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Increasing bioavailability of nifedipine from matrix granules prepared using macrogol and trilaurin [1]

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Summary

New nifedipine (NP) granules prepared using macrogol 1540 (M-1540) as a water-soluble drug carrier to improve dissolution behavior of NP in water, and a triacylglycerol, trilaurin, as a digestive (lipase-sensitive) material creating a dosage vehicle having a pH-independent dissolution profile of NP in intestinal juice, were investigated. In the dissolution test in vitro, the dissolution percentages of NP from the macrogol-trilaurin matrix granules for 2 h at pH 1.2 were very low (less than 10%), while NP from these matrix granules in pH 6.4 phosphate buffer solution (PBS) containing lipase and cholic acid was almost completely dissolved (close to 100%). The mean value of the area under the plasma NP concentration-time curve (AUC) obtained following oral administration of NP granules in rabbits was significantly ($p < 0.05$) higher (approx. 3 times) than that of the AUC in the case of NP powder. A preparation of NP matrix granules using macrogols and trilaurin may therefore provide a useful approach to achieving high bioavailability and delayed-release characteristics.

Nifedipine (NP), one of the most potent calcium antagonists in clinical use, has been successfully given to patients with ischemic heart disease (Dunn et al., 1979; Ellrodt et al., 1980), hypertension (Thibonnier et al., 1980; Aoki et al., 1982), etc. However, it is well known that gastrointestinal absorption is poor when NP is administered orally in a solid dosage form (Duhm et al., 1972) due to its very low solubility in water. In recent years, water-soluble NP preparations using hydrophilic polymers such as polyvinylpyrrolidone (PVP) and hydroxypropylmethylcellulose (HPMC) have been developed (Sugimoto et al., 1982). Rapid absorption of NP is attained with good bioavailability by oral administration of these dosage forms. On the other hand, NP is rapidly eliminated from the plasma compartment (Foster et al., 1983) and its pharmacological effects last only a few hours (Thibonnier et al., 1980). It is

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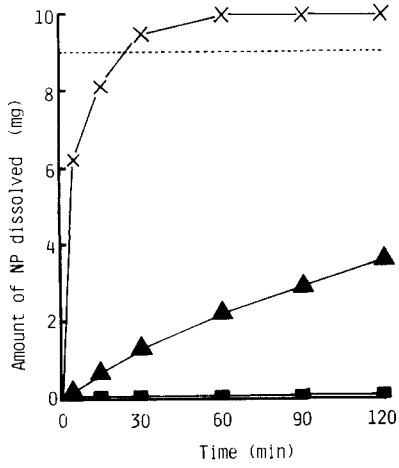

Fig. 1. Dissolution profiles of NP from powdered form and granules prepared using macrogols (1540 and 20000) or trilaurin in water. Amount of NP in each preparation was 10 mg. Results are expressed as the mean of three experiments. The dotted line indicates the level of NP solubility in water. (▲) Powder; (×) macrogol granule; (■) trilaurin granule.

therefore necessary and desirable to develop an alternative oral dosage form which allows for prolonged absorption of NP.

Attempts to develop sustained-release NP preparations, such as granules prepared using ethylcellulose (EC), hydroxypropyl methylcellulose phthalate (HPMCP) and microcrystalline cellulose (Kohri et al., 1986), and solid dispersions or coprecipitates obtained from NP with enteric-coating agents such as a methacrylic acid-methacrylic acid methyl ester copolymer (Hasegawa et al., 1985a,b) have been reported. Two types of sustained-release granules with pH-dependent or pH-independent release characteristics have been investigated.

