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Formulation and Evaluation of Nalidixic acid-PEG 6000-Surfactant Systems

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The anionic surfactant sodium lauryl sulphate was incorporated in different concentrations (1%, 2% and 3%) to solid dispersions of nalidixic acid prepared using PEG-6000 as a carrier by melt-solvent method. The prepared dispersions were characterized by release studies, X-ray diffraction, infrared spectroscopy and thin layer chromatographic analysis. The effect of aging on the release of nalidixic acid was also studied. An almost instant and complete dissolution was obtained for dispersions with 1% w/w sodium lauryl sulphate than pure drug and dispersions without surfactant. The mechanism for increase in the release rate was also investigated. The results were supported by X-ray diffraction studies, which indicated a significant decrease in crystallinity of drug in all the prepared batches. These suggestions were also supported significantly by Infrared spectroscopy and thin layer chromatographic analysis of the samples. The samples were also found to possess adequate stability.

Solid dispersion has been a proven technique to improve the aqueous solubility of poorly water-soluble drugs. Various factors like poor wetting, high crystallinity of the drug, type and concentration of the inert carrier and agglomeration of particles determines the release of drug from its solid dispersions. The release mechanism of drug from PEG solid dispersions had been reviewed[1]. The addition of surfactants has been tried to improve the release rate further from its solid dispersions and to eliminate the defects in solid dispersions. The physicochemical aspects, its structure and the effect of ionic and nonionic surfactants on release from griseofulvin-PEG 6000-surfactant systems was investigated[2-4]. The release rate of poorly soluble drugs had been improved by incorporating small amounts of different surfactants to their solid dispersions[5,6] prepared with different carriers. The role of molecular weight of carrier and type of surfactant on the release of temazepam from its solid dispersions was also studied[7]. The tendency of the drugs to interact with the carrier and the effect of counter ions on interaction in griseofulvin-PEG 6000-SLS dispersions had been estabilished[8]. In present study an attempt has been made to study the effect of concentrations of anionic surfactant (SLS) on release of nalidixic acid from solid dispersions prepared with PEG-6000 as inert carrier.

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MATERIALS AND METHODS

Nalidixic acid was a gift sample from Blue Cross Laboratories and Oscar Health Care Ltd. Delhi. PEG-6000 was procured from S. D. Fine Chemicals Ltd, Mumbai. Dichloromethane and all the other chemicals used were purchased from Loba Chemicals, Mumbai.

Preparation of nalidixic acid:PEG 6000:surfactant systems:

Drug:PEG 6000:surfactant systems were prepared by melt-solvent method[9]. Weighed amount of the drug was dissolved in dichloromethane to form a solution. PEG 6000 and surfactant was melted in a china dish with stirring. The clear drug solution was gradually added to the molten poly-

mer and surfactant with continuous stirring in ice till it solidifies. The solidified mass was dried in a vacuum oven, scrapped, pulverized and passed through sieve no. 80. The procedure was repeated with different concentrations of SLS to prepare the batches. A batch of solid dispersion without any surfactant was also prepared.

Assay of solid dispersions:

An amount of solid dispersion equivalent to 50 mg of nalidixic acid was dissolved in 50 ml of 0.1 N sodium hydroxide solution. The solution was filtered, diluted suitably and absorbance determined at 258 nm and drug content was calculated.

***In vitro* dissolution study:**

Release studies of the samples were carried out in 900 ml of phosphate buffer pH 7.4 as the dissolution medium in USP Dissolution (Type-II Paddle) at 37±1° for 1h at 60 rpm. At periodic time intervals 5 ml samples were pipetted out, suitably diluted and assayed for drug content spectrometrically at 258 nm.

X-Ray diffraction and IR studies:

X-ray diffraction and Infrared spectroscopic pattern of samples were obtained using a Philips diffractometer (PW 1140) and IR spectrophotometer (Jasco, Japan), respectively. TLC analysis was conducted using silica gel coated thin glass plates as the stationary phase and a solvent mixture of chloroform, methanol, formic acid in ratio of 90:7:3 as a mobile phase to study any interaction between drug, carrier and surfactant. The R_f values of the pure drug and the batches were calculated.

Effect of ageing:

Samples of the dispersions were stored in amber glass jars with lids at room temperature (20-23°) for 1 year. After 1 year the dissolution studies were conducted by the same procedure as mentioned in methods.

RESULTS AND DISCUSSION

The drug content in all batches was found to be within the range of ± 5% of the theoretical claim. Low value of standard deviation in the data indicates the uniform distribution of drug in dispersions and the method used was found be reproducible.

