CURRENT RESEARCH

THE ROLE OF SURFACTANTS AND POLYMERS ON THE SOLUBILITY OF NIFEDIPINE

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ABSTRACT:

Nifedipine is a calcium antagonist used in the management of hypertension. The drug is practically insoluble in water. In this study, the solubility of the drug in various surfactant solutions and polymer solutions have been investigated at three different temperatures, 28°C, 37°C and 45°C±0.5°C.

The solubility of nifedipine was found to increase in the presence of surfactants and polymers. The solubility curves in surfactant solutions were biphasic with the points of inflexion corresponding to the critical micelle concentrations of the surfactants. The dissolution of nifedipine compacts was also enhanced in ther presence of the surface active agents and polymers.

Introduction:

Nifedipine is one of the most potent calcium antagonists in clinical use and was introduced for the management of hypertension and ischaemic heart diseases (1, 2, 3). The availability of nifedipine from oral dosage forms and rectal dosage form is about 40 — 60% due to prersystemic metabolism (4). The absorption of nifedipine when administered in oral solid dosage forms is said to be inferior because of its very poor water solubility (5).

Absorption from the gastrointestinal tract is thought to be aided by some physiological surfactants which have been confirmed to be present in the gastrointestinal tract (6). Numerous reports abound on the effect of various dissolution media on the release and dissolution of drugs. The incorporation of surface-active agents in tablets was reported to improve disintegration (7). The inclusion of a surface-active agent in the dissolution medium was reported to increase the dissolution of powdered drugs and their tablets (8 and 9).

Surface-active agents may enhance disintegration by a reduction of interfacial tension which promotes wetting and penetration of the liquid into the tablet. Surface-active agents may enhance dissolution process of a poorly soluble drug in a tablet by a reduction of interfacial tension and micelle formation. In the present study we have investigated the effect of different surfactants and polymers on the solubility of nifedipine powder as well as the dissolution of its compacts with the hope of determining the most suitable system that would aid maximum drug absorption and minimal presystemic drug degradation.

Materials and Methods

Materials —

Nifedipine powder was a generous gift from Bayer Pharmaceuticals (Nig.) Ltd. Lagos. Cetrimide, Sodium lauryl sulphate, Polyethylene Glycol (PEG 1000, 4000), Hydrochloric acid, Methanol and Lactose powder were all products of British Drug Houses (BDH) and were used as received without further purification. Spectrophotometric measurements were carried out with a Pye Unicam SP8-100 double beam spectrophotometer.

Methods —

A calibration curve for nifedipine in methanol-water mixture (10%v/v) was made within the concentration range 10µg/ml — 100µg/ml and absorbances determined at 340 nonameter wavelength.

Critical Micelle Concentration (CMC):- Various concentrations of surfactant solutions — cetrimide 0.01 — 0.2%; sodium lauryl sulphate 0.5 — 1.0%; polyoxyethylene sorbitan monolaurate (Tween 20) 2.5 — 5.00×10^{-4}%, were prepared and allowed to equilibrate for about 24h at a constant temperature of 26°C. Surface tension determinations were then carried out in triplicate using a surface tension balance.

Solubility Studies:- The solubility of nifedipine in various surfactants and polymer solutions at three different temperatures 28°C, 37°C and 45°C was determined employing the following procedure — 1ml of nifedipine solution, 1mg/ml (in methanol), was introduced into a clean sample bottle and the solvent evaporated over a stream of nitrogen. The pure crystals of nifedipine produced were transferred into a clean test tube into which was now introduced different concentrations of surfactants and polymer solutions; cetrimide, 0.02 — 0.1%w/v; sodium lauryl sulphate, 0.1 — 0.5%w/v; Tween 20, 10 — 200×10^{-4}%w/v; Polyvinyl pyrollidone (PVP), 0.02 — 1.00%w/v; Polyethylene glycol 1000, 0.1 — 2.5%w/v; Polyethylene glycol 4000, 0.1 — 2.5%w/v. The test tubes were covered with screw caps, shaken with the aid of automatic shaker for 30 min and then incubated separately at 28°C, 37°C and 45°C for 24h in a rocking water-bath. At the end of this period the content of each tube was filtered and the absorbance of the clear filtrate (after serial dilution where necessary) determined at 340nm wavelength.

Dissolution Studies:- The dissolution characteristics of nifedipine compacts containing 20mg nifedipine powder and 100mg of lactose prepared in a single punch tablet press with a compaction pressure of 7 KgF were

determined in 0.1N HCl at 37°C containing either 0.2%w/v of sodium lauryl sulphate or 0.05%w/v of cetrimide or 0.005%w/v of Tween 20 or 2.0%w/v of PEG 1000 or 1.5%w/v of PEG 4000 using the USP (1985) rotating basket method.

