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BIOPHARMACEUTICAL STUDIES ON SOLID DISPERSIONS OF NALIDIXIC ACID IN MODIFIED STARCHES

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ABSTRACT

The objective of the study is to improve the dissolution rate and efficiency and bioavailability of nalidixic acid (NA) and to evaluate three modified starches namely dextrin (D) β-cyclodextrin (β-CD) and hydroxyethyl starch (HES) as carriers for solid dispersions. Solid dispersions of NA in D, β-CD and HES were prepared by common solvent method and the dispersions were evaluated by TLC, IR, DTA, X-ray diffraction, moisture absorption, dissolution rate and bioavailability studies. The three modified starches were found to be non-hygroscopic, non-interacting carriers giving solid dispersions and effective in increasing the dissolution rate, efficiency and absorption rate of NA. A marked reduction in the crystallinity and crystal size of NA in the dispersions was observed.

INTRODUCTION

Nalidixic acid, an antibacterial agent, is poorly soluble in water and aqueous fluids and its absorption is dissolution rate limited. Significant differences were observed (1,2) among the formulations of nalidixic acid with respect to lag time of absorption and availability rates. USP XXII(3) has also prescribed a dissolution rate test for nalidixic acid tablets. Among the various approaches to improve the dissolution of poorly soluble drugs, the preparation of solid dispersions has often proven to be successful(4). In the present work solid dispersions of nalidixic acid (NA) in three modified

starches namely dextrin (D), β-cyclodextrin (β-CD) and hydroxyethyl starch (HES) were prepared with a view to improve its dissolution and absorption rates. These modified starches have not been studied earlier as carriers for solid dispersions. Hence an evaluation of these modified starches as carriers for solid dispersions was also made. The results are reported here.

EXPERIMENTAL

Materials

Nalidixic acid I.P.; Dextrin white (E.Merck); β-cyclodextrin (Sigma); Hydroxyethyl starch (Sigma) and Ammonia solution 25% (Merck) were used.

Preparation of Solid Dispersions

Solid dispersions of nalidixic acid in various modified starches were prepared by common solvent method using ammonia solution as solvent. The samples were prepared by dissolving the carrier in warm water and nalidixic acid was added and dispersed. Ammonia solution was then added to the dispersion, while stirring, to get a clear solution. The solvent was then removed by evaporation at 40°C under vacuum. The mass obtained was then crushed, pulverised and sifted through mesh No.100. In each case four different concentrations of carrier namely 5, 10, 25 and 50 per cent were used in the preparation of solid dispersions.

Interaction Studies

TLC method was used to study the chemical stability of drug in solid dispersions. A solvent system consisting of chloroform : methanol : formic acid (90:7:3) was used. The drug was detected by exposing to iodine vapours.

IR spectra of NA, D, β-CD and HES and their solid dispersions (1:1) were obtained using Bomen Michelson IR spectrophotometer. IR spectra were obtained by preparing solid disc in KBr using KBr as reference.

Differential Thermal Analysis

Differential Thermal Analysis was performed on nalidixic acid, dextrin, β-cyclodextrin, hydroxyethyl starch and their solid dispersions (1:1) using Stanton Redcroft DTA 673-4 analyser with RE 571.20 Potentiometric recorder. The samples were analysed in the temperature range of 30°-260°C at a heating rate of 10°C min^{-1}.

X-ray Diffraction Studies

X-ray diffractograms were obtained by using Phillips diffractometer (PW 1140) and Cu-K_α

radiation. Diffractograms were run at a scanning speed of 2°/min and a chart speed of 2°/2 cm/2θ.

Moisture Absorption Studies

Hygroscopic nature of the carriers and the solid dispersions was evaluated by moisture absorption studies in closed desiccator at 84 per cent relative humidity (RH) and room temperature.

Dissolution Rate Studies

The dissolution rate of nalidixic acid in pure form and from solid dispersions and physical mixtures was studied using USP XXI Dissolution Rate Test Apparatus employing a paddle stirrer. In 900 ml of dissolution medium (a mixture of one volume of pH 7.4 phosphate buffer and 4 volumes of distilled water), a sample equivalent to 50 mg of nalidixic acid, a speed of 50 rpm and a temperature of 37±1°C were employed in each test. A 5 ml aliquot of dissolution medium was withdrawn at different time intervals, suitably diluted and assayed spectrophotometrically at 258 nm. The dissolution efficiency values were calculated as suggested by Khan (5). Dissolution parameters calculated are given in Table-1.