Macrogols have been successfully used as a water-soluble drug carrier to increase the dissolution rate and solubility of poorly water-soluble drugs (Chiou and Riegelman, 1971). In our preliminary experiments, macrogol (1540 and 20000) granules containing NP were prepared by the fusion method. As shown in Fig. 1, improved dissolution behavior (rapid dissolution rate and supersaturation phenomenon from the granules) in water was observed in an in vitro dissolution test using a procedure similar to the paddle method described in JP XII (dissolution medium: 900 ml, 37 ± 0.5°C, 150 rpm). However, this preparation was insufficient to prolong NP release. Recently, we successfully developed enteric aspirin granules sensitive to lipase in intestinal juice, using acylglycerols such as monostearin and trilaurin (Watanabe et al., 1990, 1991). Trilaurin, a triacylglycerol (water-insoluble material) digested by lipase (lipase-sensitive) in intestinal juice, can prevent the dissolution of drugs from its matrix in water (Fig. 1). To create an oral dosage vehicle having a pH-independent dissolution profile for NP (NP cannot be dissolved from vehicle in the low-pH region, while NP is dissolved from vehicle following digestion by lipase in intestinal juice), we investigated macrogol-trilaurin matrix granules containing NP in vitro and in vivo.

All experiments were carried out in a dark room, in view of the high sensitivity of NP to light (Ebel et al., 1978; Jakobsen et al., 1979; Sugimoto et al., 1981). The process of granule preparation was as follows: A sample of 25 g of macrogol 1540 (M-1540, Wako Pure Chemicals, Osaka, Japan; m.p. approx. 42°C) was melted in a glass beaker at approx. 80°C with heating by hot water. NP (JP XII) powder (5 g) was mixed well with melted M-1540 for approx. 20 min. After NP has completely dissolved in M-1540, 20 g of trilaurin (Tokyo Kasei Kogyo, Tokyo, Japan; m.p. approx. 45°C) was added and the mixture was stirred well for 5 min. This mixture was then cooled by stirring at room temperature until aggregated NP-M-1540-trilaurin masses were formed. The masses formed were crushed in an electric mill, and the crushed NP-M-1540-trilaurin mass was obtained by sieving the products through 12–42 mesh; thus, M-1540-trilaurin matrix granules containing NP were prepared in this manner.

Fig. 2 illustrates the dissolution profiles of NP (10 mg) from the preparations in 900 ml of pH 1.2 solution (the first fluid for the disintegration test, JP XII), pH 6.4 phosphate buffer solution (PBS), and PBS containing pancreatic lipase (EC 3.1.1.3, Sigma Chemical Co., St. Louis, MO, U.S.A.) and cholic acid (Sigma Chemical Co., St. Louis, MO, U.S.A.), as described in our previous report (Watanabe et al., 1990). In the case of the M-1540-trilaurin matrix granules, the dissolution

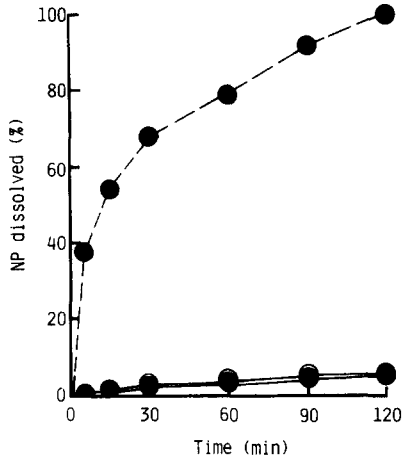

Fig. 2. Dissolution of NP from matrix granules (containing 10 mg of NP) prepared using M-1540 and trilaurin at pH 1.2 and 6.4 in vitro. Results are expressed as the mean of three experiments. Dissolution medium: (○———○) pH 1.2 aqueous solution; (●———●) PBS (pH 6.4); (● - - ●) PBS containing lipase (0.6%(w/v)) and cholic acid (0.1% (w/v)).

percentage of NP was very low (approx. 5% at 2 h) in both dissolution media at pH 1.2 and 6.4. Trilaurin markedly decreased the dissolution rate of NP from the macrogol granules. On the other hand, when lipase (0.6%) and cholic acid (0.1%) were added to the dissolution medium at pH 6.4 (Watanabe et al., 1991) the dissolution percentage increased considerably (represented by the broken line with filled circles) and a very high percentage (almost 100%) after 2 h was achieved. The increased percentage (100%) was approx. 20-times higher than that observed after 2 h in PBS without lipase and cholic acid. Lipase appears to play an important role in the digestion of trilaurin in the matrix granule. Consequently, delayed-release action of NP from the matrix granules could be expected.