Results and Discussion

A typical plot of surface tension against surfactant concentration is shown in Fig. 1 for cetrimide. The point of inflexion indicates the concentration at which the surfactant molecules begin to form micelles. The approximate critical micelle concentrations for all the surfactants used are as follows:

Sodium lauryl sulphate	0.20%w/v
Cetrimide	0.05%w/v
Tween 20	0.005%w/v

The effect of surfactants and polymeration and temperature on the solubility of Nifedipine powder is shown in Fig. 2 (a,b) for cetrimide and polyvinyl pyrollidone. Nifedipine is insoluble in pure water. However the solubility is improved in the presence of surfactants and polymers. For the surfactants, the curves are biphasic with the points of inflexion corresponding to the critical micelle concentration. The increase in solubility before the critical micelle concentration of the surfactants can be attributed to their surface properties. The surfactants reduce the contact angle of Nifedipine in the vehicle and therefore aid in its wetting. The molecules of the surfactant absorb at the Nifedipine/water interphase and reduce the tension at this interphase and hence promoting wetting of Nifedipine.

At the critical micelle concentration, the surfactants form micelles which arise from the aggregation of molecules containing distinct regions of hydrophilic and lipophilic characters which trap the drug molecules and thereby apparently increasing the solubility.

Admixtures of polymers and water increased the solubility of Nifedipine. These polymers act as cosolvents and often have a high capacity for materials with poor water solubility. This is similar to the results obtained by Groves and coworkers (10) in the solubility studies of 17-B-oestradiol using polyethylene glycol 400.

Increase in the remperature of the solubilizing systems produced a corresponding increase in the solubility of Nifedipine. There were no abrupt changes in the solubility. curves as temperature increased showing that there were no changes in the nature of Nifedipine as the temperatures were altered.

The dissolution profiles are shown in Fig. 3 (a, b). The time required for 10 per cent of the drug to be dissolved (t_{10}) was observed to be 10min., 15min. and 20min. for cetrimide, Sodium lauryl sulphate and Tween 20 respectively; and 15 min, 20min. and 25min, for Polyethylene glycol 1000, Polyvinyl pyrollidone and Polyethylene glycol 4000 respectively. Nifedipine is not soluble in water. This study has therefore shown that the solubility and the bioavailability of Nifedipine could be improved by the use of surfactants and polymers. The data available from this work act as a guide in the choice of solubilizing agent in the reformulation of Nifedipine if need be (Reformulation of Nifedipine with surfactants and polymers was not done in this study due to the high cost of pure powder of Nifedipine required). However, it must be emphasized that the acceptance of any particular solubilizing agent is dependent also on other factors that determine its suitability for internal use, prominent among these factors include possible interaction with preservative thereby decreasing preservative action as well as toxicity. The water soluble nonionic surfactants are widely preferred in formulations intended for internal use.

Conclusion

All the surfactants and polymers studied were found to greatly increase the solubility of Nifedipine. This result implies that the incorporation of surface active agents and polymers in Nifedipine tablets is likely to enhance the solubility, dissolution and hence biovailability of Nifedipine from the tablets.

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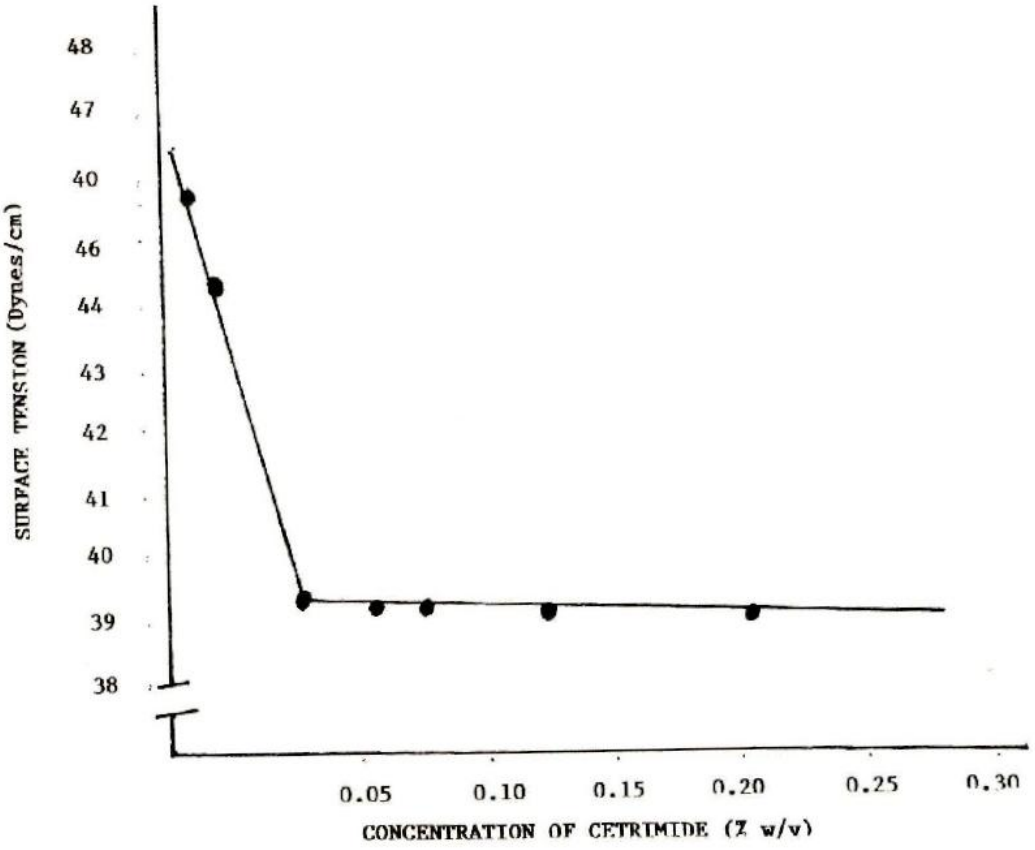

