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EFFECTS OF SURFACTANTS ON THE DISSOLUTION RATE OF SPARINGLY SOLUBLE DRUG NALIDIXIC ACID IN SOLID DISPERSIONS

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Solid dispersions of the sparingly soluble drug nalidixic acid were prepared by solvent method with dextrin as the carrier. 1,2 and 3%w/w of each nonionic(SLS), cationic (Cetrimide) and 4, 8 and 12%w/w non-ionic surfactant (Tween-80) were incorporated during the preparation. Immediate instant and complete dissolution was obtained for dispersion with 4%w/w Tween-80, but SLS and Cetrimide had no effect on the dissolution rate when compared with the dispersion without surfactant and pure drug (drug and dextrin). Beyond certain concentration (1%SLS, 1% Cetrimide and 4% Tween-80) there was a marked decrease in the dissolution rate of nalidixic acid. IR and TLC data revealed an interaction between drug and dextrin

Keywords: *Solid dispersion; Nalidixic Acid; Surfactants; Solid Solution; Dissolution*

Introduction

Solid dispersions of drugs in easily soluble carriers can be used to increase the dissolution rate of sparingly soluble drugs. However, with an increase in drug content, the dissolution rate is normally retarded(1, 2). Nalidixic acid (NA), being an antibacterial agent, has a poor aqueous solubility (0.01 mg/ml) which results with limited absorption from GIT and its bioavailability is greatly affected.

Based on the above facts, attemts have been made through this investigation to increase the aqueous solubility and thus to increase the dissolution rate of NA. To achieve this, solid dispersions of NA in dextrin carrier were prepared and the influence of various types of surfactants on dissolution rate were investigated.

Materials

NA was a gift sample (Blue Cross Lab., Bombay), dextrin (Central Drugs Hose), sodium lauryl sulphate and cetrimide (High Purity and Chemical Pharmaceticals, New Delhi), Tween-80 (S.D. Fine Chemicals Ltd., Boisar) were obtained commercially from Indian companies and were of analytical reagent grade.

Methods

Preparation of Solid Dispersions of Nalidixic Acid: Dextrin: Surfactants: The solid dispersions were prepared by the method proposed by K.P. Choudary *et al*(3). In this method drtug, dextrin and surfactants were weighed in a proportion as shown in table 1. The dextrin and surfactants were placed into a beaker and warm water was

* Correspondence

added to form a turbid solution and then the drug was dispersed in this solution. Dilute ammonia solution was added until the solution became clear. Then the mixture was dried overnight in an oven at 60^0C. Then, further dried under vacuum at 40^0C. The solid mass obtained was scraped, pulverised and passed through sieve no 80.

IR Spectroscopy: 1 mg of solid dispersion was thoroughly blended with adequate quantity of IR grade KBr (5mg) in a mortar. The mixture was then compressed into a thin film by a lever and analysed in a double beam IR Spectrophotometer (Jasco, Tokyo, Japan) using KBr film as blank.

Table 1. Ratio of drug, carrier and concentration of surfactant incorporated in solid dispersions.

S. No	Batch Code	Carrier used	Ratio of Drug: Carrier	Surfactant*		
				Anionic (SLS)	Cationic (Cetrimide)	Non-ionic (Tween-80)
1	DDA_1	Dextrin	1:9	1%w/w	-	-
2	DDA_2	Dextrin	1:9	2%w/w	-	-
3	DDA_3	Dextrin	1:9	3%w/w	-	-
4	DDC_1	Dextrin	1:9	-	1%w/w	-
5	DDC_2	Dextrin	1:9	-	2%w/w	-
6	DDC_3	Dextrin	1:9	-	3%w/w	-
7	DDT_1	Dextrin	1:9	-	-	1%w/w
8	DDT_2	Dextrin	1:9	-	-	2%w/w
9	DDT_3	Dextrin	1:9	-	-	3%w/w
10	DD	Dextrin	1:9	-	-	-

*Surfactants were added as %w/w concentration in reference to the total weight of drug and carrier

Assay of Solid Dispersions: An amount of solid dispersion equivalent to 50 mg of NA was dissolved in 50 ml of 0.1 N sodium hydroxide solution in a volumetric flask. The solution was filtered, the filtrate diluted and analysed by UV spectrophotometer (Jasco 7800, Japan) at 258 nm.

Thin Layer Chromatography (TLC): TLC was used to study the chemical stability and interactions between drug and polymer of solid dispersions. A small amount of solid dispersion was dissolved in ammonia solution and the sample was applied to silica gel plate. Then the plate was placed in a TLC chamber containing the mobile solvent chloroform: methanol: formic acid (90:7:3). The drug was detected by iodine vapour and the Rf values of the spots were calculated.

