparatus.

Methods

Adsorption experiments

The appropriate quantities of adsorbent were placed in 100-ml glass-stoppered conical flasks, then 80 ml of drug solution (0.1%) in 0.1 M phosphate buffer (pH 7.4) were added. The mixtures were adjusted to volume and the final pH checked. The suspensions were then shaken at the required temperature for 4 h. Blanks were prepared at the same drug concentration but contained no adsorbent. Blank suspensions of adsorbents were also prepared. Preliminary experiments performed over a 24-h period indicated that equilibrium between the drug and adsorbents was reached in less than 1 h. The suspensions were suitably filtered and the drug content of the filtrate was determined spectrophotometrically at a wavelength of 332 nm after appropriate dilution. The drug solutions used in these experiments were freshly prepared, protected from light and were fairly stable under the experimental conditions.

Solubility determination

Equilibrium solubility of nalidixic acid was determined by adding an excess of the drug to the test solution containing the assigned quantity of the solubilizing agent in 0.1 M KCl/HCl buffer at pH 2. The mixtures were shaken in a constant-temperature shaking water bath for 24 h. The samples were then suitably filtered, diluted, and assayed spectrophotometrically at a wavelength of 332 nm.

Results

The adsorption isotherms for nalidixic acid at 20 °C were plotted for talc and microcrystalline cellulose at pH 7.4. Although both showed a low degree of interaction, the cellulose exhibited a slightly greater capacity for adsorption of the drug (Fig. 1). The degree of adsorption on the other excipients was in the order ethyl cellulose < silicon dioxide < veegum. Also, an inverse relationship between degree of interaction and temperature was obtained (Figs. 2–4).

Studies on the solubility of the drug at 37 °C in KCl/HCl buffer (pH 2) using different concentrations of hydrophilic polymers revealed that methyl cellulose, PVP and PEG had comparable effects (Fig. 5). While methyl cellulose had the most pronounced effect, PVA caused only a marginal increase in solubility even at a concentration of 4%. The use of surface-active agents, SLS and polysorbate 80, also resulted in the solubilization

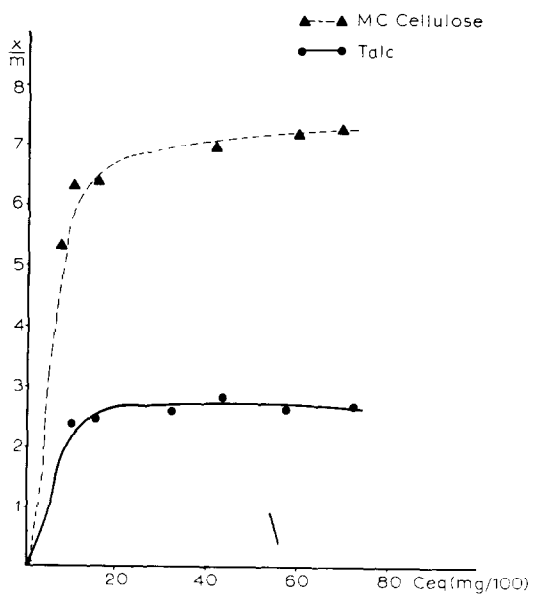

Fig. 1. Adsorption isotherm of nalidixic acid on microcrystalline (M.C.) cellulose and talc at pH 7.4 and 20 ° C.

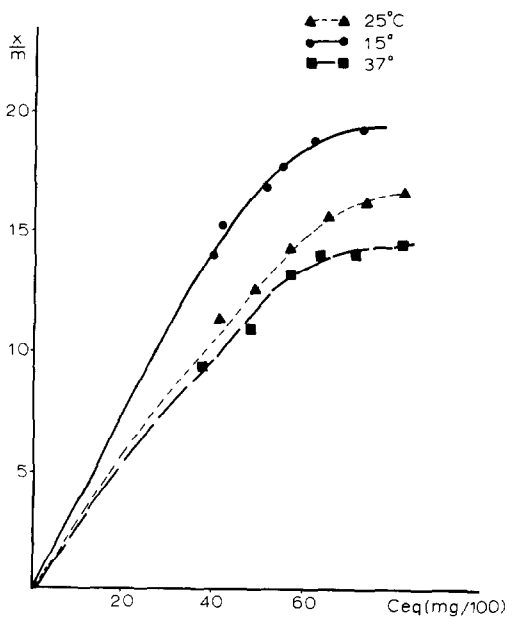

Fig. 2. Adsorption isotherm of nalidixic acid on ethyl cellulose at pH 7.4 and 15, 25 and 37 ° C.

