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DISSOLUTION OF NALIDIXIC ACID SOLID DISPERSIONS

I. Systems of NAL-Inclusion and Linear Polymeric Compounds

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ABSTRACT

The solubility and dissolution rate enhancement of nalidixic acid powder, applying solid dispersion technique, with inclusion and linear polymeric compounds were studied. At 100 g/L carrier concentration, the increase in drug solubility was 3.3, 2.0, 1.4 and 1.1 times that of the powdered drug for urea, PEG 4000, PEG 6000 and PVP, respectively. The increase in carrier ratio enhanced the drug dissolution. At four fold carrier concentrations, the amount dissoluted after one hour was 50, 55 mg/L for samples prepared by fusion with urea and PEG 6000, respectively. The coprecipitation with PVP dissoluted 65 mg/L of nalidixic acid

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after one hour compared to only 27.5 mg/L of powdered drug alone.

INTRODUCTION

The solid dispersion technique has numerous pharmaceutical applications. Such a technique can be used to obtain a homogeneous distribution of a small amount of drugs at solid state, to stabilize unstable drugs, to formulate a fast-release priming dose in a sustained release dosage form and to formulate sustained release regimens of soluble drugs by using poorly-soluble carriers (1).

The water-soluble carriers most commonly used to enhance the dissolution rate of insoluble drugs include polyethylene glycols (2,3), sugars (4), urea (5), polyvinylpyrrolidone (6,7), succinic acid (8), surfactants (9) etc.

In our previous paper (10), the effect of solid dispersion techniques, using either hydrotropic salts or Myrj 59, on the dissolution rate of nalidixic acid was studied.

In this paper, the effect of solid dispersion technique on the dissolution rate of nalidixic acid is continued. Different concentrations of inclusion and linear polymeric carriers are used in order to

select the type, concentration and technique most effective in enhancing the drug release.

EXPERIMENTAL

Materials - The following materials were used : polyethylene glycol 4000, 6000 (BDH Chemicals, Ltd., England), polyethylene glycol 20,000 (Hoechst Farbwerke A.G., Germany), polyvinylpyrrolidone (Luviskol K_{30}, mol. wt. 40,000, B.A.S.F., Germany), urea (Merck and Co., U.S.A.), nalidixic acid (NAL, Sterling-Winthrop, U.S.A.).

All other chemicals were analytical reagent grade.

METHODS

Solubility studies - An excess amount of NAL was placed in dark amber glass bottles containing 20 ml of an aqueous solution of each carrier in varying concentrations. The experiment was followed as explained in our previous paper (10).

The drug was assayed spectrophotometrically at 259 nm. None of the used carriers was found to interfere with the spectrophotometric assay of the drug at this wavelength.

Sample Preparation - The samples were prepared by a physical blending, fusion or coprecipitation technique as previously reported (10).

Dissolution Rate Studies - These were carried using the beaker method and following the same procedure (10). The amount of drug was equivalent to 50 mg.

RESULTS AND DISCUSSIONS

In order to elucidate the participation of the different thermodynamic parameters in the solubilization of nalidixic acid by aqueous urea solutions, two solubilization runs were conducted at 25 and 37°C (Fig. 1). The solubility of NAL, in different urea concentrations, is increased significantly upon increasing the temperature. The thermodynamic parameters, based on these curves, were computed and represented in table 1a.

At 37°C , Δ F has small negative values, as the negative sign is indicative of the spontaneity of the process (11). At 25°C in the range of 0.5-5 g/L, the computed Δ F showed small positive values which indicate a nonspontaneous process but preclude the possibility of complexation where the reported values of complexation are usually in the range of 2-5 K cal./mole (12). Δ H values were calculated to determine the enthalpic contribution to the solubility process. The random nature of the values within the range of 0.5-5 g/L urea concentration prevented a definite

