J. Fac. Pharm. Istanbul
29, 1 (1993)

İstanbul Ecz. Fak. Mec.
29, 1 (1993)

DISSOLUTION RATE OF NALIDIXIC ACID-AVICEL GROUND MIXTURES

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SUMMARY

Nalidixic acid is an antibacterial agent used for the treatment of urinary tract infections.

The aim of this work was to examine the degree to which various ground mixtures of nalidixic acid enhanced its dissolution rate.

Ground mixtures were prepared with Avicel, using Avicel concentrations of 5, 25, 50, 75 and 95 %. Each concentration was ground for 10, 30, 60 and 120 minute periods and the 5 % mixture was ground for additional 150, 180 and 210 minute periods in a ball mill.

The ground mixtures were compared to the physical mixtures of the same Avicel concentrations. It was found that the dissolution rates were generally higher than for those of both physical mixtures and the pure acid.

The highest dissolution rates were obtained for the following Avicel concentration/grinding-time combinations: 95%-10', 75%-60', 50%-120', 25%-120' and 5%-180'.

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Using IR spectroscopy, x-ray diffractometry, and differential thermal analysis techniques the chemical and crystalline amorphic states of the physical and ground mixtures were found to be the same.

In summary, forming a ground mixture with Avicel was found to be an effective method for the enhancement of the dissolution properties of nalidixic acid.

ÖZET

Nalidiksik asit idrar yolları enfeksiyonlarında kullanılan antibakteriyel bir ilaçtır.

Bu çalışmanın amacı nalidiksik asidin değişik öğütülmüş karışımlarının çözünme hızını ne ölçüde arttırdığını bulmaktır. Öğütülmüş karışımlar % 5, 25, 50, 75 ve 95 oranlarında Avicel ilavesi ile hazırlandı. Her bir konsantrasyondaki karışım 10, 30, 60 ve 120 dakikalık sürelerle bilyalı değirmende öğütüldü, % 5'lik karışım ilaveten 150, 180 ve 210 dakika sürelerle öğütüldü.

Öğütülmüş karışımlar aynı oranlarda hazırlanan fiziksel karışımlar ile karşılaştırıldı. Çözünme hızlarının genel olarak hem fiziksel karışımlardan, hem de saf maddeden yüksek olduğu saptandı.

En yüksek çözünme hızları şu konsantrasyon/öğütme süresi kombinasyonları ile elde edildi: % 95-10', % 75-60', % 50-120', % 25-120' ve % 5-180'.

IR spektroskopi, x-ışın difraktometri ve diferansiyel termal analiz yöntemleri ile fiziksel ve öğütülmüş karışımların kimyasal ve kristal-amorf özellikleri araştırıldı, aynı oldukları görüldü.

Sonuç olarak, Avicel ile öğütülmüş karışımlar hazırlamanın nalidiksik asit çözünme hızını arttırmada etkili bir yöntem olduğu saptandı.

Key words: Dissolution rate, nalidixic acid, Avicel, ground mixture.

INTRODUCTION

Nalidixic acid is an antibacterial agent widely used in urinary tract infections. The solubility of this naphtyridine drug in water is poor and hence its absorption is expected to be dissolution rate-limited. As high concentrations in urine are needed for its therapeutic efficacy, the formulation of its preparations is important (1). In investigations ma-

de by various workers considerable in vitro and in vivo differences between commercial nalidixic acid tablets were found, not only between brands, but also between batches of the same brand and tablets of the same batch (2-7).

The dissolution behavior of oral solid dosage forms has been shown to be a good criterion for controlling formulation and process variables that can influence the bioavailability of the active ingredients of the dosage forms. A dissolution test for nalidixic acid tablets has been included in the USP XX.

Using new formulation techniques was shown to be an effective way of enhancing the release rate of nalidixic acid, too (8, 9). One of the methods used to enhance the dissolution rates of drugs with limited solubility is grinding of mixtures. Preparing ground mixtures of a drug may be effective as a result of particle size reduction, transformation into an amorphous state or adsorption of drug particles onto the carrier particles (10-12). The purpose of this study has been to prepare ground mixtures of nalidixic acid using Avicel as carrier and to evaluate their dissolution patterns.

