DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 8(5), 683-699 (1982)

CRYSTALLIZATION OF NALIDIXIC ACID IN PRESENCE OF DIFFERENT CARRIERS

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ABSTRACT

The wettability of nalidixic acid powder was improved by using different tensioactive agents especially with Myrj 59, Brij 35 and Tween 40. There was an optimal concentration for each tenside which produced a maximal wettability.

The unique method of crystallization of nalidixic acid, in presence of different carriers, showed great enhancement in its dissolution rate. Maximum enhancing effects were shown with 1% w/v Myrj 59 or hexamine and 5% w/v each of PVP and urea. The drug yield, in general,

was high in all systems and the flow properties of the crystallized drug powder were also improved.

INTRODUCTION

Nalidixic acid is currently used as an antibacterial agent in urinary tract infections (1). Although the pharmacokinetics of this drug have been investigated (2-3), yet little information is available about the influence of formulation factors on its dissolution rate.

The wettability of several hydrophobic drugs was improved by the use of tensioactive agents (4-5). The lowering of the surface free energy by the adsorption of these tensides directly reduced the thermodynamic driving force opposing the dispersion process (6).

Chiou and co-workers (7) investigated the effect of crystallization of poorly water-soluble drugs on their in-vitro dissolution rates. Marked enhancement was observed for chloramphenicol, sulphathiazole and prednisone upon crystallization in 2.5% w/v aqueous solution of polysorbate 80.

The aim of our work is to improve the wettability of the hydrophobic drug, nalidixic acid, and to investigate the effect of crystallization in presence of different carriers, as well as their concentrations, on the in-vitro dissolution rate of its powder. These

carriers include nonionic tensides of different chemical classes and HLB values (Tween, Brij and Myrj), occlusion and linear polymeric compounds (urea, PEGs and PVP) and hexamine as a representative example of hydrotropic salts of urinary antiseptic properties.

EXPERIMENTAL

Materials - The following materials were used : Brij 35, 58 and 98; Myrj 51, 53 and 59 and Tween 40, 60 and 80 (Atlas Chemical Industries Co., USA), hexamine (B.D.H., England), nalidixic acid (NAL) Sterling-Winthrop, USA), polyethylene glycol 6000 (B.D.H., England), polyethylene glycol 20,000 (Hoechst Farbwerke, Germany), polyvinylpyrrolidone (mol. wt. 40,000 BASF, Germany), and urea (Merck, USA). All other chemicals were analytical reagent grade.

METHODS

Wettability of NAL Powder by Nonionic Tensides :

Clean dry capillary tubes (1.5 mm. diameter) were packed with 50 mg. of nalidixic acid powder (200-160 µm.) to a height of 15 cm. Each tube was fixed vertically by means of a small piece of cork in a vaccine bottle (10 ml. capacity) containing 5 ml. of the tenside solution to a depth of one centimeter. The extent of penetration of the solution through the powder column was measured in cm. at successive

time intervals and the average of four determinations was recorded.

Crystallization Technique - A quantity of 150 mg. of drug powder was dissolved in the least volume (75 ml.) of absolute ethyl alcohol at 60°C. This hot solution was gradually added to 50 ml. of an aqueous carrier solution stirred by a magnetic stirrer at 250 rpm and kept at room temperature. The drug solution was added in 5 minutes and stirring was continued for one minute more. Then the stirred solution was immediately dipped in an ice-bath till complete crystallization and then kept in a refrigerator for 24 hours. The settled crystals were collected quantitatively by filtration through a sintered glass funnel, dried in a vacuum desiccator and then weighed. The fraction that passed sieve 200 μm and retained on 160 μm (Din 1171, German Standard) was used for the dissolution study.