In VIVO Evaluation

In vivo evaluation of the solid dispersions of nalidixic acid was done in healthy human subjects by urinary excretion studies. In vivo studies were carried out on i) nalidixic acid ii) NA-D (9:1) iii) NA- β -CD (9:1) and iv) NA-HES (9:1) solid dispersions as per a crossover randomized block design (n=4) with a washout period of 15 days between the treatments. The products were tested at a dose equivalent to 500 mg of NA. Nalidixic acid in urine samples was determined by the method described by Perenyi, T. (6).

Elimination rate constant (K_{el}) and biological half-life ($t_{\frac{1}{2}}$) were calculated from urinary excretion data by using Nelson equation (7). Per cent of drug absorbed to various times and absorption rate constant (K_a) were calculated from urinary excretion data by the method of Wagner-Nelson (8,9). Cumulative amount excreted in urine $(Xu)_\infty$ was taken as a measure of bioavailability. The results were analysed statistically using Student's paired t-test. The results are given in Table-2.

RESULTS AND DISCUSSION

All the dispersions prepared were found to be fine and free flowing. Low s.d. values in per cent drug content ensured uniformity in drug content in

TABLE-1
Dissolution Parameters of Nalidixic acid from various Solid Dispersions

Solid Dispersion	Per cent Carrier Concentration	T_{50} (min)	D.E. (%)	Cube Root Dissolution Rate Constant $K(mg^{1/3}.min^{-1})$
NA	--	>120	18.83	0.0054
NA-D	5	37	39.58	0.0189
	10	12	70.00	0.0556
	25	5.5	82.25	0.0950
	50	4.5	84.17	0.1081
NA-β-CD	5	28	48.58	0.0263
	10	14	69.92	0.0594
	25	11	72.50	0.0612
	50	10	83.24	0.0696
NA-HES	5	23	54.00	0.0350
	10	17	64.58	0.0579
	25	15	70.00	0.0593
	50	14	73.66	0.0694

each batch. No ammonia was detected in products when tested with Nessler's reagent.

In TLC studies NA dispersed in various carriers showed the same R_f value as pure compound and no additional spots were detected. IR spectra of NA and its solid dispersions are identical. The principal IR absorption peaks of NA were all observed in the spectra of NA as well as its dispersions. DTA thermograms of NA, D, β-CD, HES and their solid dispersions are shown in Fig. 1. In all the thermograms of NA and solid dispersions a well defined endothermic peak around 229°C corresponding to the melting point of NA was observed. The TLC, IR spectra and DTA thus indicated no interaction between the drug and carriers in the solid dispersions. The moisture absorption by the solid dispersions was found to be very low, less than 1.0% w/w indicating that they were essentially non-hygroscopic.

TABLE-2
Pharmacokinetic and Bioavailability Parameters (Mean ± s.d.) Estimated Following Oral Administration of Nalidixic Acid and its Solid Dispersions

Solid Dispersion	$t_{1/2}$ (hrs)	Cumulative amount excreted unchanged $(Xu)_\infty$ (mg)	K_a (hr^{-1})	Per cent drug absorbed upto		
				1.0 hr	2.0 hr	3.0 hr
NA	2.71 ± 0.17	59.37 ± 8.00	0.405 ± 0.116	12.68 ± 3.67	27.80 ± 9.63	39.30 ± 14.83
NA-D (9:1)	3.07 ± 0.33	66.20 ± 8.26	2.188 ± 0.096	33.89 ± 17.91	80.14 ± 15.52	100.00 ± 0.00
NA-β-CD (9:1)	3.08 ± 0.25	43.43 ± 15.74	2.048 ± 0.386	28.51 ± 6.03	62.57 ± 13.19	87.00 ± 14.69
NA-HES (9:1)	3.34 ± 0.41	46.40 ± 9.72	2.125 ± 0.157	27.75 ± 16.68	63.69 ± 28.27	81.48 ± 23.98