2- EXPERIMENTAL

2.1. Materials

Nalidixic acid (İlsan-İltaş İlaç San., Türkiye), Avicel pH 102 (Selectchemie, Switzerland). All chemicals used were of analytical grade.

2.2. Methods

2.2.1. Preparation of Ground Mixtures

Ground mixtures of nalidixic acid were prepared with Avicel, using Avicel concentrations of 5, 25, 50, 75 and 95 %. Each concentration was ground for 10, 30, 60 and 120 minute periods and the 5 % mixture was ground for additional 150, 180 and 210 minute periods in a ball mill (Erweka). The ground mixtures prepared were sieved through 35 mesh sieve (Sieving Machine Vibro, Retsch) and assayed for their drug content.

2.2.2. Preparation of Physical Mixtures

Physical mixtures of the same Avicel concentrations were prepared by tumbling the powders in a bottle for 15 minutes.

2.2.3. **Dissolution Rate Studies**

The dissolution rates of the pure drug, the ground mixtures and the physical mixtures were studied according to the USP XXII procedure specified for nalidixic acid tablets (using apparatus 2 at 60 rpm. in a medium of pH 8.60) (13). Accurately weighed samples, equivalent to 100 mg of drug were spread over the surface of 900 mL dissolution medium. At preset time intervals, aliquots of 1 mL were withdrawn and replaced by an equal volume of dissolution medium. The samples were assayed spectrophotometrically at 258 nm after suitable dilution with 0.01 N NaOH (Varian Techtron Series 634 spectrophotometer) and the amount dissolved was determined using a calibration curve. The equation of the curve was found to be $y=0.115\ x + 0.0003$ ($r=1.0067$).

The reported data are the average of at least three determinations.

To rule out interference of the absorbents on the UV measurements, a test was carried out with the highest Avicel amount used in the study. No interference was observed at 265 nm.

2.2.4. **Particle Size Analysis**

A sample of 10 g was used for each analysis carried out by sieving for 10 minutes (Sieving Machine Vibro, Retsch). The arithmetic weight average was calculated according to the equation ($R/_{100}$. d_a), where R is the % of particles within a size range with the midpoint d_a . Summing the results of all the size ranges, the average particle diameter of the sample was found (14).

The reported data are the average of two determinations.

2.2.5. **IR Absorption Measurements**

This was carried out with Perkin-Elmer 1420 Infrared Spectrophotometer using KBr disc method.

2.2.6. **X-Ray Diffraction Measurements**

Powder X-ray patterns were measured using Philips, PW 1050 Diffractometer. Conditions: 40 kW, 20 mt, range 1000. Vertical goniometer was used.

2.2.7. Thermal Measurements

The DTA patterns were carried out with Netsch Model 429.

3- RESULTS AND DISCUSSION

Avicel pH 102 was used as carrier material in this study. Although chemically inert, Avicel can form hydrogen bonds and thus adsorb drugs (15). Avicel was used in preparing ground mixtures, too and enhanced the dissolution rate of different drugs to a certain extent depending on the drug/ingredient ratio and the grinding time (8, 11, 16).

In this study mixtures of nalidixic acid with 5, 25, 50, 75 and 95 % Avicel were ground for 10, 30, 60 and 120 minutes. The sample with 5 % Avicel was further ground for 150, 180 and 210 minutes.

Figures 1-5 show the dissolution profiles of these ground mixtures compared to the corresponding physical mixtures and the pure drug. The dissolution patterns of the physical mixtures with 75 and 95 % Avicel are better than that of the pure drug. The physical mixtures containing 5, 25 and 50 % Avicel did not differ from the pure drug in regard of their dissolution rate and the variation coefficients of the results were high.

It can easily be seen that nalidixic acid ground mixtures prepared with Avicel exhibited enhanced dissolution rates in all the studied concentrations compared to the pure drug. The drug-to-carrier ratio and the grinding time influence the dissolution profiles. Table 1 shows the average particle diameter values of all the samples. The particle sizes decrease with increasing times of grinding, only the sample containing 5% Avicel agglomerates slightly when ground for 210 minutes. Though it is obvious from the data that particle size reduction improves the dissolution of the drug, it is hardly possible to find out a good correlation for the particle size and dissolution data in common, because the particle size is not the only factor influencing the dissolution rate of nalidixic acid, the presence of Avicel and the drug-to-carrier ratio make a great difference. With higher Avicel concentrations short grinding times were appropriate, although particles get smaller with longer grinding times; the decrease of the dissolution with longer times of grinding is supposed to be caused by the adsorption of the Avicel particles onto the drug particles as a multilayer thus preventing the diffusion of the drug, due to the swelling of this excess Avicel. With lower Avicel concentrations dissolution was enhanced by increasing the grinding time, this enhancement may be due to particle size reduction, together with the increased surface area. Furthermore grinding time not only affects particle size re-