FIG.1 RELATIONSHIP BETWEEN SURFACE TENSION AND SURFACTANT CONCENTRATION

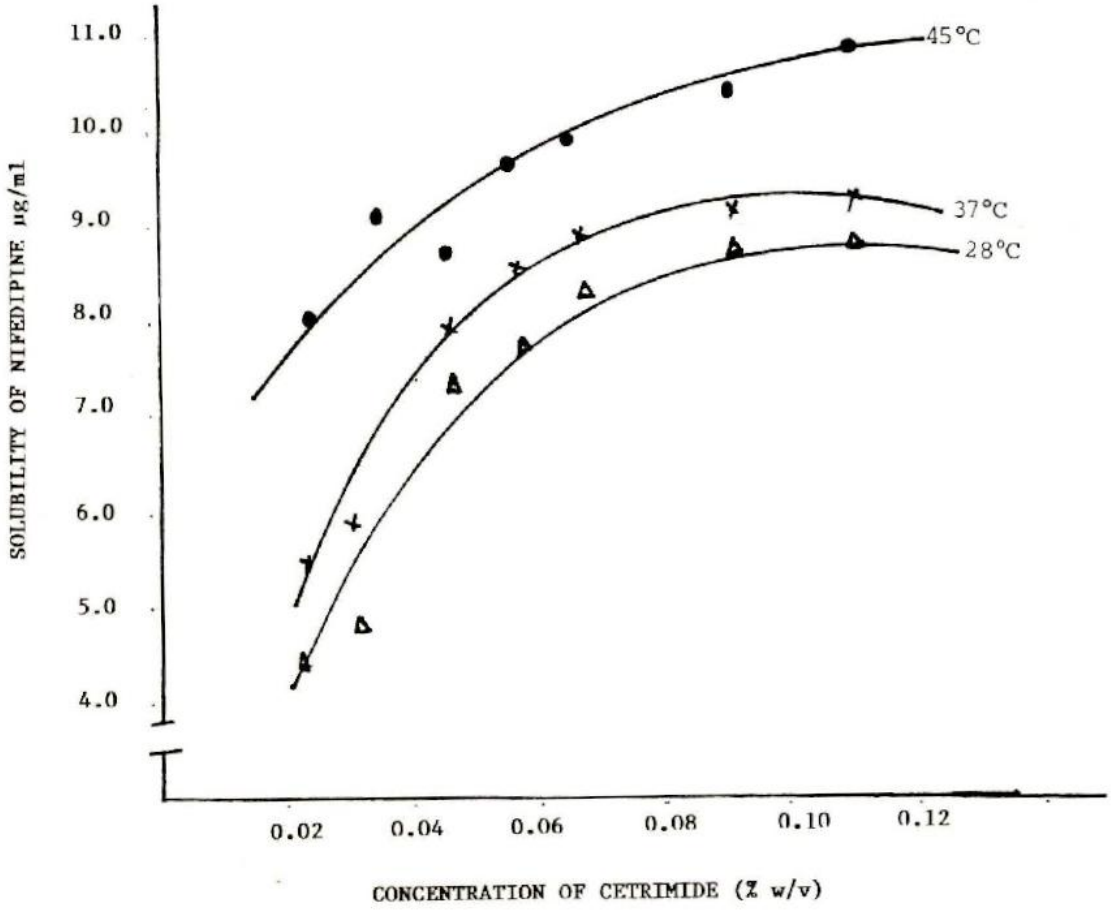

FIG.2a: SOLUBILITY OF NIFEDIPINE VS CONCENTRATION OF CETRIMIDE

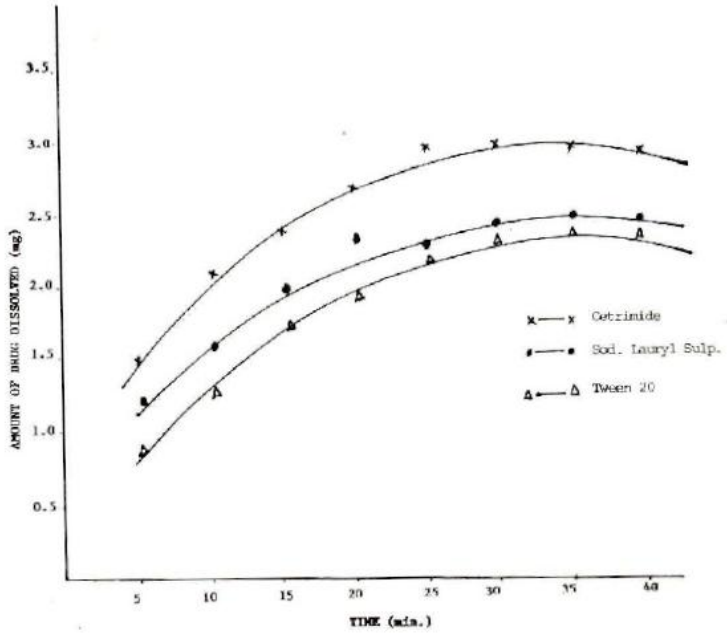

FIG.3a: DISSOLUTION PROFILES OF NIFEDIPINE IN SURFACTANT - WATER MIXTURE