From the release studies it was found that the amount released in 1 h was 40% for pure drug, 60 % for blank dispersion and an almost complete dissolution (99%) for dispersion with 1 % SLS. It was observed that the dissolution rate was found to decrease if the concentration of incorporated surfactant was increased beyond 1 %w/w of SLS. Table 1 and fig. 1 show the release data and profiles of pure drug, dispersion with and without surfactants.

TABLE 1: COMPOSITION AND RATIO OF THE SAMPLES.

BATCH	COMPONENTS	RATIO
DG	Nalidixic acid:PEG 6000	1:4
DGA_1	Nalidixic acid:PEG 6000: sodium lauryl sulphate	1:4:1%
DGA_2	Nalidixic acid:PEG 6000: sodium lauryl sulphate	1:4:2 %
DGA_3	Nalidixic acid:PEG 6000: sodium lauryl sulphate	1:4:3 %

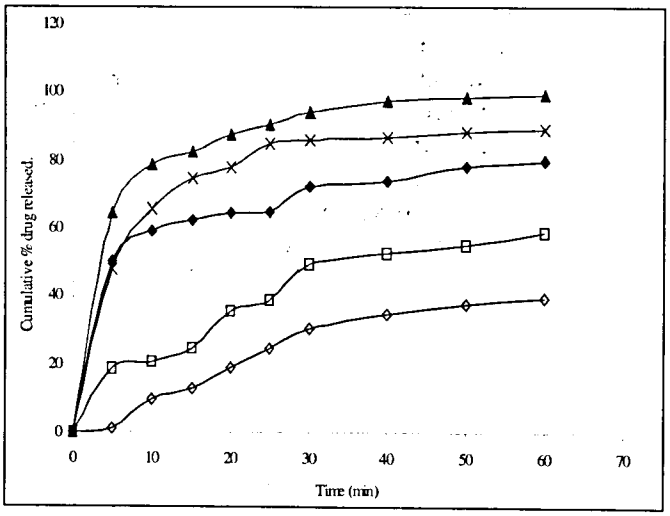

Fig. 1: Release profiles of nalidixic acid–PEG 6000-surfactant systems

Release rate profiles of (-♦-) Pure drug, (-□-) DG, (-▲-) DGA_1 (-▫-) DGA_2 and (-△-) DGA_3

The mechanism suggested for increase in release rate may be due to the formation of drug–polymer–surfactant complex or micelles, decrease in crystallinity, reduction in interfacial tension between the drug and dissolution medium by the surfactant, improved wettability of the drug particles and formation of a solid solution. Further, it was also observed that once the formation of solid solution is over with a particular concentration of the surfactant release rate tends to decrease even on increasing the concentration of surfactant. The batches with 2% and 3% SLS gave an decreased release rate than dispersion with 1% SLS confirm-

ing that the formation of solid solution is over with 1% SLS itself. The above-mentioned suggestions were well supported by the reports[4,6]

X-ray diffraction analysis was used to study the crystalline pattern of pure drug, polymer and samples. X-ray diffraction patterns of pure drug, polymer and samples indicated that the crystallinity of nalidixic acid has been significantly reduced in all the dispersions with and without surfactants (fig. 2 and 3). This finding supports the earlier suggested mechanism for increase in release rate from dispersions due to decrease in crystallinity of the drug.

IR analysis was used to study any drug-carrier-surfactant interactions. From IR data and spectra (Table 2) of pure drug and samples it was observed that a broad peak at 3050 cm^{-1} (due to carboxylic acid) was absent in all the samples with surfactant in comparison with IR spectra of pure drug. These findings clearly confirm that interaction or complexation had taken place between the drug and carrier in all samples. The presence of methyl group and N-ethyl group in the drug molecule makes the drug molecule more lipophilic and water-soluble carrier like PEG 6000 with surfactant would have assisted in the micelle formation, thereby increasing the aqueous solubility and its dissolution rate. Such interaction between drugs and carrier was supported by reports[11,12].