duction, but also homogeneous mixing and adsorption of the drug onto the carrier particles; for example, the dissolution of the mixture containing 5% Avicel and ground for 30 minutes is better than that ground for 10 minutes, although their average particle sizes are almost the same (Fig. 5, Table 1).

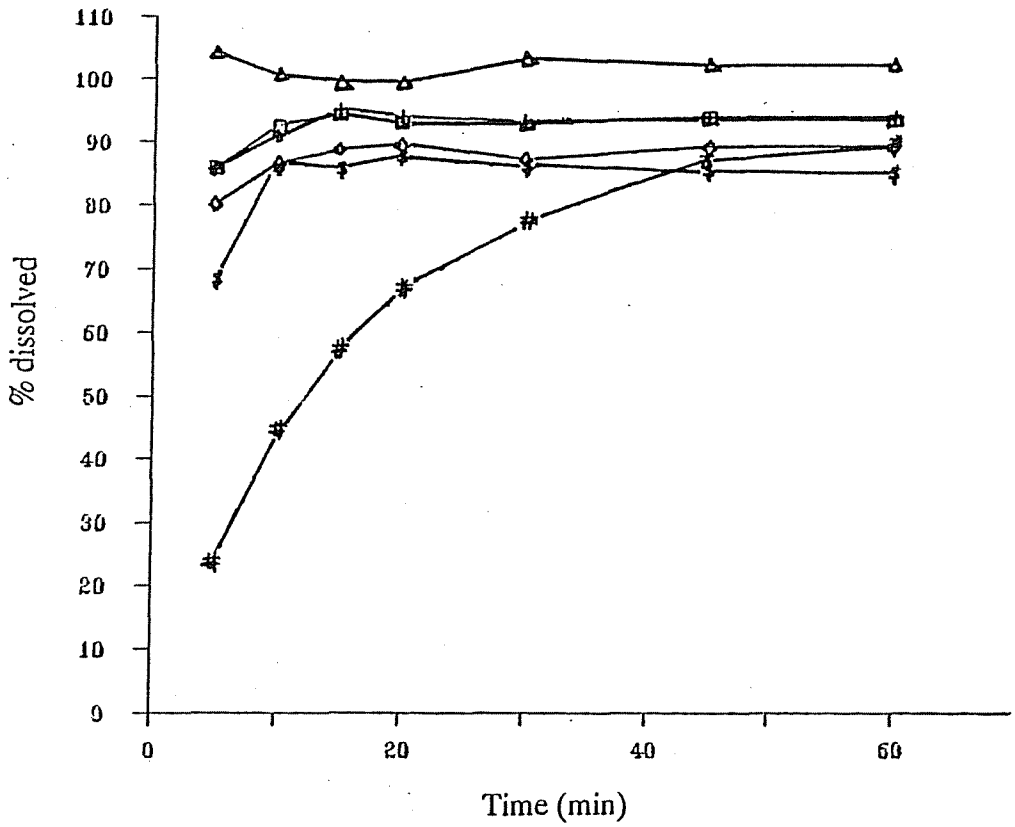


Figure 1: Dissolution Profiles of Nalidixic Acid-Avicel (95 %) Mixtures Ground for 10 (Δ), 30 (◊), 60 (+) and 120 (□) Minutes, the Corresponding Physical Mixture ($) and the Pure Drug (#).

