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European Journal of Pharmaceutics and Biopharmaceutics 43 (1997) 283–286

European Journal of Pharmaceutics and Biopharmaceutics

Research paper

Influence of traces of surfactants on nifedipine bioavailability in rats after neomycin-induced malabsorption syndrome

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Received 15 April 1996; accepted 24 January 1997

Abstract

The effect of trace concentrations of surfactants (Tween 80, egg lecithin and sodium lauryl sulphate) on the bioavailability of nifedipine was investigated in rats in normal physiological condition and with the neomycin induced malabsorption syndrome. Tween 80 and lecithin, added under their critical miscellar concentration levels, were found to enhance nifedipine bioavailability in the case of physiological equilibrium and in the induced malabsorption syndrome. An increase of bioavailability promoted by addition of lauryl sulphate of sodium was not statistically significant. © 1997 Elsevier Science B.V.

Keywords: Bioavailability of nifedipine; GC-MS nifedipine determination; Neomycin induced malabsorption; Trace surfactant addition

1. Introduction

Nifedipine, one of the most potent calcium antagonists in clinical use, is proving of considerable value in the treatment of many cardiovascular disorders, principally angina pectoris and hypertension. The drug is only slightly soluble in water and intestinal fluids. Therefore, the primary absorption parameters of the drug, its solubility and dissolution characteristics, are influenced by formulation factors [1]. Nifedipine is almost completely absorbed from the gastrointestinal tract, but its systemic bioavailability amounts to only 40–70% of the administered dose, mostly because of pre-systemic metabolism. The metabolites have no pharmacological activity. The bioavailability of nifedipine administered in different oral dose forms was described [2], as well as the effects of a number of factors on the bioavailability of nifedipine administered orally and intravenously [3].

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PII S0939-6411(97)00057-X

The bioavailability of drugs depends on factors that indirectly influence the process, e.g. they influence dissolution, and also on factors directly influencing the bioavailability of drugs.

Surfactants belong to the group of direct factors. they do not possess any therapeutical properties but are adjuvants which added in small amounts below their critical micellar concentration increase the bioavailability of many therapeutical substances.

There is evidence [4–6] of a positive influence of lecithin, Tween 80 [7,8] and sodium lauryl sulphate on the absorption of indomethacin, cefradine, *p*-amino salicylic acid sodium salt and bunazosin hydrochloride [9].

The published results suggested, that the bioavailability of nifedipine could be generally influenced by addition of surfactants.

The aim of our work was to examine the effects of selected surfactants, i.e. Tween 80, egg lecithin and sodium lauryl sulphate on nifedipine bioavailability under normal physiological conditions and in the case of malabsorption syndrome induced by neomycin.

2. Materials and method

2.1. Materials

Nifedipine, obtained from Hexel-Pharma GmbH, Germany, neomycin sulphate, diazepam (used as internal standard), from Polfa, Poland, and the following surfactants: Tween 80, egg lecithin, sodium lauryl sulphate, from BDH Chemicals Poole, GB, were used in investigations.

A population of 112 males WISTAR race rats, weighing 200 g ± 10% each, were selected for investigation. These rats were fed with allmash feed, and 24 h before the experiment they were kept without any feed.

2.2. Method

To induce experimental malabsorption syndrome a solution of neomycin sulphate (125 mg/kg body weight) was administered intragastrically by means of a stomach pump during the following 5 days as described by Manton [10].

When the MS had been induced, the bioavailability was investigated for the following preparations of nifedipine:

1. The reference nifedipine preparation composed of nifedipine suspension (1 mg/kg body weight) in 0.9% sodium chloride solution [1];
2. Nifedipine suspension (1) plus 0.0003% of Tween 80; (dose: 1.0 mg/kg body weight);
3. Nifedipine suspension (1) plus 0.001% egg lecithin (dose of 1.0 mg/kg body weight);
4. Nifedipine suspension (1) plus 0.05% sodium lauryl sulphate, (dose of 1.0 mg/kg body weight);

The nifedipine NaCl suspension as well as the nifedipine suspensions with surfactants were administered intragastrically by means of a stomach tube.

The blood samples were collected at the following time intervals: 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0 and 12.0 h after administration.