Determination of Drug Content in the Crystallized Powder:

In a 25-ml. measuring flask, 25 mg. of crystallized drug was dissolved in and completed to volume with N/10 NaOH. One ml. was taken, diluted to 100 ml. with N/10 NaOH and assayed spectrophotometrically at 259 nm. If no carrier was included, the previous dilution should give a reading of 1.085 (E 1%, 1 cm. = 1085). The percentage of carrier included with the drug powder while crystallization was calculated as follows :

$$\% \text{ carrier included} = 100 - \frac{\text{reading}}{1.085} \times 100$$

The amount of carriers included were found not to exhibit any shift in U.V. spectrum of nalidixic acid. Hence these carriers were found not to interfere with the spectrophotometric assay of the drug at 259 nm.

Properties of the Crystallized NAL Powder :

a) Flow Properties - The angle of repose (θ), for the crystallized powder was determined by the method of the Fixed Funnel and Free Standing Cone (8).

b) Porosity - The porosity or voids ϵ of the crystallized powder, the bulk volume and the packed volume were determined as previously reported (9).

c) Melting Point Depression - Few particles of the crystallized drug powder in different carriers were taken on a glass slide, covered with a cover slip, and placed on the pressed part of the hot stage of the microscope (Böetius, German Democratic Republic). The melting point was carefully recorded.

Dissolution Rate Determination - The dissolution profile of the drug powder crystallized in the presence of different carriers was followed using the beaker method suggested by Levy and Hayes (10). The dissolution apparatus was a 500-ml. beaker containing 400 ml. of distilled water placed in a thermostatically controlled water-bath maintained at 37°C. Agitation was provided

by an over-head mounted stirrer with a stainless steel paddle 5.5 x 1 cm., rotated centrally at a constant rate of 50 r.p.m. The powdered samples (quantity equivalent to 50 mg. of NAL) were gently sprinkled on the surface of the dissolution medium and no aggregation of the particles was observed. At each time interval, an aliquot was withdrawn by means of a filter-pipette, suitably diluted with N/10 NaOH and assayed for drug content spectrophotometrically at 259 nm. Each sample was replaced with distilled water prewarmed at 37°C. All samples were run at least in duplicate.

RESULTS AND DISCUSSION

Three different classes of nonionic tensioactive agents, namely Tween, Brij and Myrj, were chosen on the basis of having difference in HLB values, number of ethylene oxide units or length of hydrophobic moiety and type of chemical linkages. These tensioactive agents were used in a screening wettability study of nalidixic acid powder as shown in figure 1. It is apparent that the penetration height (wettability) was the highest with Myrj 59, Brij 35 and Tween 40. Inspection of the results revealed that the stearate ester of polyoxyethylene (POE) exhibited better wetting power to NAL powder than either the lauryl ether

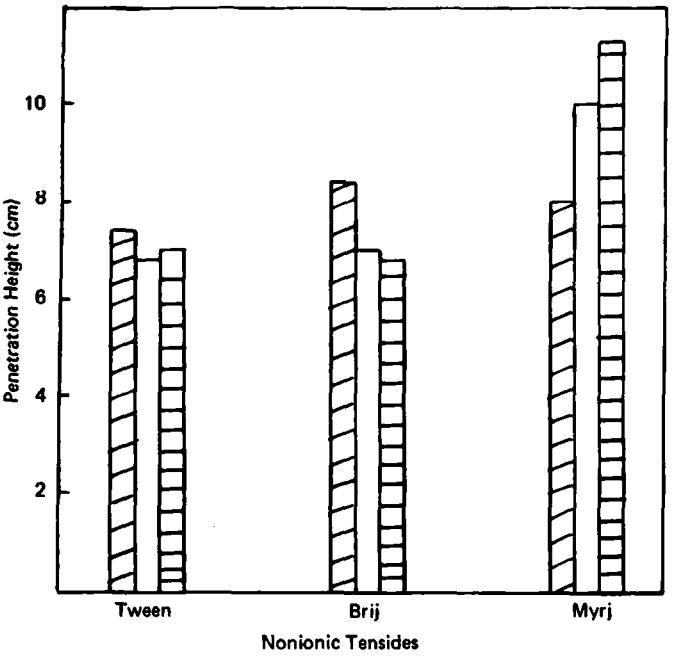

FIGURE 1

Wettability of nalidixic acid powder after one hour using 4 g/l tenside solution.