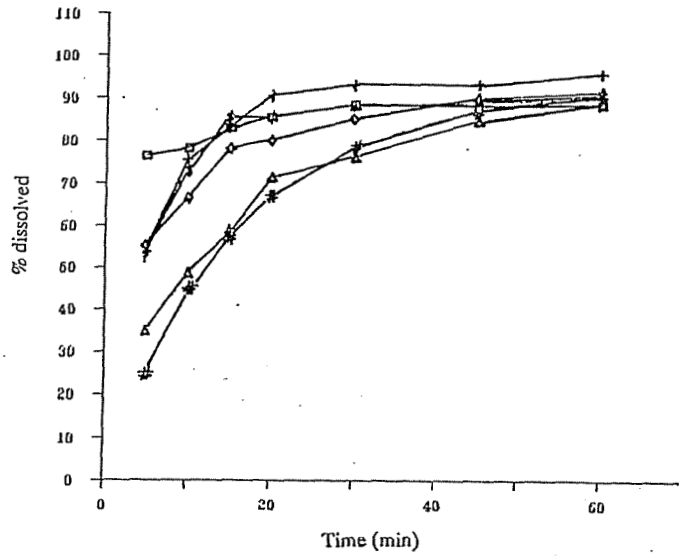


Figure 2: Dissolution Profiles of Nalidixic Acid-Avicel (75 %) Mixtures Ground for 10 (Δ), 30 (◊), 60 (+) and 120 (□) Minutes, the Corresponding Physical Mixture ($) and the Pure Drug (#).

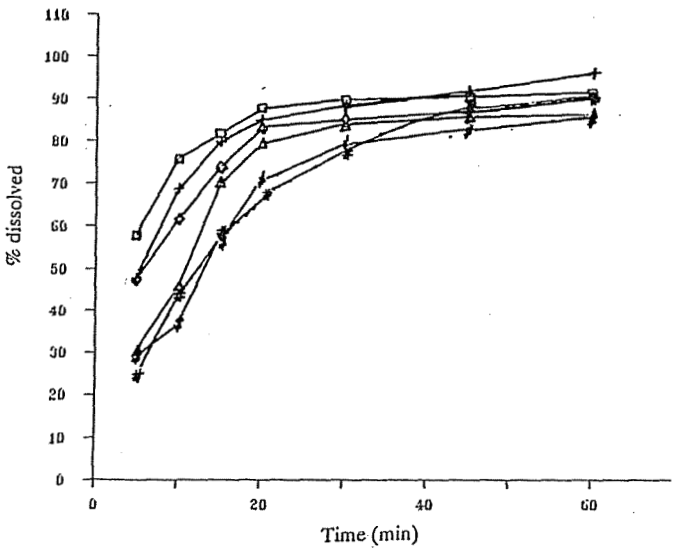
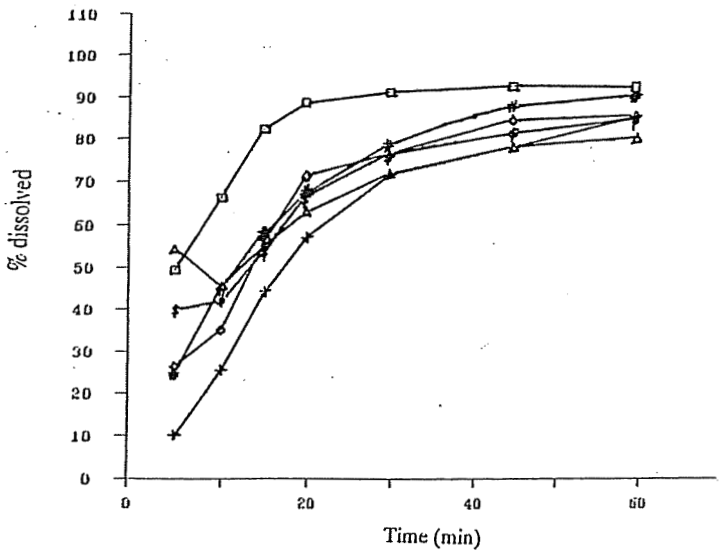
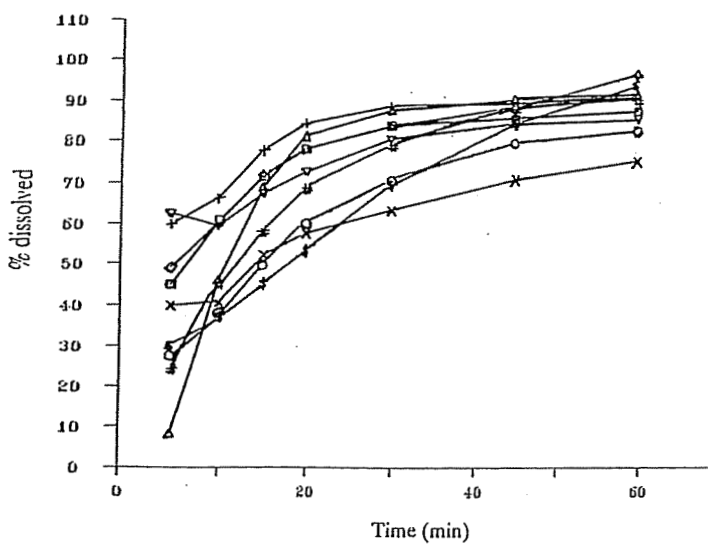