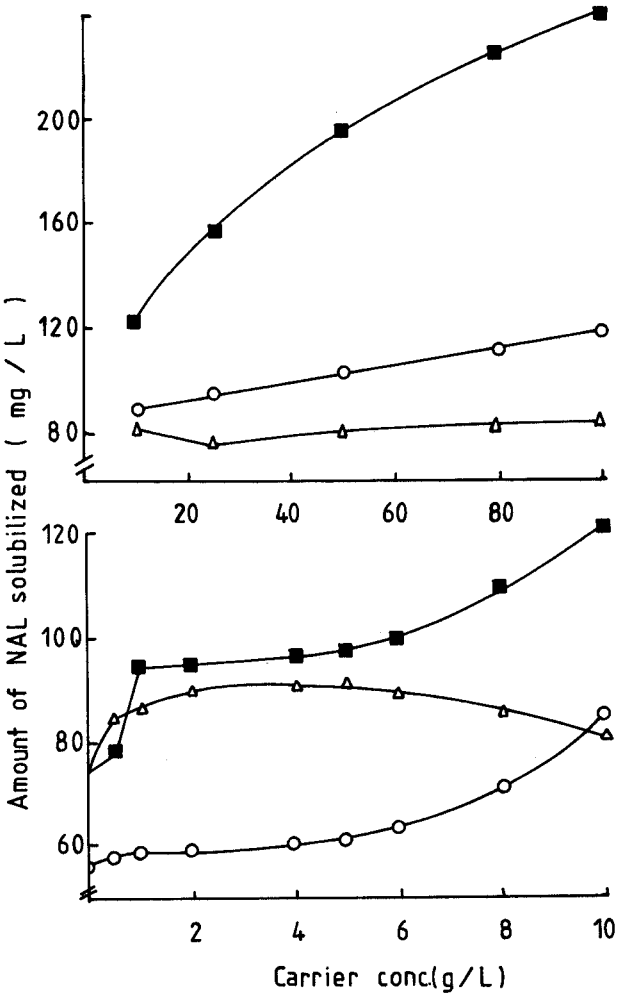

FIGURE 1

Solubility of NAL with different carriers
o——o urea at 25°C. Δ——Δ PVP at 37°C.
■——■ urea at 37°C.

statement as to whether the process is endothermic, exothermic or athermal.

It can be concluded that both the positive Δ H values as well as the negative Δ F values indicate

TABLE 1

Thermodynamic parameters for nalidixic acid

a) In urea solutions

Concentration g/L	ΔF (Kcal/mol) 25°C	ΔF (Kcal/mol) 37°C	ΔH Kcal/mole	ΔS e.u.*
0.5	+0.133	-0.042	+ 4.513	+14.694
1.0	+0.133	-0.161	+ 7.507	+24.737
2.0	+0.133	-0.161	+ 7.507	+24.737
5.0	+0.073	-0.182	+ 6.462	+21.433
10.0	-0.101	-0.341	+ 5.899	+20.129
25.0	-0.175	-0.454	+ 6.784	+23.348
50.0	-0.216	-0.610	+ 9.640	+33.063
100.0	-0.271	-0.776	+12.371	+42.411

* e.u. = entropy unit.

b) In solutions of linear polymeric compounds

Concentration g/L	ΔF (Kcal/mol) at 37°C PVP	PEG 4000	PEG 6000
5.0	-0.139	-0.117	-0.106
10.0	-0.068	-0.104	-0.204
25.0	+0.076	-0.183	-0.204
50.0	-0.146	-0.290	-0.204
100.0	-0.117	-0.404	-0.244

that the solubility increase is entropic in origin (11). The positive ΔS values indicate spontaneity of the reaction. Urea, in other words, may solubilize nalidixic acid by "breaking up" water clusters surrounding the nonpolar molecule, increasing the entropy of the system, and producing a "driving" force for the solubilization. This assumption is in agreement with the systems of benzoic acid-urea and salicylic acid-urea investigated by Feldman and Gibaldi (11).

The solubility profiles of NAL with PVP and PEGs are shown in figures 1 and 2. PVP was found to interact with NAL in solution, as manifested by the slight increase in the drug solubility accompanied by an increase in the free energy change, ΔF, (Table 1b). This might indicate a decreased spontaneity of the process, but did not involve complexation (12). At 25 g/L w/v, ΔF exhibited a net positive value, indicating a nonspontaneous reaction at this critical concentration. PEG 4000 showed nearly a similar solubility pattern to that of PVP with a larger enhancement in the solubility and much smaller ΔF values. PEG 6000 showed only a slight enhancement in the solubility of NAL accompanied by a spontaneous reaction and no complexation. PEG 20,000 revealed a slight enhancement in the solubility of NAL up to 1 g/L w/v carrier. This was followed by a solubility decrease even below the water-solubility of the drug.