	Tween	Brij	Myrj
▨	40	35	51
□	60	58	53
▤	80	98	59

derivative of POE (Brij 35) or the palmityl ester of POE sorbitan derivative (Tween 40). Accordingly, the used tensides could be arranged according to their wetting power as follows : Myrj 59 Brij 35 Tween 40 and this is in agreement with their HLB values. Figure 2 shows the wettability (in cm.) of the drug powder

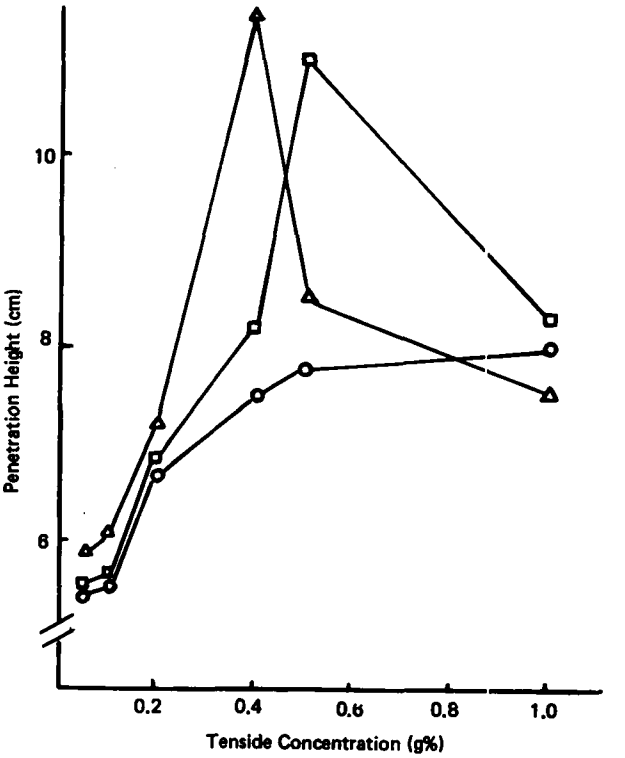

FIGURE 2

Wettability of nalidixic acid powder by different non-ionic tensides after one hour.
o—o Tween 40, □—□ Myrj 59, Δ—Δ Brij 35

after one hour of contact with different concentrations of each of the three selected tensides. The figure indicates that there is an optimal concentration for each tenside which produces a maximal wettability i.e. 0.4% Myrj 59 > 0.5% Brij 35 > 1% Tween 40. Brij 35 was chosen, being of intermediate HLB and wetting

TABLE 1

Physical properties of NAL powder prepared by crystallization in aqueous 5% w/v Brij 35 solution

Contact Time with Tenside (hrs.)	% Tenside Included	Tan θ	% Porosity	Adhesion to Glass Wall
4	3.28	1.37	63.912	++
8	4.20	1.29	59.902	+
12	5.10	1.21	55.913	-
24	5.99	1.13	51.923	-
Untreated Nalidixic Acid		1.60	75.862	++++

The (-) sign means no adhesion to glass wall.

property, to reveal the effect of the contact time of NAL crystals with the tenside solution on the amount of tenside included and, in turn, on the flow properties of the drug (Table I).

The results show that the amount of included tenside and hence the flow properties were increased, while the % porosity and adhesion to the glass container were reduced, with the increase in the contact time.