In vitro Dissolution Studies: Dissolution tests for all the batches were carried out in triplicates in USP XIX Dissolution Rate Test Apparatus using 900 ml of phosphate buffer (pH 7.4) as the dissolution medium maintained at 37 ± 0.2^0C. An accurately weighed amount of the sample equivalent to 100 mg of NA was suspended on the surface of the dissolution medium and the paddle was stirred at 60 rpm. 5 ml of samples were withdrawn at appropriate time intervals with the help of a G_2 sintered glass filter fitted into a sampling tube. Same volume was replaced with freshly prewarmed buffer. Withdrawn samples were diluted suitably and the absorbances were measured spectrophotometrically at 258 nm,

Results and Discussions

Assay Of Solid Dispersions: The drug content in all the batches of solid dispersions were in the range of 95-105% (Table 2) which ensures that the drug content variation was ±5%, indicating the uniformity of the solid dispersions.

Table 2. Assayed drug content of solid dispersions (Drug-dextrin –surfactant).

S.No	Batch code	Theoretical drug content		Assayed drug concent	
		Amount (mg)	Expressed as %	Amount (mg)	Expressed as %
1	DDA_1	5	100	4.88	97.6
2	DDA_2	5	100	5.25	105.00
3	DDA_3	5	100	5.16	103.2
4	DDC_1	5	100	4.8	96.00
5	DDC_2	5	100	4.78	95.60
6	DDC_3	5	100	4.8	96.40
7	DDT_1	5	100	5.16	103.20
8	DDT_2	5	100	5.16	100.80
9	DDT_3	5	100	5.21	104.20
10	DD	5	100	4.79	95.80

*Average of 3 assays Limit of druf content in solid dispersion = ±5% of theoretical drug content

IR Spectroscopy: In case of pure drug a weak and broad peak was observed at 3050 cm^{-1} in IR spectra indicating that hydrogen bonding with carbonyl group may be present (COOH-OH bond). But the IR spectral data shown in table 3 indicates that any peak at this position was absent for all the batches. Including the batch without surfactants(DD). This indicates that interaction might have taken place between drug and the carrier.

Table 3. IR data of drug-dextrin –surfactant system.

NA peak positions cm^{-1}	Drug-dextrin-surfactant systems									
	DDA_1	DDA_2	DDA_3	DDC_1	DDC_2	DDC_3	DDT_1	DDT_2	DDT_3	DD
3050	-	-	-	-	-	-	-	-	-	-
1715	+	+	+	+	+	+	+	+	+	+
1620	+	+	+	+	+	+	+	+	+	+

- Absent + Present

Thin Layer Chromatography: The R_f values (Table 4) of the prepared batches were higher when compared with those of the pure drug. The different concentrations of surfactants did not exhibit any significant effect on the R_f value for all prepared solid dispersions. From the IR data it was evident that interaction had taken place between drug and carrier in the formulation. The R_f values calculated also confirmed this fact.

Table 4. TLC data of drug-dextrin –surfactant system.

S. No	Batch code	R_f values
1	Pure drug	0.658
2	DDA_1	0.763
3	DDA_2	0.750
4	DDA_3	0.763
5	DDC_1	0.736
6	DDC_2	0.736
7	DDC_3	0.723
8	DDT_1	0.698
9	DDT_2	0.782
10	DDT_3	0.792
11	DD	0.786

In-vitro Dissolution rate

Drug: Dextrin: Surfactant (anionic) systems: The cumulative % dissolution profiles for solid dispersion with 1,2 and 3%w/w of SLS in comparison with that of pure drug and dispersions without surfactant are shown in fig. 1. Dispersion with 1%w/w SLS showed a dissolution of 89.59% in 60 minutes which was not much increased when compared with that of dispersion without surfactant(DD). Dispersion with 2 and 3% w/w of SLS exhibited a decreased rate and extent of drug dissolution as compared to dispersions containing 1%w/w SLS indicates that increasing surfactant concentration would not necessarily increase dissolution.