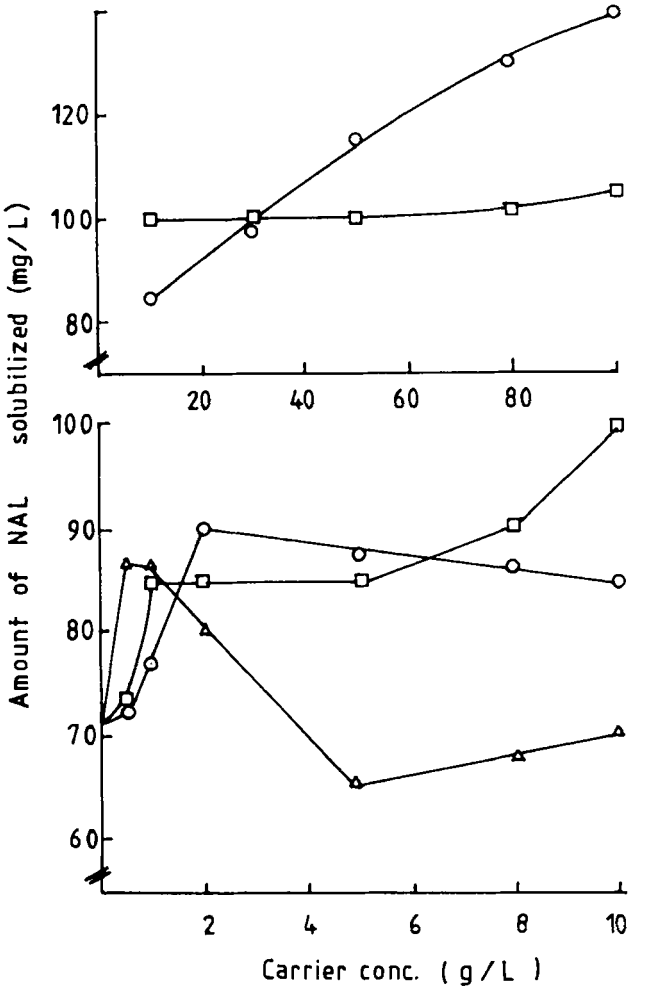

FIGURE 2

Solubility of NAL with different polyethylene glycols at 37°C.

o—o PEG 4000 Δ—Δ PEG 20000 □—□ PEG 6000

Thus, at 100 g/L w/v carrier concentration, the following rank order could be considered, regarding the solubility enhancement by using inclusion and linear polymeric compounds : Urea > PEG 4000 > PEG 6000 > PVP.

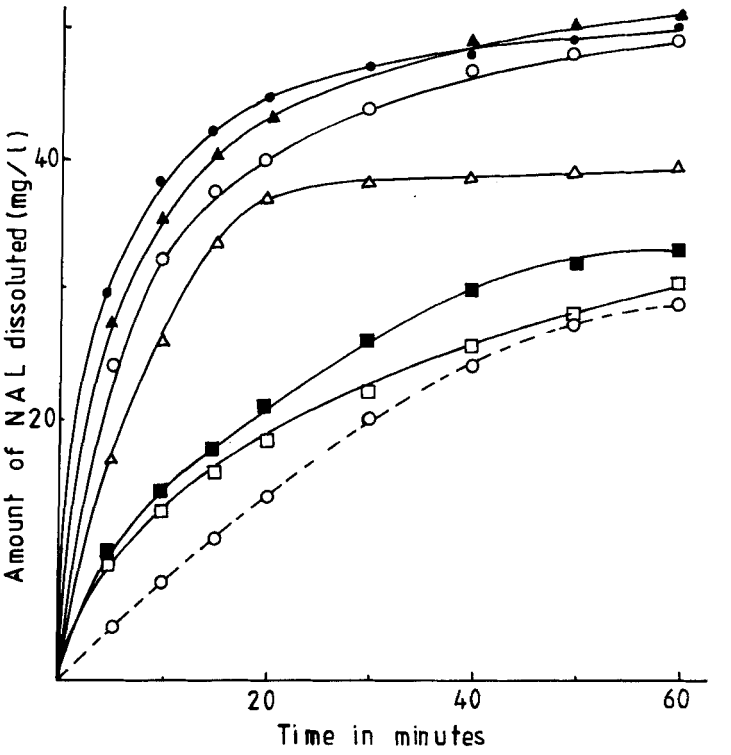

FIGURE 3

Effect of different techniques on the dissolution rate of equiportions (o) or 1:4 NAL to urea (●) powder.
o---o drug alone
o——o fusion
□——□ physical blending
△——△ coprecipitation.