The dissolution rate of nalidixic acid powder crystallized in 5% w/v solution of the selected tensides is represented in figure 3. Inspection of the results revealed that the crystallization of NAL in presence of any of these tensides enhanced its dissolution rate to a varying extent. The increase in dissolution rate has the following ascending order : Myrj 59 < Tween 40 < Brij 35, which is in accordance

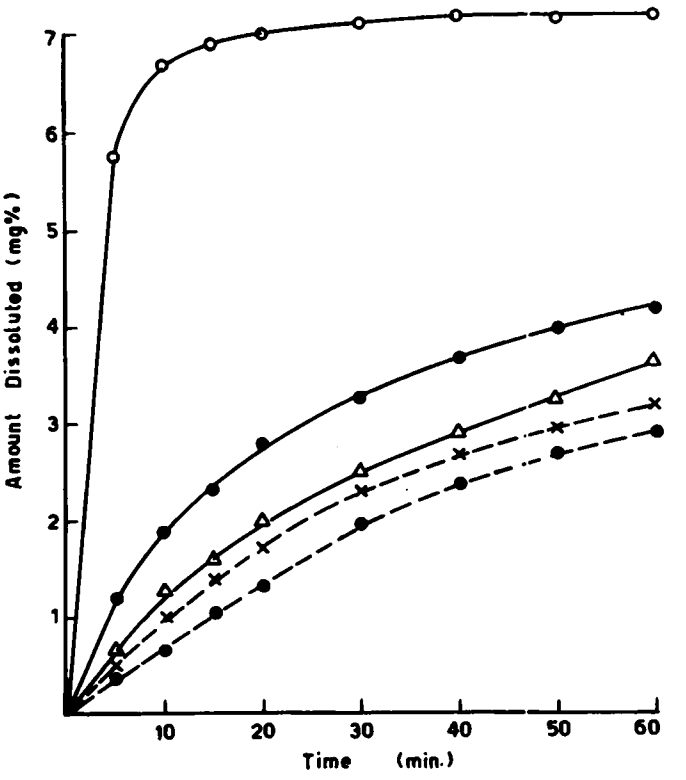

FIGURE 3

Dissolution rate of NAL powder crystallized in 5% w/v of different tensides.

●– – –● untreated drug ×– – –× crystallized drug

△——△ Myrj 59 o——o Brij 35

●——● Tween 40

with the amount of carrier included (Table 2). Contrary to our expectation, Myrj 59 with the highest number of ethylene oxide units, gave the least enhancement in NAL dissolution rate. Upon decreasing Myrj concentration from 5% w/v to 1% w/v, the dissolution

TABLE 2

Effect of type of carriers and concentrations on the yield and relative dissolution rate of crystallized NAL powder

Carrier	Concentration (% w/v)	Amount of Carrier Included (% w/v)	Yield (mg)	R_{D_5}*
Tensio-Active Agents :				
Tween 40	5.0	3.23	148.0	3.00
Brij 35	2.5	4.53	148.0	4.83
Brij 35	5.0	5.99	146.5	14.42
Myrj 59	1.0	4.15	146.0	14.66
"	2.5	3.23	130.0	11.80
"	5.0	1.11	113.0	1.48
Inclusion and Polymeric Compounds :				
Urea	5.0	5.99	146.5	5.67
PVP	5.0	5.07	147.5	8.33
PEG 20,000	5.0	3.69	148.5	4.00
PEG 6,000	5.0	4.15	147.5	4.17
Hydrotropic Salt :				
Hexamine	1.0	2.76	138.5	2.42
"	2.5	0.92	110.0	1.33
Crystallized drug alone		-	146.5	1.13

* The relative dissolution rate calculated by dividing the amount of NAL dissoluted at any time by that dissoluted from the untreated sample at the same time.