Figure 3: Dissolution Profiles of Nalidixic Acid-Avicel (50 %) Mixtures Ground for 10 (Δ), 30 (◊), 60 (+) and 120 (□) Minutes, the Corresponding Physical Mixture ($) and the Pure Drug (#).



gure 4: Dissolution Profiles of Nalidixic Acid-Avicel (25 %) Mixtures Ground for 10 (Δ), 30 (◊), 60 (+) and 120 (□) Minutes, the Corresponding Physical Mixture ($) and the Pure Drug (#).



ure 5: Dissolution Profiles of Nalidixic Acid-Avicel (5 %) Mixtures Ground for 10 (0), 30 (▽), 60 (X), 120 (Δ), 150 (◊), 180 (+) and 210 (□) Minutes, the Corresponding Physical Mixture ($) and the Pure Drug (#).

TABLE 1: Average Particle Diameter Values of the Nalidixic Acid-Avicel Ground Mixtures Compared to Pure Nalidixic Acid, Pure Avicel and the Corresponding Physical Mixtures.

Grinding time (min)	Average Particle Diameter (μm)						
			Ground Mixtures with Avicel Content of				
	Pure N. Acid	Pure Avicel	5%	25%	50%	75%	95%
0	352.68	115.83	284.54	172.33	158.22	137.36	133.33
10	343.53	98.83	252.15	142.65	142.62	128.49	129.51
30	349.60	82.84	253.96	125.59	133.95	120.02	124.82
60	289.18	71.64	263.87	133.74	130.22	121.51	114.17
120	236.42	74.33	251.58	127.80	121.60	112.69	113.84
150	—	—	224.52	—	—	—	—
180	—	—	228.60	—	—	—	—
210	—	—	240.12	—	—	—	—

The ground mixtures with the Avicel concentration/grinding time combinations 95 % - 10 min., 75 % - 60 min., 50 % - 120 min., 25 % - 120 min. and 5 % - 180 min. exhibited the highest dissolution rates in their groups, as shown in Table 2.

The mixture with 95 % Avicel ground for 10 minutes exhibited the most predominant dissolution rate of the drug and the lowest coefficients of variation, all the drug went into solution within 5 minutes, the rate being fourfold of the pure drug.

TABLE 2: Dissolution Rate Data of the Ground Mixtures which Exhibited the Highest Dissolution Rates and Percentages in their Groups: A_5, A_{30}, A_{60} (% dissolved in 5, 30 and 60 min respectively).

Sample	A_5 (C.V.)	A_{30} (C.V.)	A_{60} (C.V.)
Pure nalidixic acid	25.039 (24.198)	77.114 (8.877)	87.423 (5.635)
% 95-10'	104.250 (2.398)	103.350 (5.782)	102.300 (2.031)
% 75-60'	53.550 (5.111)	93.300 (1.213)	96.150 (2.702)
% 50-120'	57.875 (8.154)	89.550 (1.811)	91.350 (1.776)
% 25-120'	49.425 (42.476)	91.350 (4.209)	95.250 (5.455)
% 5-180'	59.963 (31.731)	88.800 (2.340)	91.575 (4.294)

C. V.: Coefficient of variation

In the IR spectra of the ground mixtures which exhibited the best results, no change in the absorption bands was observed (Fig. 6), showing that grinding with Avicel did not affect the chemical structure of nalidixic acid.

X-ray diffraction pattern of the sample with 5 % Avicel ground for 180 min. indicate that the amorphous state of nalidixic acid was not obtained by grinding with Avicel (Fig. 7).

