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DISSOLUTION OF NALIDIXIC ACID SOLID DISPERSIONS

1. NAL-Hydrotropic salts and NAL-Myrj systems

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ABSTRACT

The effect of solid dispersion techniques on the dissolution rate of nalidixic acid powder was investigated.

The thermodynamic parameters of all tested systems revealed a spontaneous reaction with no complex affinity to the drug.

Hexamine and sodium citrate showed very powerful solubilizing capacity towards NAL powder.

For piperazine citrate in spite of its low interaction with NAL in the aqueous phase, it proved to be efficient carrier in the solid dispersion system. Myrj 59 caused the greatest enhancement in NAL dissolution rate of all carriers examined. After 5 minutes, the RDR of the four-fold NAL-Myrj 59

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co-precipitate system was 16.5 times the untreated drug.

INTRODUCTION

There has been a great deal of interest in concern with the enhancement of dissolution rate achieved by using the solid dispersion technique since the early reports of Sekiguchi and Obi (1). It was believed that solid dispersion techniques can play an important role in increasing dissolution, absorption and therapeutic efficacy of drugs (2,3).

Ford and Rubinstein (4) investigated the dissolution rate of glutethimide-Renex 650 melt system. They were able to study the dissolution rate of the different portions of the phase diagram which showed a simple eutectic mixture at 35°C.

Kaur and Grant (5) studied the solid dispersions of drugs in polyoxyethylene (40) stearate (Myrj 52). They compared the dissolution rate of solid dispersions of tolbutamide, griseofulvin and frusemide in Myrj 52 with those in PEG 2000.

The present study forms an attempt to investigate the effect of solid dispersion techniques on the in-vitro dissolution rate of nalidixic acid powder. The dispersion techniques included were physical blending, co-precipitation and fusion systems.

EXPERIMENTAL

Materials - The following materials were used : Myrj 59 (Atlas Chemical Industries Co., USA), hexamine (B.D.H., England), nalidixic acid (NAL, Sterling-Winthrop, USA), anhydrous piperazine citrate (El-Nasr Co. for Pharmaceutical Chemicals, Egypt), sodium citrate USP XVI (VEB Jenapharm, Germany).

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 bottles were allowed to rotate at 50 r.p.m. in a thermostatically controlled water-bath equipped with a rotating device at 37±0.5°C. At the end of this period, an aliquot was withdrawn with a filter pipette, suitably diluted with 0.1 N sodium hydroxide and assayed spectrophotometrically at 259 nm. None of the used carriers was found to interfere with the spectrophotometric assay of the drug at this wavelength.

Techniques used for Sample Preparation :

a. Physical blending - A fraction of the powder having a particle size 200-160 µm (Din 1171, German Standard) was used. The required weight of the drug

was thoroughly mixed with the carrier in a gradual increasing order using a mortar and pestle for 10 minutes. The proportions prepared were 1:1 or 1:4 drug to carrier weight ratio, respectively.

b. Fusion Technique - Accurately weighed amounts of nalidixic acid powder and Myrj 59 were intimately mixed at the proportions of 1:1 or 1:4 w/w (drug to carrier, respectively) in a small porcelain dish. Then the mixtures were heated on a sand bath with constant stirring till melted. The molten mass was kept in a freezer for 24 hours before pulverization with a razor blade. The particle size of 400-315 μm fraction was used for the dissolution study.

Hexamine, being a sublimable urotropic agent (6), its solid dispersion system was prepared with great care. NAL and hexamine powders were intimately mixed, then filled into glass ampoules, 2 ml capacity. The ampoules were sealed then top-suspended by a copper wire and dipped in a boiling paraffin oil bath till complete melting. The ampoules were then removed, cooled and broken. The solid particles were pulverized, sieved and the 200-160 μm fractions were used for the dissolution study.

c. Co-precipitation Technique - The drug and carrier (piperazine citrate, hexamine or Myrj 59) were dissolved in 1:1 chloroform-ethanol solvent system.