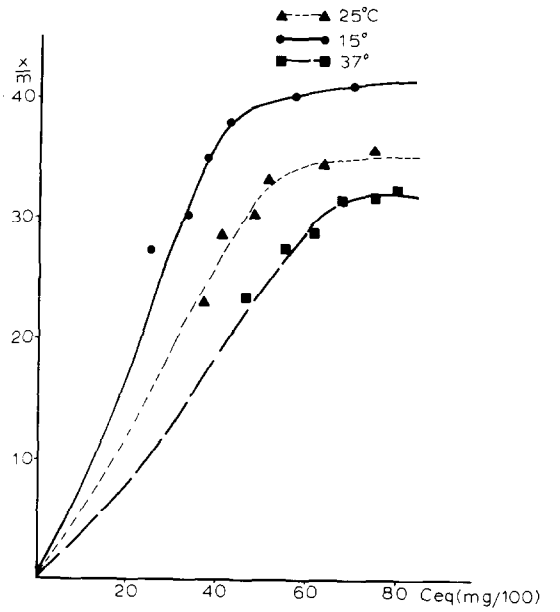

Fig. 3. Adsorption isotherm of nalidixic acid on silicon dioxide at pH 7.4 and 15, 25 and 37 ° C.

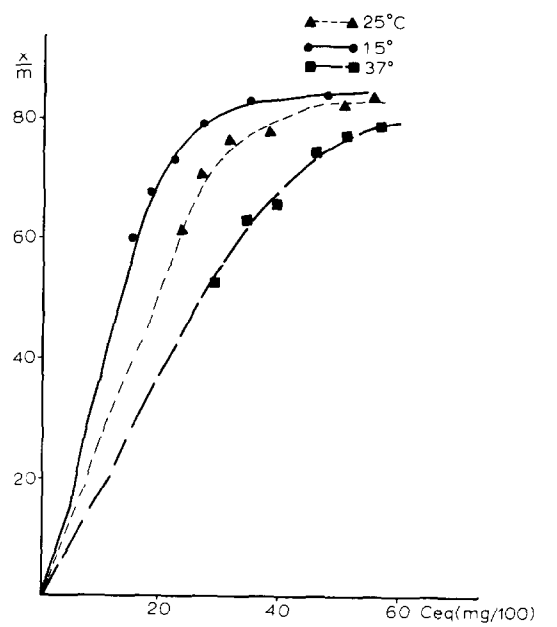

Fig. 4. Adsorption isotherm of nalidixic acid on aluminium magnesium silicate at pH 7.4 and 15, 25 and 37 ° C.

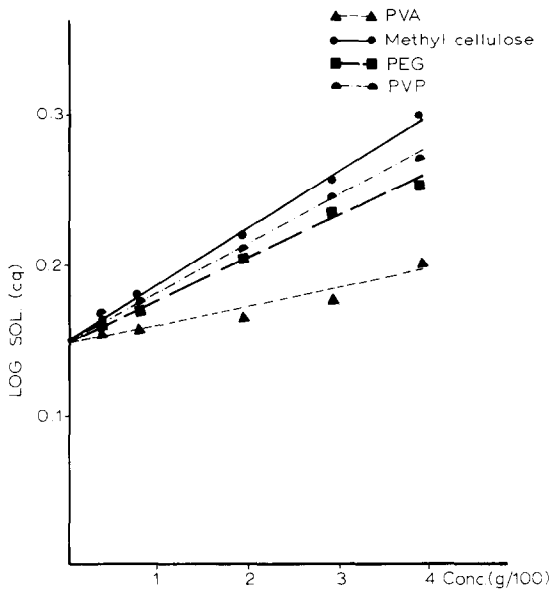

Fig. 5. Effect of hydrophilic polymers on the solubility of nalidixic acid at pH 2 and 37 °C.

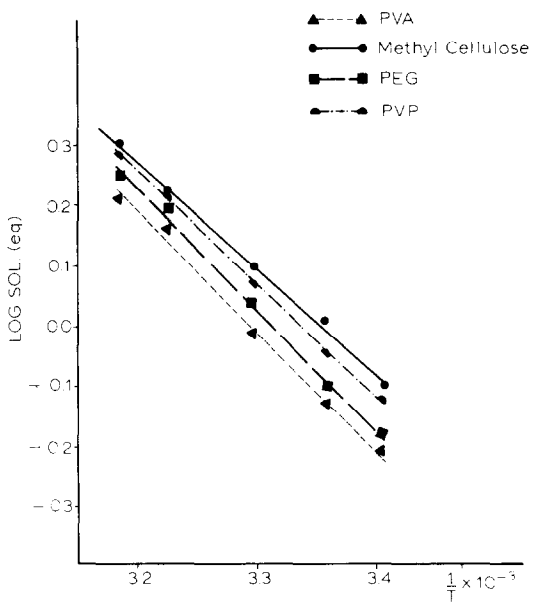

Fig. 7. Van't Hoff plots for nalidixic acid at pH 2 in the presence of hydrophilic polymers.

of the drug, albeit to different degrees; polysorbate 80 causing a less marked effect on solubility. Under these conditions, cetyl alcohol had no apparently noticeable effect on the solubility of nalidixic acid even when increased concentrations of this agent were used (Fig. 6).