These NP granules were orally administered to male rabbits (Japan White, weighing approx. 3.5 kg), and plasma NP concentration-time curve profiles were compared between the powdered form and granules. Prior to each experiment, the 'stomach-emptying-controlled rabbits' (Maeda et al., 1979) were controlled by fasting for 24 h with a slight modification. NP powder (10 mg) or M-1540-trilaurin matrix granules containing 10 mg of NP were encapsulated in hard gelatin capsules (JP XII, no. 3), and each capsule was administered orally by gastric intubation. Immediately after administration, rabbits were given 5 ml of water. 2-ml blood samples were taken from the auricular vein at predetermined intervals. NP in

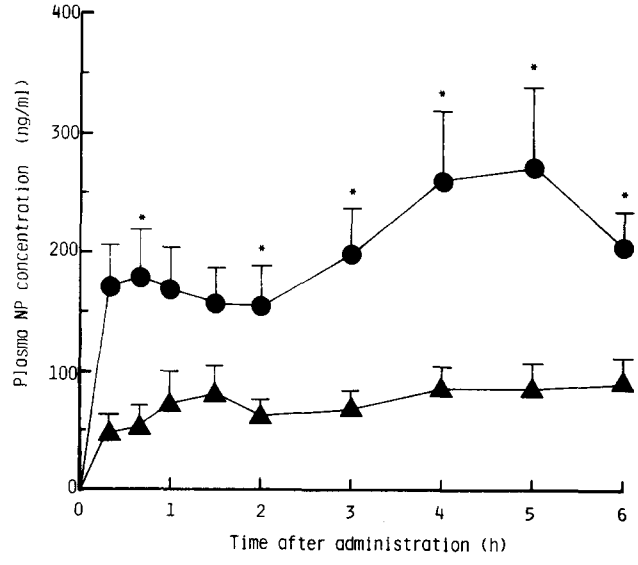

Fig. 3. Mean plasma NP concentration-time curves following oral administration of capsule containing NP-M-1540-trilaurin matrix granule or NP powder in rabbits. Amount of NP in each preparation was 10 mg. Each point represents the mean ± S.E. (vertical bar) of six rabbits. (▲) Powder; (●) granule. Statistically significant differences: * $p < 0.05$ in granule vs powder.

plasma was assayed by the high-performance liquid chromatographic (HPLC) method of Miyazaki et al. (1984) with a slight modification. Statistical analysis of the results was performed by one-way ANOVA and Dunnett tests. The significant difference was estimated using $p = 0.05$ as the minimum level of significance. The mean plasma NP concentration-time curves following oral administration are shown in Fig. 3. In the case of the powdered form, NP levels in plasma were low (less than 100 ng/ml) during the experimental period of 6 h, whereas the NP concentration rapidly increased and maintained levels between 150 and 200 ng/ml within 3 h following administration of granules. The plasma concentrations tended to increase to approx. 250 ng/ml at 4–5 h. On comparison of the area under the plasma NP concentration-time curve (AUC) from 0 to 6 h for the powdered and granule forms, the mean value of the AUC (1224 ± 233 h ng ml^{-1}) obtained for granules was found to be significantly ($p < 0.05$) higher (approx. 3 times) than that (447 ± 95 h ng ml^{-1}) obtained for the powdered form. For the enteric preparations, it is generally accepted that a multiple-unit-type dosage form such as a granule is superior to the single-unit form. The granules would be successively transported through the gastrointestinal tract after oral administration and more reproducible absorption behavior would occur as compared with single unit enteric preparations (Hasegawa et al., 1985b). NP would be released from these matrix granules following digestion by lipase and bile salts in the small intestine.

In conclusion, we have demonstrated that NP matrix granules prepared from M-1540 and trilaurin have properties of pancreatic lipase-sensitive dissolution and improved dissolution behavior of NP. Consequently, their bioavailability is significantly increased as compared with NP powder. A preparation of NP matrix granules using macrogols and trilaurin may therefore provide a useful approach to achieving high bioavailability and delayed-release characteristics. The pH-independent (lipase-sensitive) dissolution property of these granules would be preferable in terms of prolongation of the effective plasma concentration.

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