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Short Communications

Effect of pH on the dissolution of drug particle dispersed in solid matrix of hydrogenated soya phospholipid

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Summary

Granules of theophylline were prepared with hydrogenated soya phospholipid, without addition of any binder. Despite very slow dissolution of drug from granules in 0.01 N HCl, the dissolution in phosphate buffer (pH 6.8) occurred rapidly with disintegration of granules and was further accelerated by the presence of bile in the medium. The granules prepared in this study behave as enteric granules.

Recently, we have reported on sustained-release formulations prepared with hydrogenated soya phospholipid (cationic phospholipid), including suppositories (Nishihata et al., 1986, 1988a), tablets (Nishihata, 1987; Nishihata et al., 1987), and granules (Hirotani et al., 1987; Nishihata et al., 1988b). The mechanism of sustained-release from these formulations may be due to poor water-solubility of the phospholipid as diluent, and binding-forces, which occur in the presence of cholesterol (granules) or triglyceride (suppository), or by simple retardation of water uptake required for disintegration (tablet). Retarded disintegration of formulations, due to such binding-forces, leads to sustained release of drug by a leaching mechanism proposed by Higuchi (1963).

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However, in the case of tablet with only press-induced binding-forces, disintegration at pH 6.8 required about 8 h, while no disintegration in 0.01 N HCl was observed within 24 h (Nishiahata et al., 1987). Thus, in the present report we investigated the effect of pH on the dissolution of drugs from granules prepared with the phospholipid, without addition of binding compounds or mechanical interferences. Theophylline was used as the model drug, because there is no significant difference in its solubility in 0.01 N HCl or in the buffer at pH 6.8 (Nishihata et al., 1987).

The granules tested contain drug particles dispersed in a homogenous phospholipid matrix, and were prepared according to the following method (tablets prepared previously were only a physical mixture of drug particles and the phospholipid particles; Nishihata, 1987).

Ten grams of the phospholipid (70% phosphatidylethanolamine and 30% phosphatidylcholine) were dissolved in chloroform, and designated

TABLE 1

Constituents of granules and dissolution parameter of theophylline from granules

Formulation		Dissolution parameters [b]		
constituents ratio of weight	content of drug [a]	% of drug dissolved after 2 h		k at pH 6.8
(in preparation) drug : phospholipid	(measured) mg/100 mg	0.01 N HCl	pH 6.8	
T-1 1 : 2	34.6 ± 2.9	20.2 ± 4.5	87.6 ± 7.1	0.24 ± 0.04
T-2 1 : 3	27.1 ± 2.3	14.9 ± 2.1	75.2 ± 5.7	0.18 ± 0.03
T-3 1 : 4	21.4 ± 2.2	8.7 ± 1.4	58.4 ± 4.2	0.11 ± 0.01
T-4 1 : 6	13.9 ± 0.7	3.1 ± 1.5	39.1 ± 3.6	0.07 ± 0.02

[a] Results from 4 batches of each formulation.

[b] Results from 4 batches of each formulation type. Three experiments were performed for each batch, and k value was obtained from the slope of straight line in Fig. 1B, according to Eqn. 1. Each value represents the mean ± S.D. ($n = 4$ for drug content, and $n = 12$ for dissolution parameter).

amounts of drug particles (10–30 μm) were suspended in the chloroform solution at 4 °C. Chloroform was evaporated gradually with agitation. The residual solid was pulverized with a mortar and pestle, and granules with a size of 1.0–2.0 mm were collected as test formulations. The codes of formulations and drug content in 1 g of granules are listed in Table 1. The content of drug was measured after extraction with 500 ml of 0.001 N NaOH at 80 °C.

The dissolution study was performed at 37 °C according to a method described previously (Hirotani et al., 1987), using a rotating basket method (basket was covered with cotton gauze) in JPX at 100 rpm. Granules containing 30 mg of theophylline were examined. Dissolution media were either 500 ml of 0.01 N HCl or 500 ml of 0.2 M KH_2PO_4–NaOH phosphate buffer, pH 6.8. Assay of theophylline (Nishihata et al., 1981) was performed by a HPLC method.

Dissolution of theophylline from granules occurred rapidly in the phosphate buffer (pH 6.8) compared to that in 0.01 N HCl (Fig. 1A). Dissolution of drug was further delayed with an increase in phospholipid content (Table 1).

