
Release Enhancement and Reduction in Ulcerogenicity of Naproxen by Polyvinylpyrrolidone

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Solid dispersion of naproxen (NPX) was prepared with polyvinylpyrrolidone (PVP) by solvent method. The spectroscopic studies of the dispersion indicated the interaction of NPX with PVP mainly through hydrogen bonding between the carboxylic acid group and the nitrogen of the pyrrolidone ring of PVP. Aqueous solubility of NPX was found to increase with a corresponding increase in PVP levels. A marked increase in drug release was also observed. It was found that NPX:PVP complex system in a dose corresponding to NPX, 29 mg/Kg p.o., exhibited ulcer protecting effect in rats.

Naproxen [(+)-6-methoxy- α -methyl-2-naphthalene acetic acid], is a frequently prescribed non-steroidal anti-inflammatory agent (NSAIDs) with antiinflammatory, analgesic and antipyretic properties. Its efficacy is offset by significant incidence of gastrointestinal ulceration. The principal limiting side effect of acidic NSAIDs is the gastrointestinal damage which occurs as a result of dual insult¹. This effect is further aggravated due to poor dissolution of the drug in stomach. The enhancement of drug dissolution through dispersing it in a water soluble polymer matrix such as, PVP is well established²⁻⁵. Various mechanisms such as, formation of a high energy complex⁶⁻⁸, coacervate formation⁹ and molecular dispersion² have been reported for increasing the dissolution of NPX. This paper communicates the effect of PVP (mol. wt. 40 000) on the dissolution characteristics and ulcerogenicity of NPX by the solid dispersions of NPX and PVP prepared by the solvent evaporation technique.

MATERIALS AND METHODS

Naproxen (NPX) was gifted by Rallis India Ltd., India and Polyvinylpyrrolidone (PVP; mol. wt. 40 000) was purchased from Loba chemie, India. All other chemicals

were of analytical or reagent grade.

Solubility determinations:

An excess of NPX (200 mg) was added to 15 ml water or solutions of varying levels of PVP in 25 ml flasks which were shaken horizontally at 70 strokes/min at 37 \pm 1 $^{\circ}$ for 24 h. The supernatant liquid, after filtering through a membrane filter (0.8 μ), was diluted with an appropriate portion of 0.1N HCl and mixed for 2 min and subsequently analysed with reference to the standard solution of NPX at 271.1 nm. Each measurement is the mean of duplicate determinations.

Preparation of the solid dispersions:

NPX-PVP solid dispersions (1.5:1, 1:1 and 1:1.5 w/w) were prepared by dissolving the required amount of each, in a minimum volume of chloroform. The solvent was then removed under vacuum, pulverised and sieved through # 150 μ m screen, after storing overnight at - 10 $^{\circ}$.

Dissolution studies:

The release of the drug from the complex systems (equivalent to 100 mg NPX) were determined using 900 ml of 0.1N HCl as the dissolution medium at 37 \pm 1 $^{\circ}$ using USP apparatus II (paddle method). The paddle speed was

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maintained at 100 rpm. At suitable time intervals, 5 ml of the sample was withdrawn, filtered and replaced with 5 ml of fresh dissolution medium. The drug content was determined spectrophotometrically (Milton Roy Spectronic 1201, USA) at 271.1 nm.

Instrumental methods of analysis:

IR spectra (Model 882, Perkin Elmer, USA) were recorded using KBr pellets. ^1H NMR spectra were obtained on Varian EM 390-NMR (90 MHz) spectrometer using tetramethylsilane as the internal standard and CDCl_3 , DMSO-d_6 as solvents.

Ulcerogenic activity:

Male albino rats (120-170 g), fasted for 36-48 h, were randomly divided into five groups, each consisting of a minimum of five rats. An aqueous suspension containing 29 mg/kg of NPX, or its equivalent of NPX-PVP dispersion system or their physical mixture, or PVP or placebo was administered orally, twice a day over a period of 2 days. During this period no food or water was allowed. On the day after the final dose, after sacrificing the animals, the stomachs were removed, opened along the length of greater curvature and cleaned of debris. Gastric mucosal damage was examined by focusing under a dissecting microscope (10X) scored according to the severity of damage. A lesion index was computed for each by counting the number of lesions (x) in each of different size classes (y) and adding the products of x and y. Statistical analysis of the data was performed by students t-test and the values of $p < 0.05$ were considered to be statistically significant.

RESULTS AND DISCUSSION

It is evident from dissolution profiles (Fig. 1) that the release of NPX *in vitro* is significantly enhanced by the NPX-PVP systems at all time intervals studied ($p < 0.05$). At 10, 30 and 60 min, NPX-PVP complex (1.5:1) system released the active ingredient 5-, 3- and 2-times, respectively as rapid as than the drug alone, which might imply a better bioavailability. The enhanced dissolution rate of the dispersion is in direct correlation with its increased solubility (C_s) in the same vehicle. However, the initial drug release from NPX-PVP system (1:1 and 1:1.5) was slower as compared to that of the former. This might be due to the variation in particle size and stickiness of these dispersions. As a rule, solubility of the drug