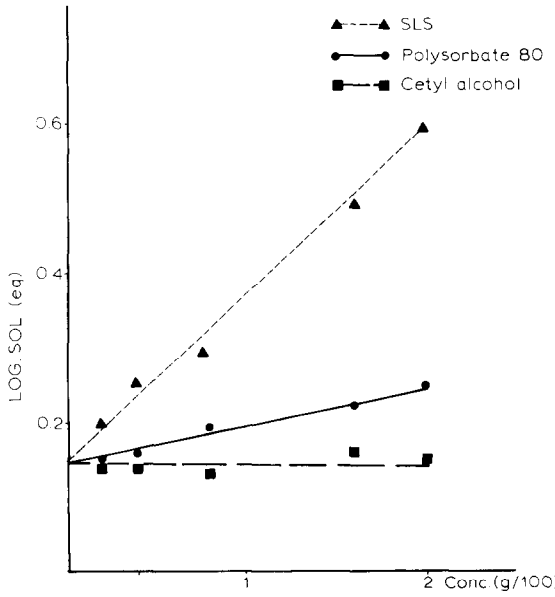

Fig. 6. Effect of surface-active agents on the solubility of nalidixic acid at pH 2 and 37 °C.

The Van't Hoff plots were also constructed at pH 2 and at different temperatures using 2% and 1% concentrations of hydrophilic polymers (Fig. 7) and surface active agents (Fig. 8), respectively. From these plots, both values of the heat of solution (ΔH) and the free energy changes at 37 °C (ΔG) were calculated (Table 1). The values of heat of solution for all systems were comparable, but

TABLE 1

Thermodynamic values for nalidixic acid-solubilizing agent systems

Agent	ΔH (kcal·mol^{-1})	ΔG at 37 °C (cal·mol^{-1})
Methyl cellulose	26.9	−100.2
PVP	27.2	−85.8
PVA	25.2	−71.5
PEG	27.8	−28
SLS	27.1	−314.8
Polysorbate 80	22.4	−71.4
Cetyl alcohol	22.1	0

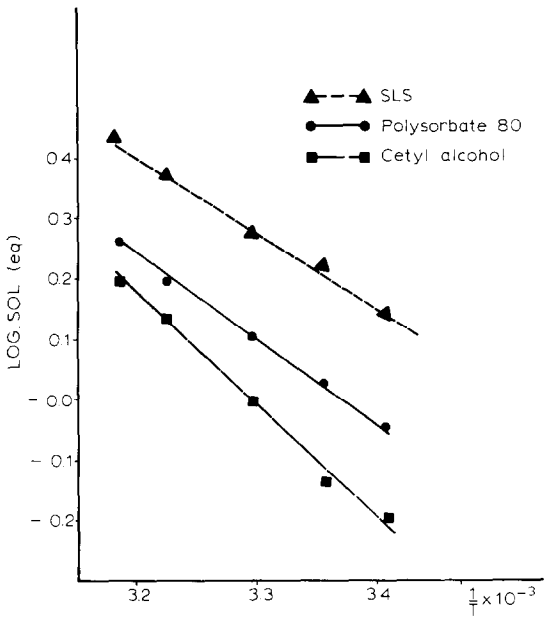

Fig. 8. Van't Hoff plots for nalidixic acid at pH 2 in the presence of surface-active agents.

the free energy changes have indicated that SLS causes the most marked effect on the solubility of nalidixic acid.

Discussion

In view of the potentially serious effects that some additives may have on certain physical properties of drugs and the subsequent deleterious influence on the bioavailability from dosage forms, the need exists to be able to assess the risk which may be involved before adopting or indicating an excipient. The objectives here were to determine the extent of adsorption of nalidixic acid onto silicon dioxide, aluminium magnesium silicate (veegum), ethyl cellulose, microcrystalline cellulose and talc. Also, the effects of several surface-active agents and hydrophilic polymers on the solubility of the drug were investigated.