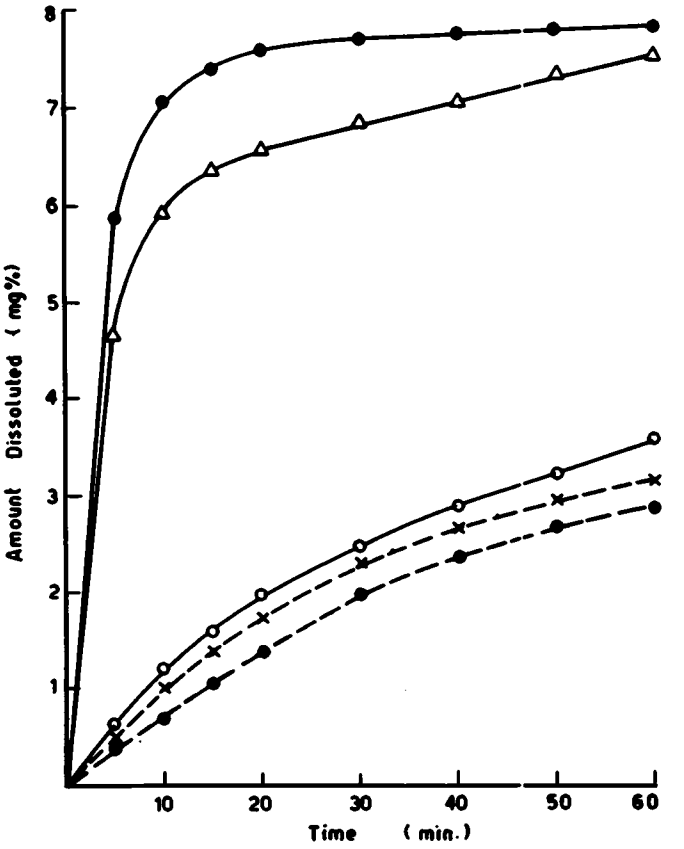

FIGURE 4

Effect of Myrj 59 concentrations on the Dissolution Rate of NAL (●– – –●) powder.

×– – –× crystallized NAL Δ——Δ 2.5% w/v

o——o 5% w/v ●——● 1% w/v

rate of NAL powder was found to increase significantly (Fig. 4) and the yield of the crystallised drug together with the amount of tenside included increased as well. The relative dissolution rate (RDR) showed the highest

values with 1% w/v Myrj 59 and 5% w/v Brij 35 after 5 minutes.

It was reported that during crystallization some tenside molecules, due to their surface activity, may be adsorbed onto the hydrophobic surface of the crystals. This adsorption would undoubtedly increase the wettability of the powder or crystals and thereby increases their dissolution rate (7).

The effect of occlusion and linear polymeric compounds on NAL dissolution rate is shown in Figure 5. Using urea, PVP, PEG 6000 or PEG 20,000 (5% w/v of each) a marked increase in the rate of dissolution of the drug powder was noticed, but in varying degrees. Urea and PVP showed similar dissolution profile with PVP being faster in the first 15 minutes. Also the amount of carrier included reached about 6% and 5% w/w, for urea and PVP respectively, of the crystallized NAL powder. After one hour, the amount of drug dissoluted using either PEG 6000 or 20,000 was nearly double that dissoluted from the uncrystallized drug.

The order of dissolution rate enhancement for occlusion and linear polymeric compounds could be summerized as follows : PEG 20,000 < PEG 6000 < urea < PVP. These results may be due to the great ability of urea to occlude (11) and PVP to complex (12) drugs. Close values were obtained for the yield of crystallized NAL with all inclusion and linear polymeric