The dissolution profiles of powdered NAL-urea binary mixtures prepared by different techniques are shown in figure 3. The equiportion physical blend of urea and NAL showed a slight enhancement in the dissolution rate of NAL powder, accounted to a RDR (relative dissolution rate) of 2.08 after 5 minutes (Table 2). This may be due to the lack of intimate contact between the two components in the powder

TABLE 2

Samples of powdered NAL-carrier binary mixtures used in the dissolution rate studies

Carrier	NAL:carrier w/w	Condition	RDR* at 5 min.
Urea	1:1	Physical blend	2.08
	1:4	" "	2.42
	1:1	Fusion system	6.01
	1:4	" "	7.67
	1:1	Co-precipitate	4.17
	1:4	" "	6.92
PVP	1:1	Physical blend	2.33
	1:4	" "	2.33
	1:1	Co-precipitate	9.67
	1:4	" "	14.42
PEG 6000	1:1	Fusion system	7.34
	1:4	" "	12.83
	1:1	Co-precipitate	6.50
	1:4	" "	10.50

* RDR : (relative dissolution rate) = amount of NAL dissoluted at any time / that dissoluted from the untreated drug at the same time.

mixture. The co-precipitate system started with a rapid dissolution rate at the first 20 minutes followed by a slower one, where the RDR was 4.17 after 5 minutes. The fusion system showed the highest dissolution rate enhancement all over the dissolution period with a RDR of 6.01 after 5 minutes. These findings may be explained on the basis of particle size reduction of the drug (1), in addition to the inherent properties of urea as an inclusion compound (13). Therefore, the following rank order could be considered regarding the solubilizing capacity of the techniques : fusion $>$ co-precipitation $>$ simple blending.

The 1:4 NAL-urea systems showed the same order for the dissolution behaviour, but with a higher enhancement (Fig. 3).

The dissolution rate profiles of NAL-PVP systems are shown in figure 4. The equiportion co-precipitate system showed a rapid dissolution rate during the first 20 minutes, then approached equilibrium. The 20% NAL system showed the same behaviour but with a higher enhancement. The RDR for the co-precipitate systems, after 5 minutes, was 9.67 and 14.42 for the 1:1 and 1:4 NAL-PVP respectively. This marked enhancement in the dissolution characteristics of the co-precipitates, most probably reflects a significant

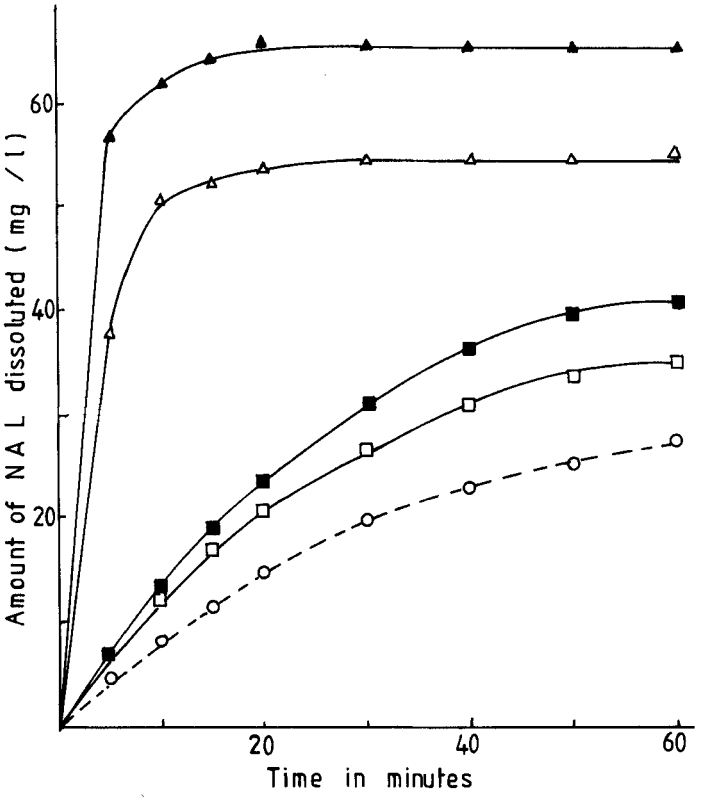

FIGURE 4

Effect of different techniques on the dissolution rate of equiportions (o) or 1:4 NAL to PVP (●) powder. o---o drug alone □——□ physical blending △——△ coprecipitation.