Due to the limited water solubility of nalidixic acid, adsorption experiments were carried out at pH 7.4 where the drug ($pK_a = 6.0$) exists predominantly as the ionized species. The extent of adsorption was estimated at 15, 25 and 37 °C and showed a slight drop with this rise in temperature. This is probably related to increased free drug concentration going into solution. The adsorptive capacity of the additives used in this work towards the drug increased in the order talc < microcrystalline cellulose < ethyl cellulose < silicon dioxide < veegum.

Examples of adsorption and similar interactions are frequently encountered in the literature, and several medicinally important substances have been shown to interact with various substances, such as diluents (Franz and Peck, 1982), disintegrants (Chein et al., 1981; Hollenbeck et al., 1983), surfactants (El-Sourady et al., 1985) and others (Naggar et al., 1986). Interactions leading to decreased bioavailability are well established (Ismail et al., 1987; Moustafa et al., 1987) and the bioavailability of nalidixic acid was shown to be affected by formulation (Moore et al., 1965). Also, more satisfactory blood levels were obtained when the drug was given before meals (McChesney et al., 1967). Other interactions involving nalidixic acid have also been reported. It has been shown to be highly bound to plasma protein (Koch-Wesser and Sellers, 1971) and the drug is also known to interact in a way as to interfere technically with the laboratory estimations of several substances (Llerena and Pearson, 1968).

The extent of adsorption onto cellulose was lower than would have been expected and is probably a function of the negatively charged nature of the surfaces of these polymers. This is most likely due to the ionization of carboxyl groups on the cellulose surface. These carboxyl groups are formed by oxidation of the hydroxyl groups on individual anhydro-glucose units (McBurney, 1954; Mark et al., 1965). At the pH level used in these experiments, the number of negatively charged carboxylate groups on the surface of cellulose is increased. The increased number of anionic surface sites leads to decreased adsorption of the predominantly negatively charged drug at the surface of the particles. The possibility, therefore, exists that such a hydrophobic drug is adsorbed from solution as the non-ionized free acid. As free acid is removed from solution more free species will replace it from the ionized excess. This

would continue until an equilibrium is established between the free acid in solution and the acid adsorbed to the cellulose surface.

The highest order of adsorption observed with veegum may be attributed to both electrostatic and non-electrostatic forces operating at the same time. Nalidixic acid in its ionized form may interact with both the aluminium and magnesium components of this substance. Adsorption on silicon dioxide was also relatively pronounced at the pH level used in this work. Again, this is probably related to both ionic and non-ionic attractive forces between the drug and silicon dioxide particles. A very low order of adsorption was observed when talc was used as adsorbent event when included in fairly large proportions. The small surface area associated with the large particle size of such powder may be responsible for the lower degree of adsorption of nalidixic acid.

In the present investigation, the effects of certain hydrophilic polymers and surface active agents, commonly included in pharmaceutical preparations, on the solubility of nalidixic acid were determined. Reports of increased in vitro solubility of poorly water-soluble drugs by such agents are frequently encountered in the literature (Shihab et al., 1970; Florence, 1981).

With the exception of cetyl alcohol, all 6 agents tested in this work resulted in distinct increase in the solubility of the drug. With regard to the hydrophilic polymers, methyl cellulose, PVP and PEG, the increase in the equilibrium solubility of the drug was of comparable degree at all polymer concentrations and temperatures used. Although PVA also enhanced the solubility of nalidixic acid, this effect was less pronounced. Both surface-active agents have improved the solubility picture of the drug, but the effect of SLS at 37 °C was approximately twice that of polysorbate 80.

Despite the close similarity in the values of the heat of solution (ΔH) for all systems when calculated from the slopes of the van't Hoff plots (Table 1), the free energy changes (ΔG) at 37 °C have indicated that highest solubility of nalidixic acid could be observed in the system containing SLS. The free energy changes were calculated from the equation $\Delta G = RT \ln S_w/S_s$, where S_w and S_s are the solubilities of the drug in water and solubilizing agent, respectively, at temperature T, and R is the gas constant (Feldman and Gibaldi, 1967).

In conclusion this investigation has demonstrated that several pharmaceutical additives may interact with a poorly water-soluble drug such as nalidixic acid and result in either reduction of the amount of drug in solution through ionic and non-ionic adsorptive forces or result in a relative improvement of its water solubility. Water-insoluble additives seem to have adsorbed the drug resulting in its loss from solution, while hydrophilic polymers and surface-active agents increased its solubility. In any case, changes in the amount of drug in solution may influence the rate and extent of absorption of the drug and therefore its bioavailability from oral dosage forms.

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