The solvent was then evaporated on a sand bath with frequent stirring and the co-precipitates were dried in vacuo to constant weight. The mass was pulverised, sieved and the 200-160 µm fractions were subjected to the dissolution study. The co-precipitates of NAL-Lyrj 59 were kept in freezer for 24 hours before pulverization. The fractions 400-315 µm were used for the dissolution study.

Dissolution Rate Studies - These were conducted using the beaker method and following the same procedure as in our previous publication on the crystallization of nalidixic acid powder (7). The amount of drug was equivalent to 50 mg and was measured spectrophotometrically, after dilution with 0.1 N sodium hydroxide, at 259 nm.

RESULTS AND DISCUSSION

NAL-Hydrotropic Salts Systems :

The equilibrium solubility isotherms of NAL with each of piperazine citrate, hexamine and sodium citrate are shown in figure 1. It can be noticed that piperazine citrate did not show any effect on the solubility of NAL with a constant ΔF value (+ 0.076 K cal./mole), indicating a nonspontaneous reaction (8).

On the other hand, hexamine increased the solubility of NAL to a high extent (11.29 times that

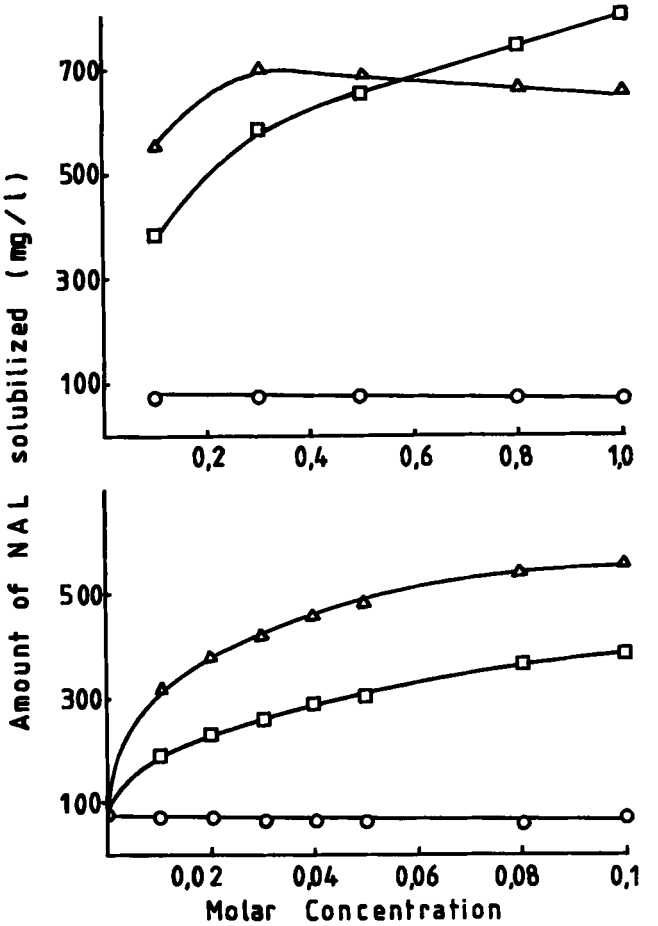

FIGURE 1

Solubility of NAL with hydrotropic salts at 37°C.
o—o piperazine citrate, □—□ hexamine,
Δ—Δ sodium citrate

in water at 1 M hexamine concentration). Hexamine did not alter significantly the pH of the dissolution medium beyond neutrality, since a 0.3 M hexamine solution has a pH of 7.6 (6). Therefore, the enhanced solubility of NAL may not be attributed to an imparted alkalinity. The negative Δ F figures reveals

TABLE 1

Free energy change (Δ F) of solubilization of nalidixic acid in aqueous hydrotropic salts solutions

Carrier concentration M	Δ F (K cal/mole) at 37°C. Hexamine	Sodium citrate	Piperazine citrate
0.02	-0.743	-1.031	↑
0.03	-0.743	-1.116	
0.04	-0.907	-1.153	
0.05	-0.907	-1.186	+0.076
0.10	-1.047	-1.261	
0.30	-1.299	-1.396	
1.00	-1.491	-1.334	↓

a spontaneous reaction (8), with no possibility of complexation (9).