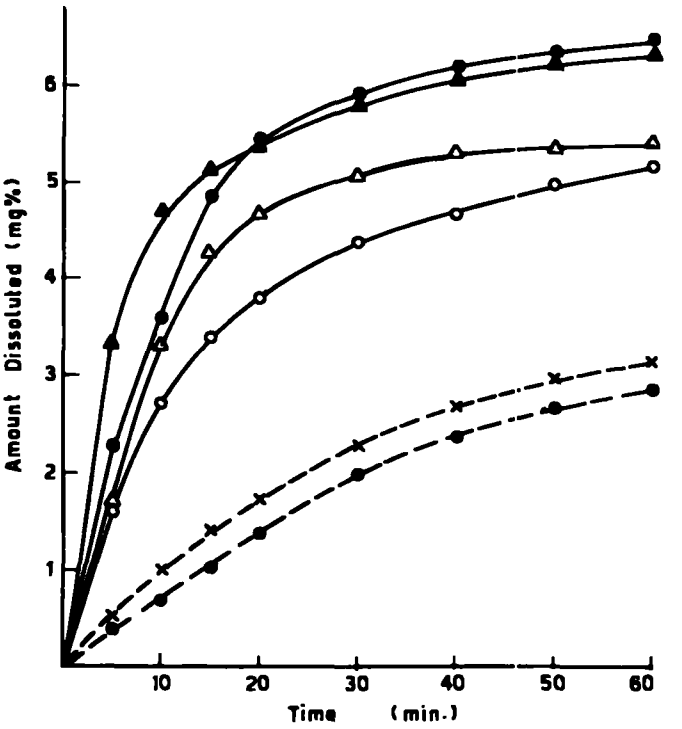

FIGURE 5

Dissolution rate of NAL (●- - -●) powder crystallized in 5% w/v of different carriers.
×- - -× drug crystallized with no carrier.
○———○ PEG 20,000 ▲———▲ PVP
△———△ PEG 6,000 ●———● urea.

compounds which accounted to be more than 91% w/w of the added NAL (Table 2).

Hexamine was chosen as an example of hydrotropic salts with the advantage of having urinary antiseptic properties (1). Using 2.5% w/v hexamine, a very small amount of carrier was included (less than 1% w/w)

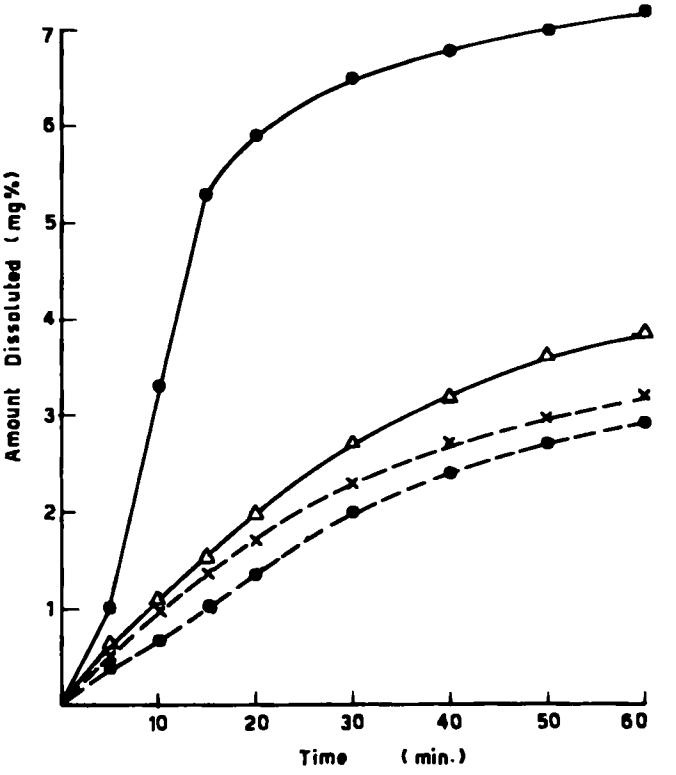

FIGURE 6

Effect of hexamine concentrations on the dissolution rate of NAL (●– – –●) powder. ×– – –× crystallized drug with no carrier. Δ——Δ 2.5% w/v ●——● 1% w/v.

resulting in a slight enhancement in NAL dissolution rate (Table 2 and Fig. 6). Upon decreasing hexamine concentration to only 1% w/v, a reasonable amount of this carrier was included (2.76% w/w) and the yield of NAL powder was also increased.

A depression of melting point of all the recrystallized samples by 0.5-2.0°C. was found. This depression might reflect the presence of a certain amount of carrier with the drug crystal which caused a defect in the crystal structure. The crystal would become thermodynamically unstable and so dissolve faster (7).

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