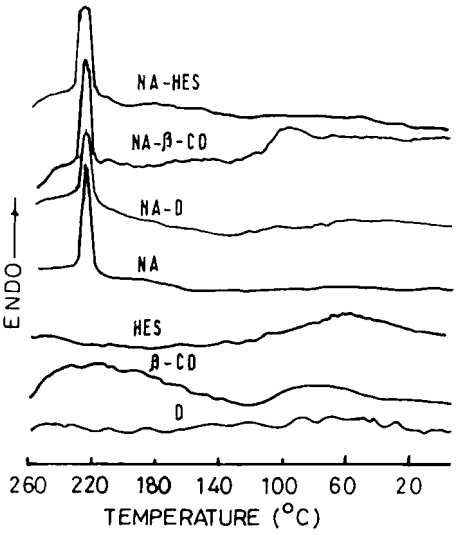

FIGURE 1

DTA THERMOGRAMS OF MODIFIED STARCHES, NALIDIXIC ACID AND THEIR DISPERSIONS (1:1).

Solid dispersions gave fast and rapid dissolution of NA when compared to pure drug and physical mixtures (Table-1). The dissolution of NA from solid dispersions obeyed Hixson-Crowell's cube root dissolution rate equation(10). With all the three carriers as the carrier concentration in solid dispersion was increased the dissolution rate also increased. Among the three modified starches studied dextrin gave highest dissolution. An eleven fold increase in the dissolution rate was observed with dextrin at 50% carrier concentration. There was considerable improvement in the dissolution efficiency of NA in the case of solid dispersions.

In X-ray diffraction studies NA exhibited characteristic crystalline diffraction patterns whereas in the case of solid dispersions the peak heights were much reduced (Fig.2) indicating that the crystallinity and crystal size of NA was much reduced in solid dispersions. Thus the increased dissolution rate in the case of solid dispersions may be due to

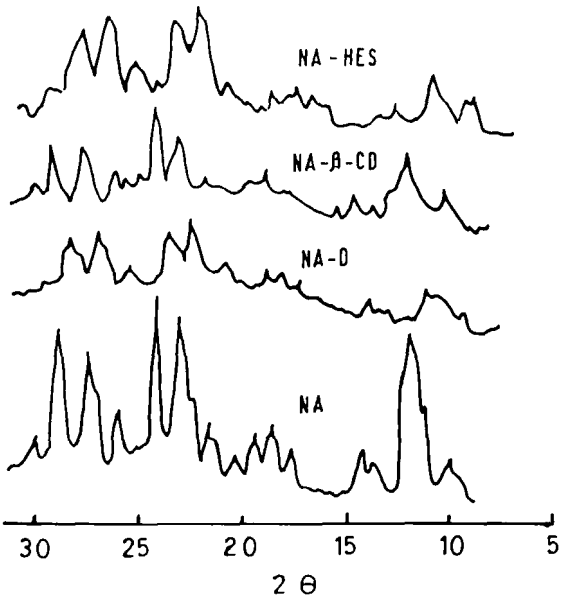

FIGURE 2

X-RAY DIFFRACTION SPECTRA OF NALIDIXIC ACID AND ITS DISPERSIONS (1:1) IN MODIFIED STARCHES.

the reduction of crystallinity and crystal size of the drug dispersed. In addition other factors like absence of aggregation and agglomeration between drug particles and good wettability and dispersibility of dispersed drug might have also contributed to the observed increase in the dissolution rate of NA from solid dispersions.

Table-2 gives the pharmacokinetic and bioavailability parameters estimated following the oral administration of NA and its solid dispersions. The biological half-life ($t_{\frac{1}{2}}$) of NA was found to be 2.71 $\pm$ 0.17 hrs. and this value was in good agreement with that of 2.7 hrs. reported in the literature (11). No significant difference was observed in $t_{\frac{1}{2}}$ of NA and its dispersions in modified starches. Thus the elimination characteristics of NA remained unaltered when it was solid dispersed in modified starches.

Absorption rate constant (K_a) and per cent drug absorbed to various times, calculated as per Wagner-Nelson method were significantly higher with solid dispersions indicating fast and rapid absorption of NA from solid dispersions when compared to pure drug. However, no significant difference was observed in $(Xu)_\infty$ of NA and its dispersions indicating that the extent of bioavailability remained the same with all the products.

CONCLUSIONS

The results of the study indicated that the modified starches dextrin, β-cyclodextrin and hydroxyethyl starch were non-hygroscopic, non-interacting carriers giving solid dispersions; effective in increasing the dissolution rate and efficiency and absorption rate of nalidixic acid, a poorly soluble drug.

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