The solubilization mechanism could be regarded as a simple hydrotropy between NAL and hexamine solution.

Sodium citrate showed enhancement in the solubility of NAL up to 0.3 M carrier concentration after which the decreased solubility may be a result of a salting out effect. Also, the calculated Δ F values revealed a spontaneous reaction (8) with no complexation (9).

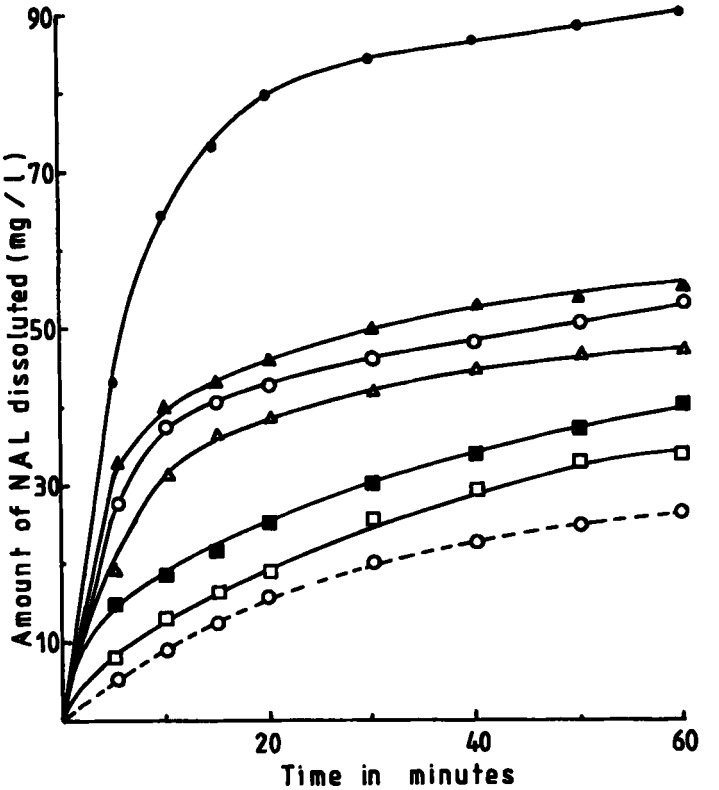

FIGURE 2

Effect of different techniques on the dissolution rate of equiportions (o) or 1:4 NAL to hexamine (●) powder.
o---o drug alone
▲——▲ fusion
▫——▫ physical blending
o——o co-precipitation.

The equiportion physical blends of NAL-hexamine systems showed a slight enhancement in the drug dissolution rate (Fig. 2). This may be due to the lack of intimate contact between the powder components. The equiportion melt and co-precipitate systems showed nearly the same pattern of dissolution with a faster co-precipitate system. The following rank order could

be considered for the technique-induced enhancement of the dissolution rate (at 1:1 NAL to hexamine ratio): co-precipitation > fusion > physical blending.

Upon increasing the carrier proportion to four fold that of the drug, the rank order was invariant. The fusion or co-precipitate systems, at this ratio, showed a high and smooth dissolution rate enhancement.