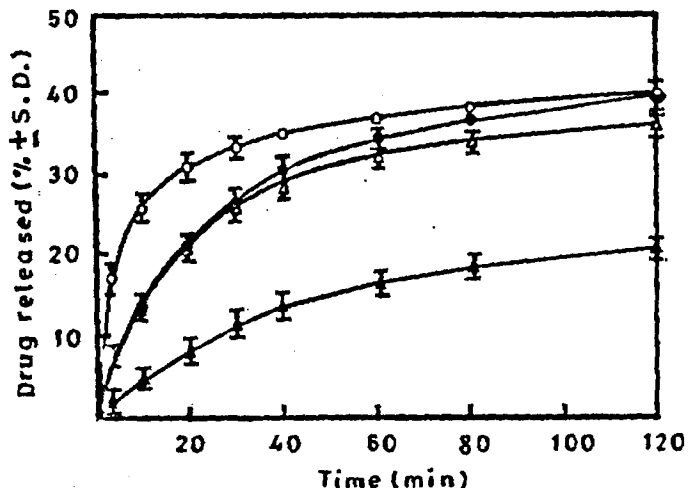


Fig. 1 : Percentage naproxen released from naproxen : PVP complex systems 1.5:1 (O) ; 1:1 (Δ) ; 1:1.5 (\bullet) and naproxen (\blacktriangle).

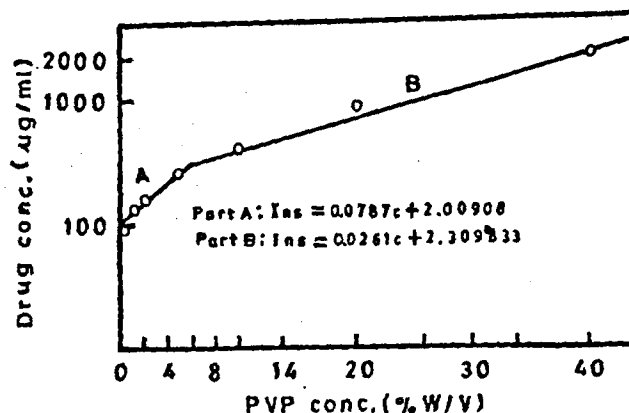


Fig. 2 : Solubility profile of naproxen versus PVP concentration

increased with a corresponding increase in PVP levels (Fig. 2).

The estimated water solubility of NPX ($S_{\text{WA}} = 91.03 \mu\text{g/ml}$) is in reasonable agreement with the literature¹⁰ value ($>10,000$) suggesting that the first part of the curve is due to the solubility of NPX in water containing PVP. The inflection point in the solubility curve is perhaps due to the nonavailability of free water in the solubilizing system.

NPX-PVP complex system (1.5:1) was chosen for ulcerogenic activity, because of its marked increase in drug release. As shown in Fig. 3, coadministration of PVP with NPX did not markedly affect the ulcerogenic effect of NPX (ulcer index was 69.6 and 64.1 for NPX alone

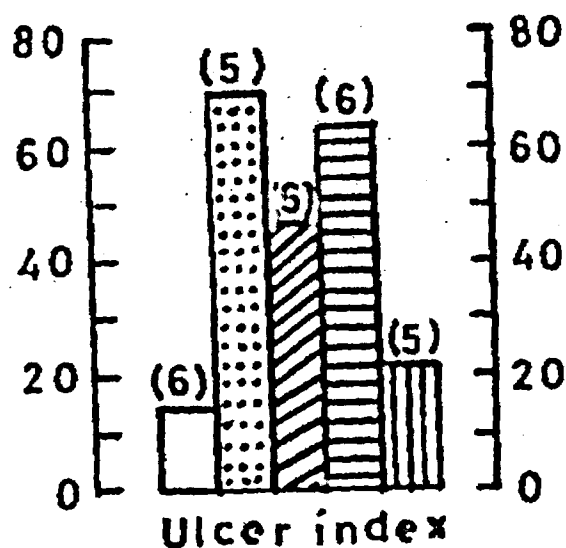


Fig. 3 : Effect of drugs on ulcer index in rats. Number of animals used for each experiment denoted in percentheces. Bars indicate (□) control, (◻) naproxen, (▨) naproxen : PVP (1.5:1) complex system, (▩) naproxen and PVP (physical mixture) and (▧) PVP, respectively.

and NPX plus PVP, respectively). However, its solid dispersion with PVP showed a significant effect ($p < 0.05$) in reducing gastric ulcers (ulcer index was reduced from 69.6 to 47.3) against drug alone. In addition, the presence of blood in the rectum, which might be due to the hemorrhaging ulcers, was observed in some rats treated with NPX alone. A low solubility of NSAIDs, which delays absorption¹¹ results is gastric irritation and bleeding from the erosive action of the crystals of the drug or possible from its acidity¹². A reduction in the ulcer index of the solid dispersion with PVP might be due to masking of the free carboxyl group of NPX which is responsi-

ble for gastrointestinal damage and enhanced solubility (0.094 mg/ml) from the dispersion, as compared to that of NPX alone (0.039 mg/ml) in 0.1 N HCl. The results are consistent with the observations reported for NPX- β -cyclodextrin complex¹³⁻¹⁴.

From these findings, it can be concluded that NPX interacts with PVP mainly through hydrogen bonding between the carboxylic acid group and the nitrogen of the pyrrolidone ring of the polymer as indicated from IR and NMR spectral studies. The use of NPX-PVP complex system may be advantageous compared to NPX alone.

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