reduction in the particle size of the drug during sample preparation (7). The reduced particle size and the concomitant increase in the surface area of nalidixic acid exposed to the dissolution medium appears to be the major factor responsible for the observed potentiation.

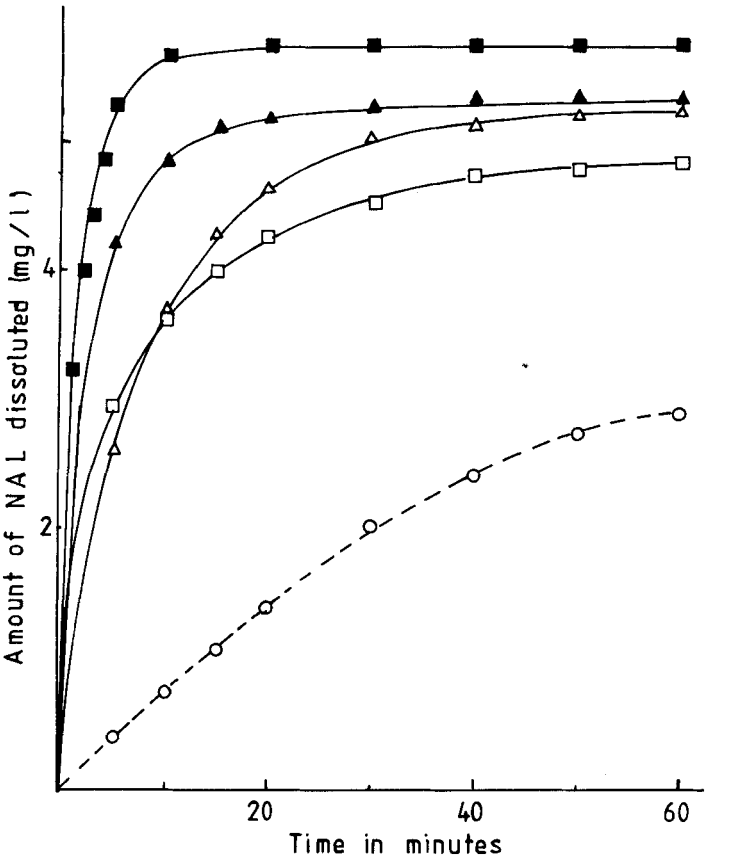

FIGURE 5

Effect of different techniques on the dissolution rate of equiportions (o) or 1:4 NAL to PEG 6000 (•) powder. o---o drug alone △—△ coprecipitation □—□ fusion.

The equiportion melt system of NAL-PEG 6000 (Fig. 5) showed a marked and smooth dissolution enhancement, where the 1:4 melt system showed a very fast dissolution up to 10 minutes followed by a limiting dissolution value. The 1:1 NAL-PEG 6000 co-precipitate system revealed a dissolution enhancement of

about 6.5 times the untreated drug after 5 minutes, while the 20% NAL system gave a RDR of 10.5 at the same time interval. Since NAL-PEG melt was allowed to solidify rapidly, the crystallization of the drug is retarded due to reduced solute migration and difficulty in nucleation of the drug in the viscous medium (1). There are some other factors which may contribute to the enhancement of dissolution rate of drugs in PEG melt system, namely high viscosity, supercooling effect, and physicochemical interaction between the drug and polymers (1).

Although certain carriers exhibited low interaction with NAL in the aqueous phase as manifested by their low solubilizing capacity e.g. PVP and PEG 6000, yet they proved to be powerful carriers when used in solid dispersion systems.

To conclude, fusion of 20% NAL with urea or PEG 6000, and coprecipitation with PVP can be used for the enhancement of the dissolution rate of nalidixic acid powder.

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