No significant difference was observed between the DTA curves of the ground and physical mixtures with 5 % Avicel (Fig. 8). These results pointed out that the improvement of the dissolution patterns of nalidixic acid can only be attributed to particle size reduction, the enhancing effects of Avicel, which must have facilitated wetting due to its hydrophilicty.

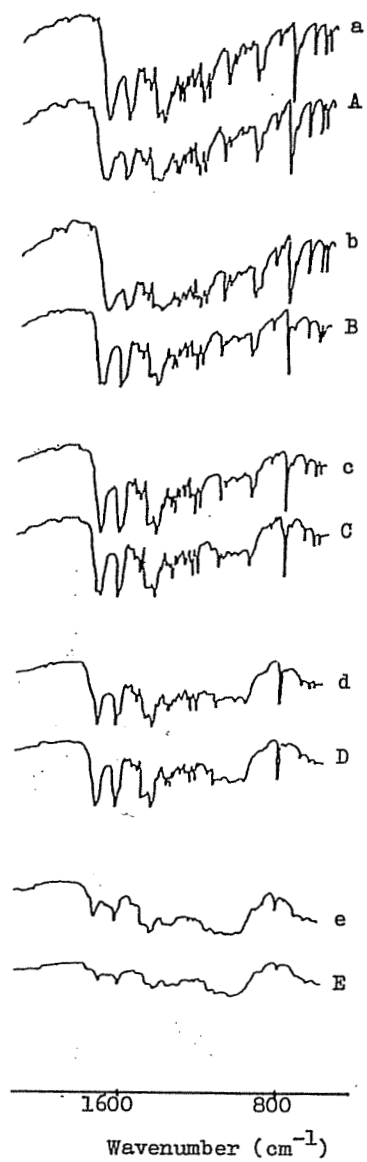


Figure 6: IR Spectra of the Ground Mixtures Shown in TABLE 1 Compared to the Corresponding Physical Mixtures. Key:
A: Mixture Ground with 5 % Avicel for 180 min.
B: Mixture Ground with 25 % Avicel for 120 min.
C: Mixture Ground with 50 % Avicel for 120 min.
D: Mixture Ground with 75 % Avicel for 60 min.
E: Mixture Ground with 95 % Avicel for 10 min.
a, b, c, d, e: Corresponding Physical Mixtures.