Since nifedipine is sensitive to daylight, blood withdrawal and preparation of serum samples were performed under subdued light.

Gas chromatography/mass spectrometry was used to determine the serum concentrations of nifedipine as described by [11,12]. A Hewlett–Packard gas chromatograph model 5890 A with mass detector MSD 5970 equipped with a fused silica capillary column (25 m length, 0.2 mm ID, covered with 0.1 μm film of the chemically bonded poly(dimethylsiloxane) stationary phase) was used. The operation conditions were: carrier gas He 1.4 ml/min, column temperature program from 70 to 220°C (°C/min), ionisation voltage 70 eV, ionisation current 300 μA, ion source temperature 230°C.

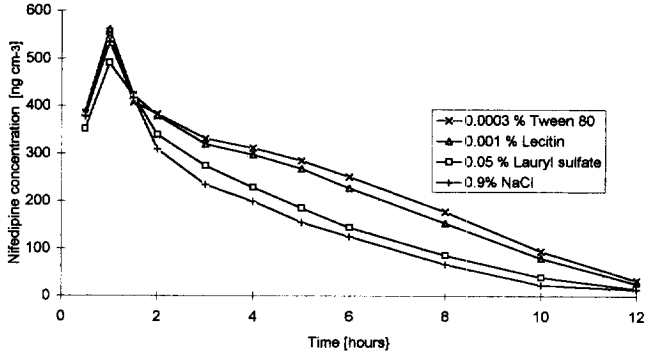

Fig. 1. Concentration of nifedipine in serum in rats in normal physiological condition after intragastrical administration of nifedipine suspension with surfactants. (Mean values of $n = 8-10$ samples).

The 0.1% methanolic solutions of samples were injected with a Hamilton 1 μl syringe.

Under these conditions, proposed by [12], the degradation products (nitro and nitroso compounds), the internal standard (diazepam) gave the baseline separated chromatographic elution peaks.

The Student's t-test was used for statistical analysis of results.

3. Results and discussion

Fig. 1 presents the mean values (for $n = 8-10$ samples) of nifedipine concentration in serum from rats in normal physiological condition after intragastrical administration of nifedipine suspension containing surfactants (Tween 80, lecithin and sodium lauryl sulphate) and the reference nifedipine suspension in 0.9% NaCl solution.

Fig. 2 presents the mean values (for $n = 8-10$) samples) of nifedipine concentration in serum from rats with the neomycin-induced malabsorption syndrome after intragastrical administration of the a.m. preparations.

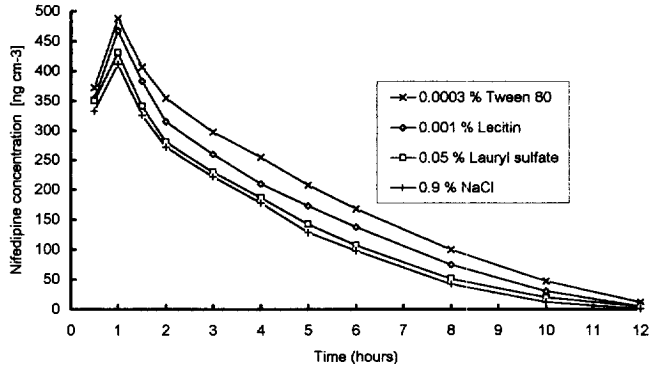

Fig. 2. Concentration of nifedipine in serum in rats with neomycin-induced malabsorption after intragastrical administration of nifedipine suspension with surfactants. (Mean values of $n = 8-10$ samples).

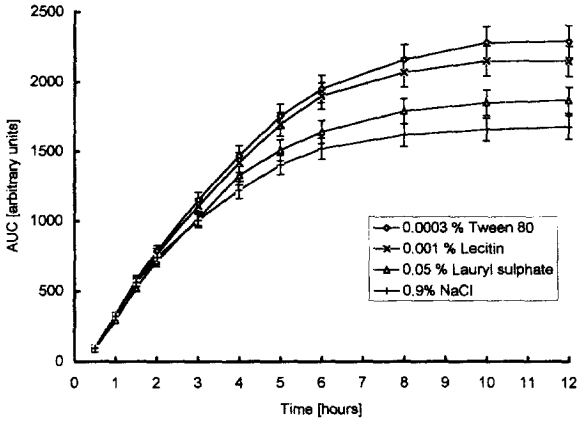

Fig. 3. Area under the curve of nifedipine concentration in serum determined for rats in normal physiological condition after intragastrical administration of nifedipine suspension with surfactants. (Error bars indicate relative error of 5.0% of the estimate).