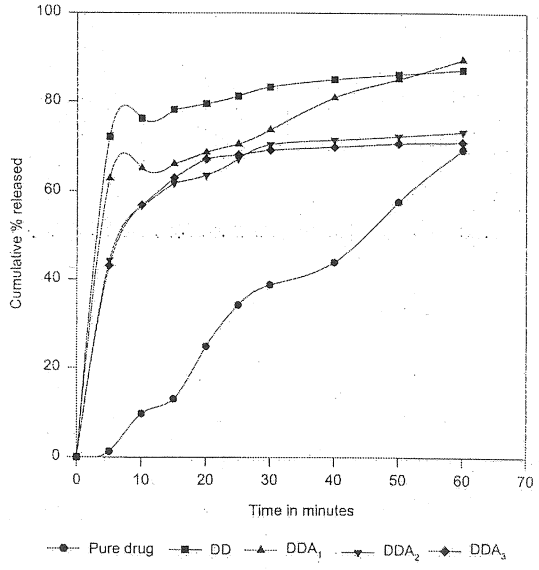

Fig. 1. In vitro drug release profiles showing the effect of different concentrations of anionic surfactants.

Drug: Dextrin: Surfactant (cationic) systems: The cumulative % dissolution of dispersions with 1,2 and 3% w/w of surfactant (Cetrimide) was compared with that of pure drug and dispersions without surfactants and are shown in Fig. 2. Dispersions with 1 and 2%w/w cetrimide provided 81.85% and 81.25% of drug dissolution in 60 mts respectively, which are marginally less when compared with the dispersion without surfactant (87.28% in 60 mts). However the cationic surfactant cetrimide at 3%w/w concentration significantly reduced the extent of dissolution as compared to solid dispersion without surfactant.

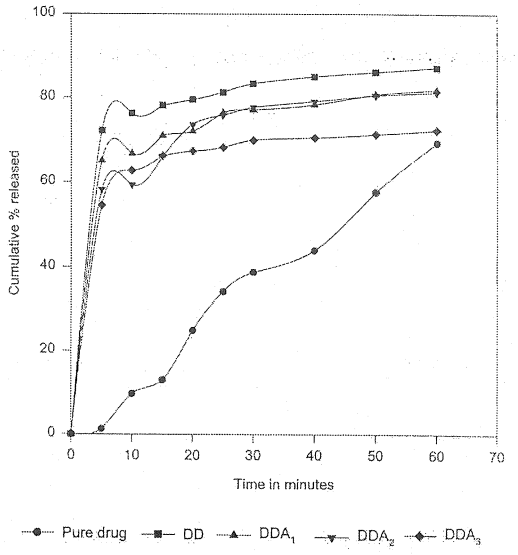

Fig. 2. In vitro drug release profiles showing the effect of different concentrations of anionic surfactants.

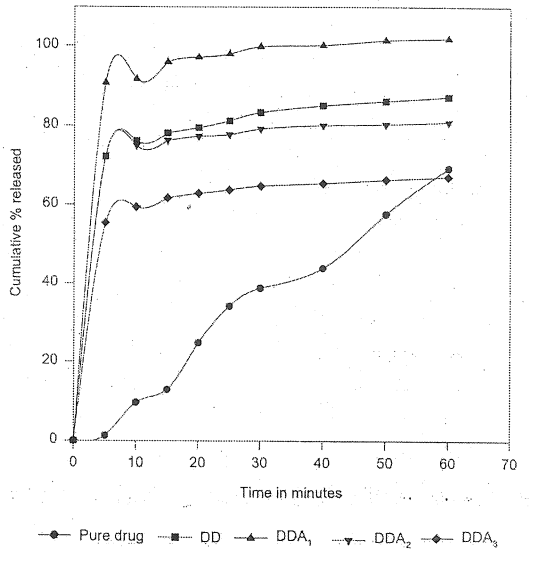

Fig. 3. In vitro drug release profiles showing the effect of different concentrations of anionic surfactants.

Drug: Dextrin: Surfactant (non-ionic) systems: Dispersions with 4%w/w of Tween-80 provided a complete dissolution (101.91 %) in 60 mts. This was much higher in comparison to dispersion without surfactant (87.26%). The surfactant used might have helped in the formation of micelles by forming solid solution as suggested by Chiou and Niazi(4). However dispersions with 8 and 12%w/w of Tween-80 exhibited a decreased dissolution rate confirming that the formation of solid solution had occurred in dispersions with 4%w/w of Tween-80 itself. This was supported by the reports of Corrigon (5) and Fernandez(6).

Conclusion

In the NA: dextrin solid dispersion system the additions of anionic and cationic surfactants were ineffective in increasing the dissolution of the drug. However, the addition of non-ionic surfactant (Tween-80) in low concentrations (4%w/w) provided a complete dissolution. It indicates that non-ionic surfactants can be used in low concentrations in solid dispersions (NA: Dextrin) to increase the solubility of poorly water soluble drugs like NA.

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