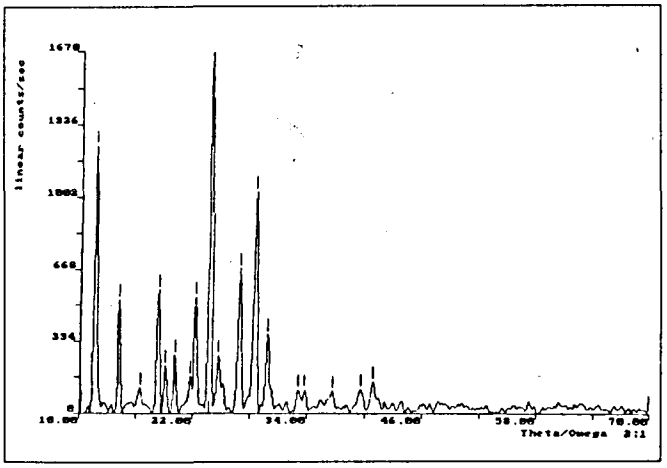

Fig. 2: X-Ray diffraction pattern of nalidixic acid.

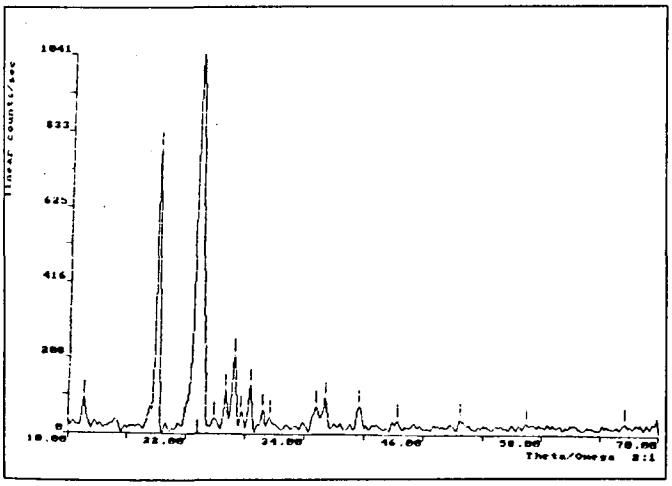

Fig. 3: X-Ray diffraction pattern of DGA_1 .

TABLE 2: IR DATA.

NA Peak cm^{-1}	Nalidixic acid – PEG 6000 – Surfactant Systems		
	DGA_1	DGA_2	DGA_3
3050	-	-	-
1715	+	+	+
1620	+	+	+

(-) Denotes absence of characteristic peaks and (+) denotes presence of characteristic peaks.

TLC analysis method was used to study the interaction theory between drug, polymer and the surfactant. Deviation in R_f values (Table 3) of the samples from pure drug clearly indicates that interaction had taken place between the drug and the carrier. It was also suggested that the added surfactants would have assisted in the interaction and thereby increasing the release rate of drug by micellar solubilisation.

The dissolution profiles fig. 4 of the stored dispersions (for 1 year at 20-23°) indicated that the release rate of dispersions with surfactant and without surfactant was found unchanged after the storage period indicating more stability under the provided storage conditions. These observations clearly suggest that the samples have adequate stability. It can be concluded that by incorporating small amount of anionic surfactants to solid dispersions prepared with carriers a significant increase in aqueous solubility of the

TABLE 3: TLC DATA .

BATCH	R_f
DGA_1	0.875
DGA_2	0.875
DGA_3	0.861
Pure Drug	0.693

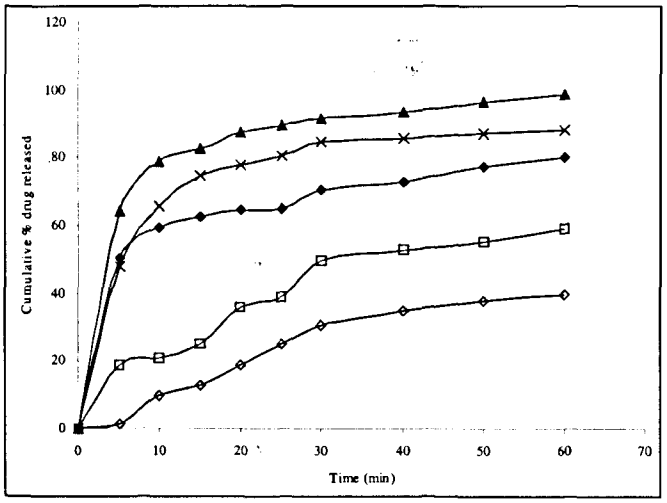

Fig. 4: Release profiles of aged nalidixic acid–PEG 6000-surfactant systems

Release rate profiles of (-♦-) Pure drug, (-□-) DG, (-▲-) DGA_1 (-□-) DGA_2 and (-△-) DGA_3

poorly soluble drugs can be achieved with much ease.

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