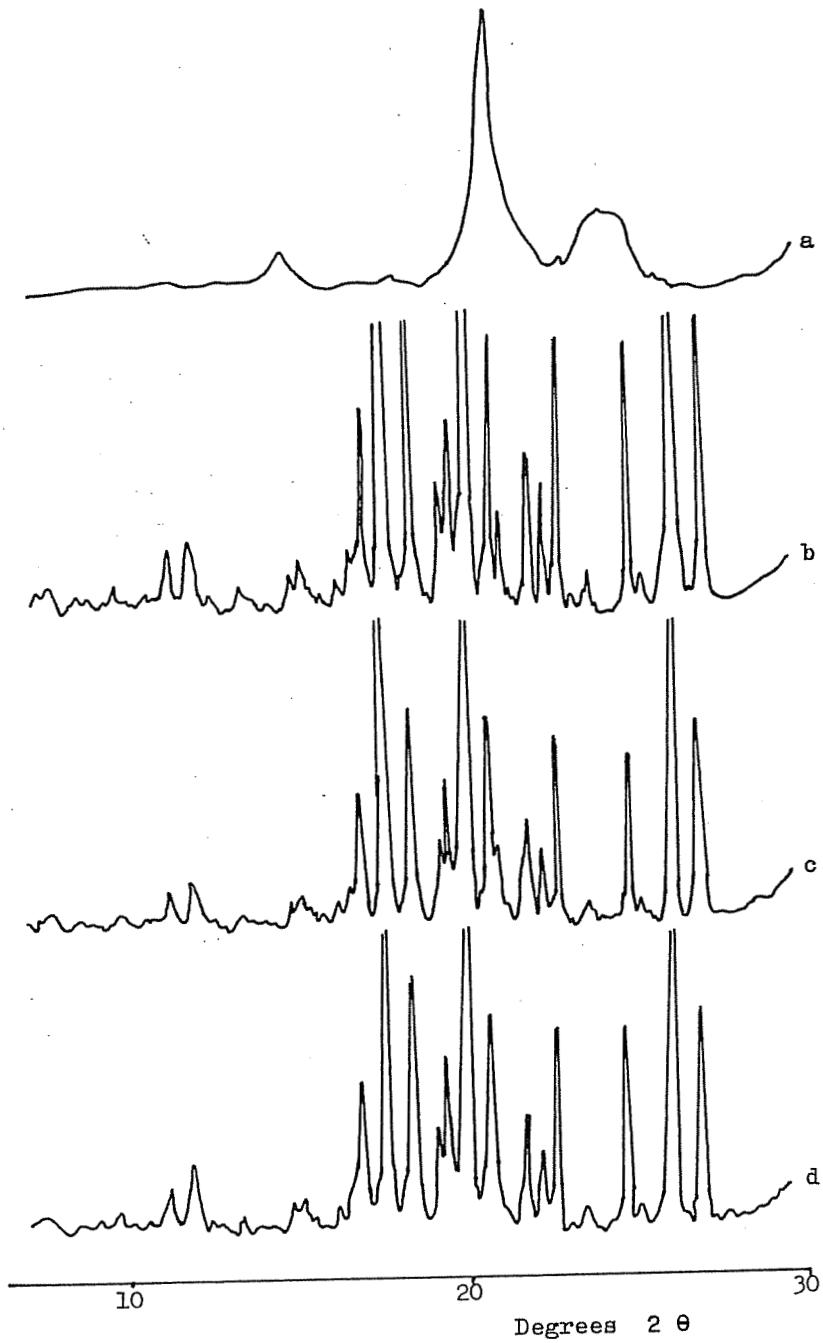


Figure 7: X-Ray Diffraction Patterns of Avicel (a), the Pure Drug (b), the Physical Mixture (c) and the 180 min. Ground Mixture (d) of Nalidixic Acid with 5 % Avicel.