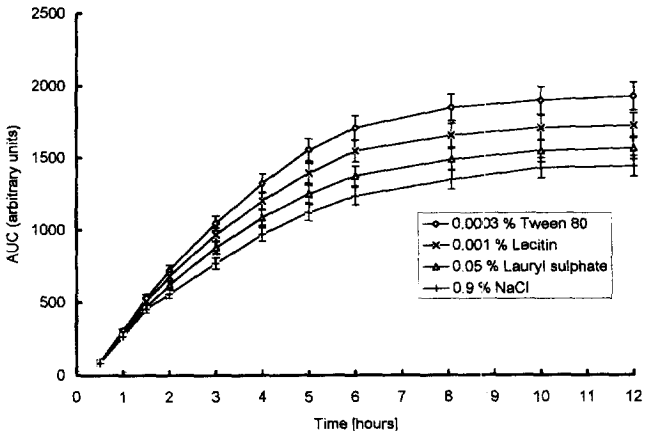

Fig. 4. Area under the curve of nifedipine concentration in serum determined for rats with neomycin-induced malabsorption after intragastrical administration of nifedipine suspension with surfactants. (Error bars indicate relative error of 5.0% of the estimate).

In Fig. 3 and Fig. 4 are given the calculated values of the area under the concentration curve, (AUC), representing the changes of nifedipine concentration in time, for both the physiological conditions studied, i.e. the normal state, and the neomycin-induced malabsorption syndrome.

On each AUC diagram the central line indicates the tendency of mean values and the bars indicate 95% normal confidence interval for the mean values.

The mean values of maximal nifedipine concentrations in serum were obtained 1 h after administration to the reference rats and to the rats with neomycin induced MS.

These plots demonstrate that the AUC curves converge rapidly to parallel lines (parallel to the time-axis). The AUC values at 12 h were used to estimate the bioavailability changes of the nifedipine preparations studied.

In Table 1 the estimated changes of bioavailability are given. It was observed that the surfactants used had a very positive influence on nifedipine absorption and its bioavailability.

Lecithin increased nifedipine bioavailability for the rats in normal physiological conditions by ca. 28%, and in the case of rats with neomycin induced MS by ca. 19%. Tween 80 increased the bioavailability of dihydropiridine in the first case by ca. 37% and ca. 33% in the second case, respectively. Sodium lauryl sulphate did not significantly increase nifedipine bioavailability.

Statistical analysis revealed that the differences in nifedipine absorption in rats with normal absorption and in rats with neomycin induced MS are significant for the probability level of $P < 0.05$ in comparison to the reference rats. The same tendency is true for the differences related to the parameters determining bioavailability, i.e. the values of concentration and surfaces under the curves reflecting the dependence of concentration versus time for nifedipine absorption in MS and under standard physiological conditions.

The results obtained suggest that in animals with experimentally induced MS, nifedipine bioavailability decreases. However, it should be noted, that the surfactants used increased drug bioavailability as well as the therapeutic activity in the neomycin-induced MS.

Table 1
Changes in bioavailability of the studied preparations of nifedipine in rats estimated from the AUC diagrams

	Nifedipine preparations containing:			
	0.9% NaCl	0.0003% Tween 80	0.005 Lecithin	0.005% Lauryl sulphate
Rats in normal physiological condition				
AUC value after 12 h	1675 ± 84	2290 ± 152	2150 ± 107	1870 ± 107
Change related to the reference preparation	1	1.367	1.28	1.11
Rats with neomycin-induced MS				
AUC value after 12 h	1444 ± 73	1930 ± 96	1727 ± 86	1570 ± 78
Changes related to the reference preparation	1	1.33	1.19	1.08
Changes caused by neomycin-induced MS	0.86	0.84	0.80	0.84

This effect, observed for the surfactants concentrations lower than critical micellar concentration, could find an application in drug technology.

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