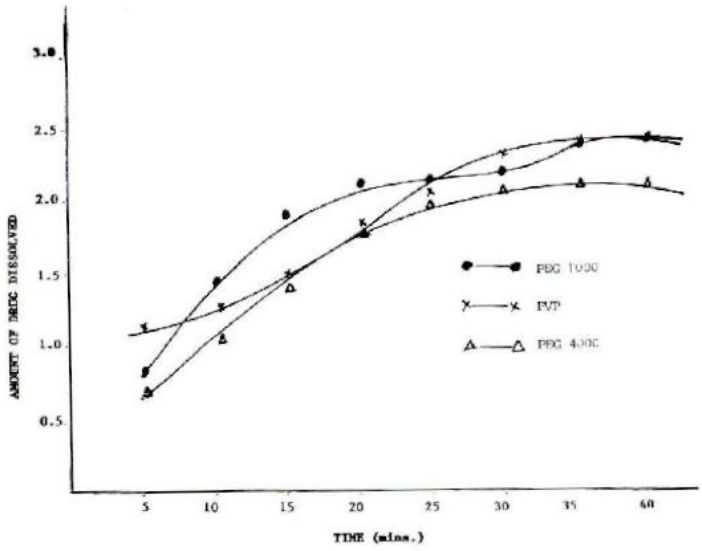

FIG.3b: DISSOLUTION PROFILES OF NIFEDIPINE IN POLYMER - WATER MIXTURE

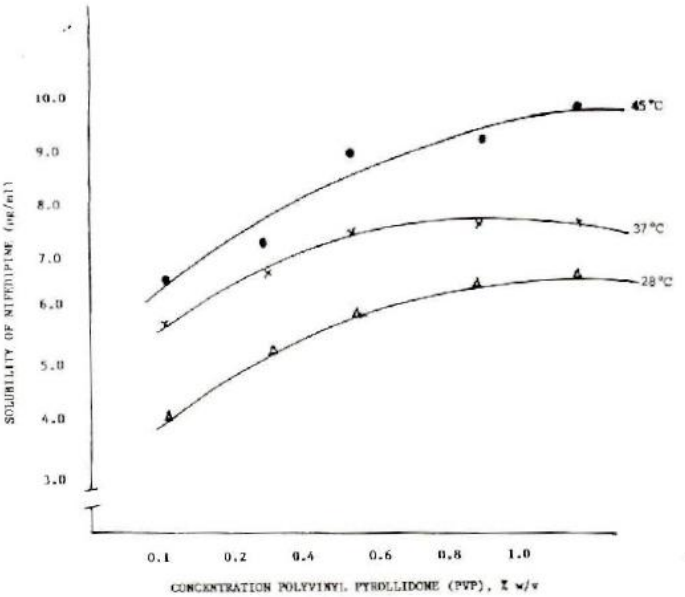

FIG. 2b: SOLUBILITY OF NIFEDIPINE VS CONCENTRATION OF POLYVINYL PYRROLLIDONE