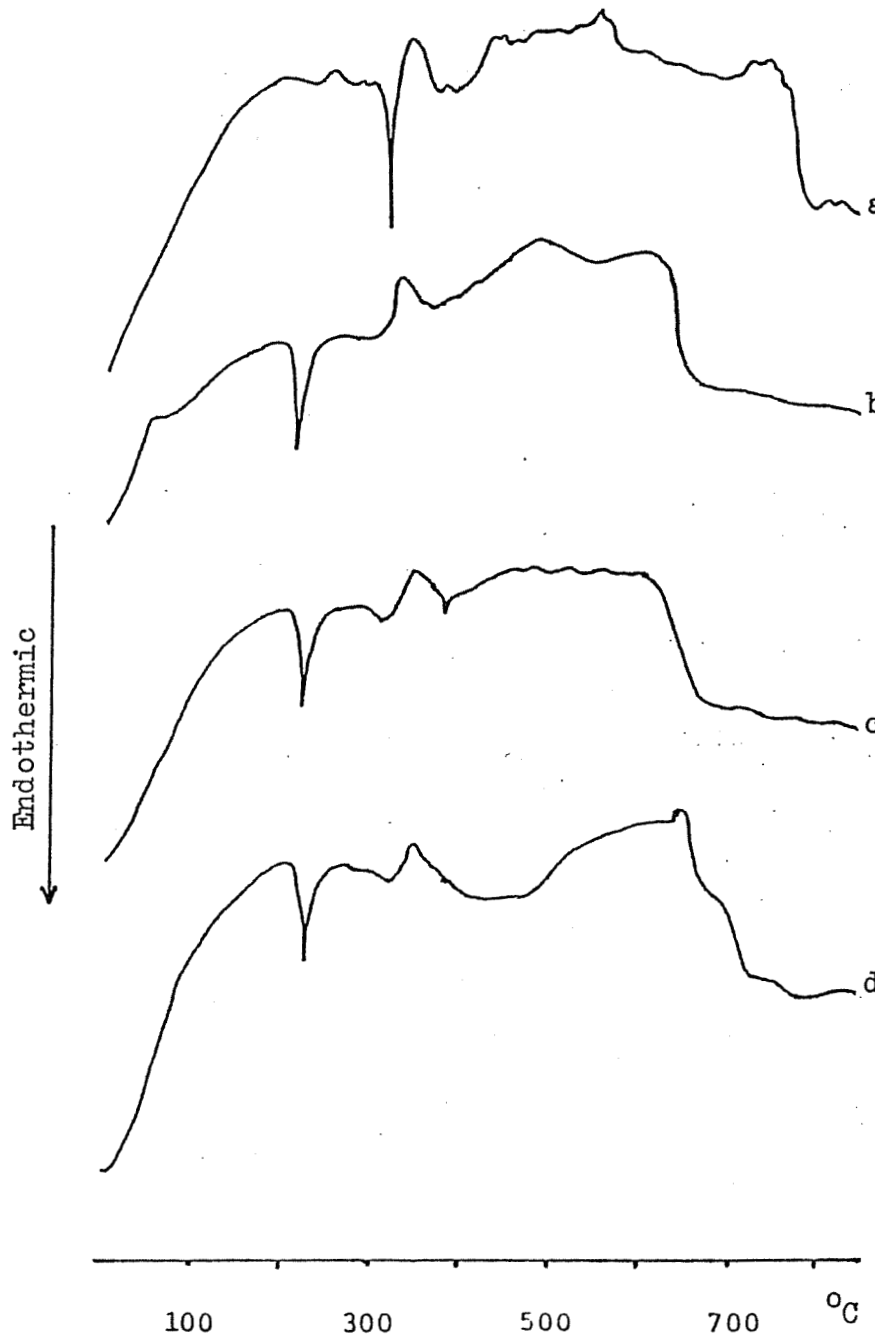


Figure 8: DTA Thermograms of Avicel (a), the Pure Drug (b), the Physical Mixture (c) and the 180 min. Ground Mixture (d) of Nalidixic Acid with 5 % Avicel.

To conclude preparing ground mixtures was found to be an effective means of increasing the dissolution of the poorly water soluble drug nalidixic acid. These systems can be used in formulations to achieve more rapid and reproducible rates of dissolution.

REFERENCES

1. Martindale, "The Extra Pharmacopeia", 28th Ed., The Pharmaceutical Press, London, 1982.
2. Moore, W. E., Portmann, G. A., Stander, H. and Chesney, E. W., *J. Pharm. Sci.*, **54,** 36-41 (1965).
3. Ragazzi, E., *Boll. Soc. İtal. Farm. Osp.*, **26,** 213-228 (1980).
4. Khalafallah, N., Darwish, M. and Khalil, S. A., *Drug Dev. Ind. Pharm.* **8,** 579-589 (1982).
5. Bernabei, M. T., Forni, F., Coppi, G., Cameroni, M. C., and Pietramaggiori, F., Boll. Soc. *İtall. Farm. Osp.*, **29,** 107-118 (1983).
6. Ogata, H., Aoyagi, N., Kaniwa, K., Shibazaki, T., Ejima, A., Takasugi, N., Mafune, E., Hayashi, T. and Suwa, K., *Int. J. Clin. Pharmacol. Ther. Toxicol.*, **22,** 175-183 (1984).
7. Dortunç, B., *FABAD J. Pharm. Sci.* **16,** 9-16 (1991).
8. Çelebi, N. and Nagai, T., *S. T. P. Pharma,* **3,** 868-871 (1987).
9. El Gindy, N. A., Shalaby, A. and Khalek, M. A., *Acta Pharm. Technol.* **28,** 291-296 (1982).
10. El Gendy, G. A., Terada, K., Yamamoto, K. and Nakai, Y., *Int. J. Pharm.* **31,** 25-31 (1986).
11. Baba, K., Takeichi, Y. and Nakai, Y., *Chem. Pharm. Bull.* **38,** 2542-2546 (1990).
12. Nozawa, Y. and Yamamoto, A., *Pharm. Acta Helv.* **64,** 24-29 (1989).
13. The United States Pharmacopeia, XXII., U. S. Pharmacopeial Convention, Inc. Rockville, MD, 1990.
14. Thoma, K. and Schlütermann, B., *Pharmazie* **47,** 198-202 (1992).
15. Avicel (Technical Bulletin) FMC Corporation, U.S.A.
16. Yamamoto, K., Nakano, M., Arita, T., Takayama, Y. and Nakai, Y., *J. Pharm. Sci.* **65,** 1484-1487 (1976).

ACKNOWLEDGEMENTS

The authors wish to thank TÜBİTAK-Marmara Institute of Scientific and Industrial Research for the X-Ray diffraction and DTA examinations of the samples.