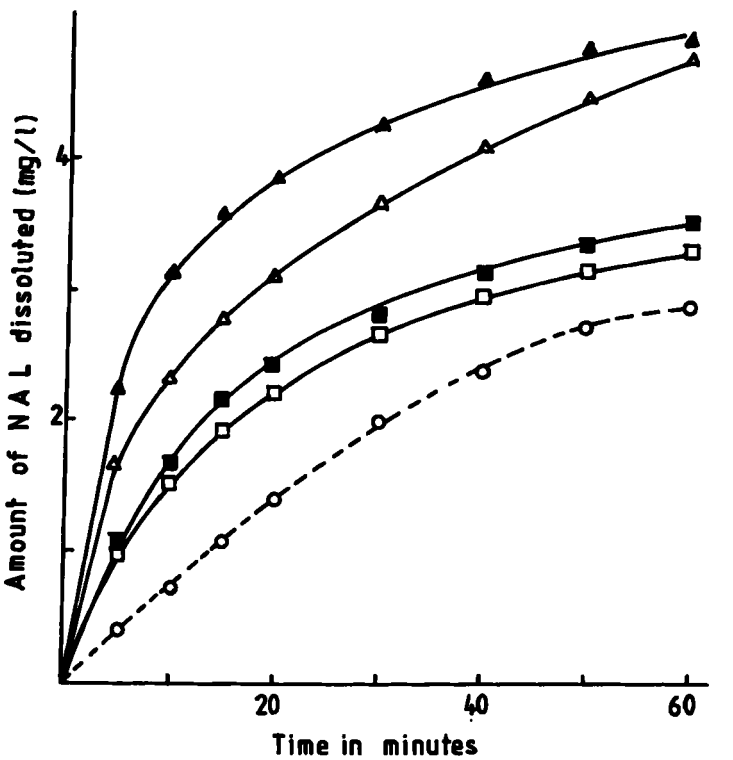

FIGURE 3

Effect of different techniques on the dissolution rate of equiportions (o) or 1:4 NAL to piperazine citrate (●) powder.

o---o drug alone ▫—▫ physical blending

▲—▲ co-precipitation.

The former yielded an amount of dissoluted NAL 8.42 times the powdered drug at 5 minutes, while the latter gave the highest enhancement of all tested systems. This may be attributed to the ultrafine dispersion of the drug on the molecular level in addition to the inherent effect of hexamine as a potential solubilizer for nalidixic acid.

The 20% NAL co-precipitate system showed the highest enhancement of all the NAL-piperazine citrate systems. The dissolution rate enhancement takes the following ascending order : 1:4 NAL to piperazine citrate physical blends < 1:1 physical blends < 1:1 co-precipitate < 1:4 co-precipitate. It was noticed that although piperazine citrate exhibited low interaction with NAL in the aqueous phase, as manifested by its low solubilizing capacity, yet the salt proved to be a powerful carrier when used in the solid dispersion systems.

NAL-Myrj 59 Systems :

Few literatures were reported on the use of solid dispersion technique with tensio-active agents to enhance the dissolution rate of water-insoluble drugs (4,5).

Myrj 59 was chosen from a series of surfactants on the basis of a screening wettability study previously reported (7).

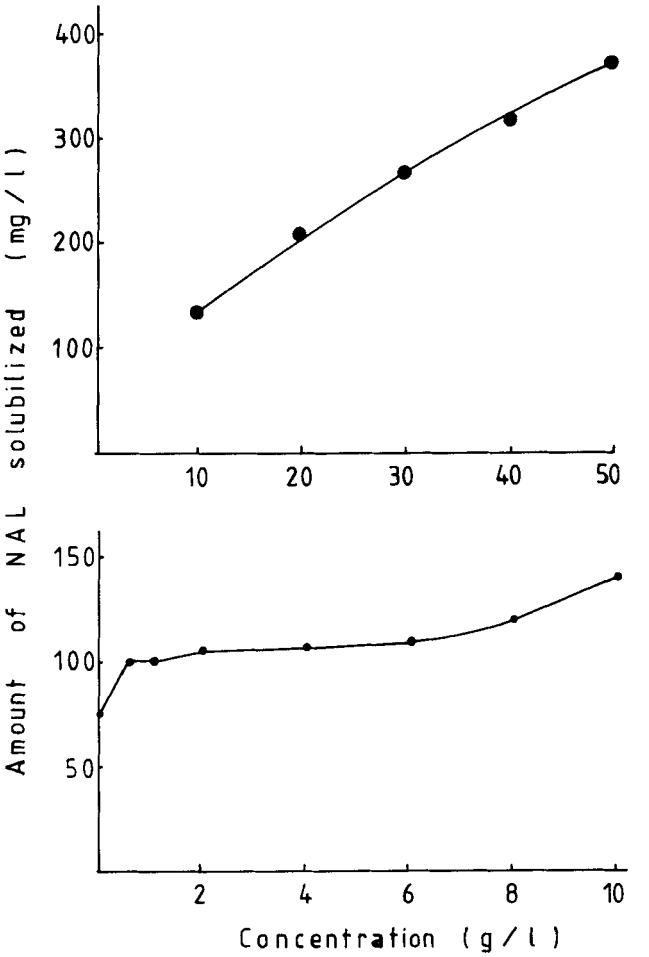

FIGURE 4
Solubility of NAL in Myrj 59 solutions at 37°C.