Dissolution from granules can occur according to the Hixson–Crowell cube-root law (Martin et al., 1983). In this case, drug dissolution may be presented by Eqn. 1.

$$1 - (W_t/W_0)^{1/3} = kt \qquad (1)$$

where W_0 and W_t represent the total amount of drug in granules and the remaining amount of drug in granules after time t, respectively. The k is a constant for each type of granule. Data analyzed according to Eqn. 1 produced straight lines for the dissolution in the phosphate buffer (Fig. 1B). Thus, dissolution of drug seems to relate to a mechanism of granule disintegration at pH 6.8. Since medium out of the basket became cloudy during experiment, deaggregation (disintegration) of granules is considered.

Further it was observed that the initial dissolution was greater than expected from Eqn. 1, since these straight lines have a positive y-intercept

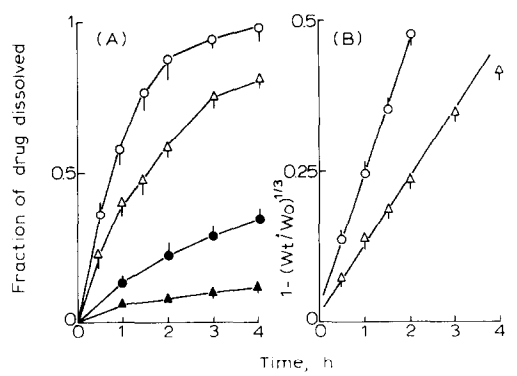

Fig. 1. Dissolution profiles of theophylline from granules of formulation T-1 (circles) and Code T-3 (triangles) in 0.01 N HCl (closed symbols) or in 0.1 M sodium phosphate buffer of pH 6.8 (open symbols). Each value represents the mean ± S.D. ($n = 12$).

(Fig. 1B). This initial burst may reflect rapid dissolution of drug which was exposed on the granule surface in the process of pulverization.

The amounts of theophylline dissolved in 0.01 N HCl were very low (Fig. 1 and Table 1). Disintegration (deaggregation) of granules in 0.01 N HCl was not apparent to the naked eye, at least during the experimental period (4 h). To estimate the disintegration of granules in the media, residue of formulation T-3 in the basket was collected after 1 h when 1.0 g of granules were examined, and was dried for 24 h at 25°C under nitrogen gas. For this study, granules without theophylline (T-0) were prepared to compare with the T-3. The weight of dried residue after incubation in the phosphate buffer was 529.6 ± 63.4 mg for T-3 ($n = 4$) and 598.9 ± 55.1 mg for T-0 ($n = 4$, no significant difference versus T-3). The dried residue after incubation in 0.01 H HCl was 959.7 ± 31.1 mg for T-3 ($n = 4$, $P < 0.001$ versus the value at pH 6.8) and was 971.6 ± 30.4 for T-0 ($n = 4$, $P < 0.001$ versus the value at pH 6.8). These results indicate that T-3 and T-0 granules disintegrated markedly at pH 6.8. The slow disintegration of granules tested in 0.01 N HCl may be due to the cationic properties of these phospholipids. However, since we did not measure the size of the residue, these data did not represent an intrinsic disintegration.

The rapid disintegration of granules in the phosphate buffer may be due to a more rapid hydration of the cationic phospholipid at neutral and basic pH (Lunberg et al., 1978). Since the solubility of theophylline is greater than that of the phospholipid, it is considered that an increase in drug content caused a more rapid disintegration of granules by causing a more rapid infiltration of incubation medium.

The findings in the present study indicate that the granules tested behave as enteric granules. To estimate the dissolution of theophylline from granules in intestinal luminal fluid, the granules of formulation T-3, containing 5 mg theophylline, were incubated in 10 ml of the phosphate buffer containing 20% v/v bile (collected from rats) for 0.5 h at 37°C (shaken at 50 cpm). The small volume of medium in this study is due to limited collection of bile from rats. As a control study, the phosphate buffer without bile was used. The dissolution of theophylline from granules in the control study was $20.6 \pm 3.7\%$ ($n = 4$), while that of theophylline in the medium containing bile was $31.2 \pm 4.9\%$ ($n = 4$, $P < 0.05$ vs control). Therefore, bile seems to accelerate the dissolution of theophylline, probably through accelerated disintegration of the granules.

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