The solubility isotherm of nalidixic acid in the POE stearate tenside, Myrj 59, is shown in figure 4. The curve showed an increased solubility with increasing tenside concentration. At 6 g/l tenside concentration, an abrupt change in the solubility isotherm was noticed, thereafter, the solubility was progressively increased, and this may reflect a change in size and

TABLE 2

Free energy change (ΔF) of solubilization of nalidixic acid in Myrj 59 solutions and samples used in dissolution rate studies (Fig. 5)

Myrj 59 g/l	ΔF (K cal/mole)	NAL:Myrj w/w	Technique	RDR* at 5 minutes
5	-0.263	1:1	fusion	10.33
10	-0.404	1:4	fusion	13.08
25	-0.768	1:1	co-precipitation	13.83
50	-1.015	1:4	co-precipitation	16.50

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

shape of the micelles to those which accomodate higher solute concentrations (10).

Table 2 showed the magnitude of the free energy change (ΔF) accompanying the micellar solubilization of NAL by Myrj 59. The small negative values of ΔF indicated spontaneity of the reaction and precluded the possibility of complexation (9).

Irrespective of the technique applied, the dissolution rate of NAL-Myrj 59 systems showed a considerable enhancement (Fig. 5). A 20% w/w co-precipitate system showed the highest dissolution rate enhancement of all the NAL-Myrj systems. After

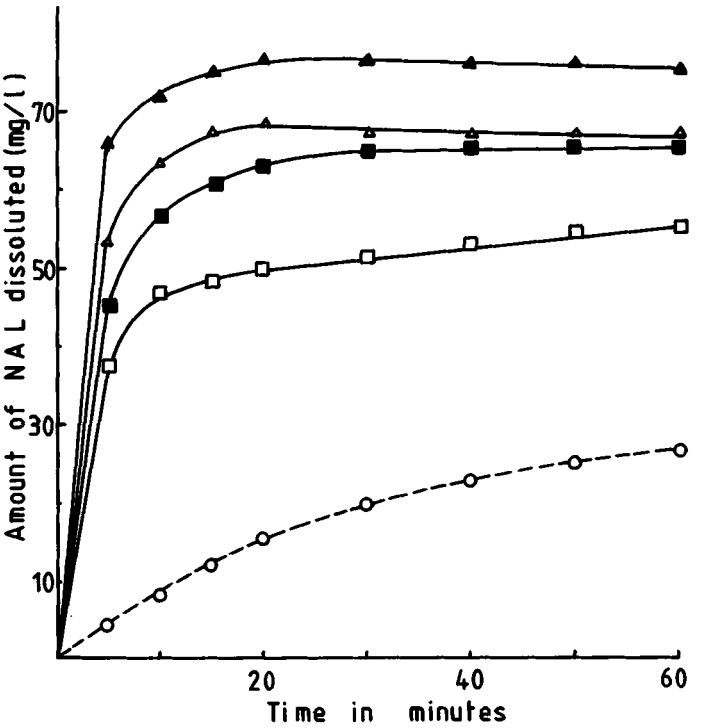

FIGURE 5

Effect of different techniques on the dissolution rate of equiportions (o) or 1:4 NAL to Myrj 59 (●) powder.
o---o drug alone
■——■ fusion ▲——▲ co-precipitation.

5 minutes, the RDR (relative dissolution rate) of this system reached 16.5 times the untreated drug, which denote the potential use of this technique to enhance the solubility of water-insoluble drugs.

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