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Interaction of Drugs with Bile Components. I. Effects of Bile Salts on the Dissolution Behavior of Indomethacin and Phenylbutazone[1]

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The effects of bile salts on the dissolution behavior of indomethacin and phenylbutazone were investigated. Bile salts such as sodium desoxycholate and sodium cholate considerably enhanced the dissolution of both drugs in pH 7.3 buffer at 37°.

The results indicated that the enhancement of the dissolution of indomethacin in the presence of bile salts was mainly due to micellar solubilization. On the other hand, the enhanced dissolution of phenylbutazone may be due to the wetting effect, increasing the effective surface area of the powder.

Keywords——indomethacin; phenylbutazone; bile salts; dissolution behavior; micellar solubilization; wetting effect

It is well known that components of bile such as bile salts and lecithin, which are physiological surfactants, play an important role in intestinal absorption.

Some investigators have suggested that bile salts may influence drug absorption from solution by affecting the membrane permeability[3–7] and gastric emptying.[8–9]

On the other hand, drug solubility and dissolution rate may also be affected by bile salts. Bates *et al.*[10,11] have shown that bile salts markedly increase the solubility and dissolution rate of poorly water-soluble drugs. These findings suggest that one of the steps in the intestinal absorption of relatively insoluble drugs involves the preliminary solubilization of the drugs by bile salts.[12]

However, there are very few reports concerning the effect of bile salts on the dissolution rates of poorly soluble drugs and the mechanism of action of bile salts.

The purpose of this investigation was to study the effect of bile salts on the dissolution characteristics of two non-steroidal antiinflammatory drugs, indomethacin and phenylbutazone, which are very poorly soluble in water. The mechanism of interaction between these drugs and bile salts was also studied.

Experimental

Materials——Sodium desoxycholate, sodium glycocholate, and sodium taurocholate were obtained from Tokyo Kasei Kogyo Co. Sodium cholate, indomethacin, and phenylbutazone were obtained from Sigma Chemical Co. They were used without further purification.

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1) This work was presented at the 98th Annual Meeting of the Pharmaceutical Society of Japan, Okayama, April, 1978.
2) Location: *1-1 Keyakidai, Sakado, Saitama 350-02, Japan.*
3) M. Gibaldi and C.H. Nightingale, *J. Pharm. Sci.*, **57**, 1354 (1968).
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Procedure for Dissolution Studies——The dissolution behavior of crystalline powders was determined as described previously,[13] except that the volume of the dissolution medium was increased to 2 ml.

The concentration of a drug in solution was determined by the ultraviolet (UV) absorption method using a Jasco Uvidec-2 spectrophotometer. Bile salts were found not to interfere with the spectrophotometric analysis in the concentrations present in the diluted samples.

Solubility Determination——The solubilities of drugs were determined in pH 7.3 phosphate buffer containing various concentrations of bile salts at 37°. Excess amounts of samples were suspended in 2 ml of the bile salt solutions. These suspensions were shaken for 24 hr in a Taiyo M-100T incubator. Aliquots were filtered with a Millipore filter (0.45 μ) and assayed spectrophotometrically.

Micellar Interaction by the Molecular Sieve Method——The interactions between bile salts and drugs were studied by the molecular sieve method.[14]

Results and Discussion

Effect of Bile Salts on the Dissolution Behavior of Drug Powders

A study was undertaken to determine the influence of bile salts dissolved in pH 7.3 phosphate buffer. Figure 1 shows the dissolution behavior of indomethacin and phenylbutazone in 40 mM[15,16] bile salt solutions at 37°. Each curve is drawn through points obtained during at least two experimental runs, and the results were satisfactorily reproducible. As can be seen from these curves, both sodium desoxycholate and sodium cholate markedly increased the dissolution rate of the drug compared to that observed in the buffer. For example, at 5 min the concentration of the drug in solution was more than 4 times higher in the bile salt solutions than in the buffer. Sodium glycocholate and taurocholate also appeared to increase the dissolution rates.

The dissolution curves for phenylbutazone in each dissolution medium are also shown in Fig. 1. Phenylbutazone was also more soluble in the sodium desoxycholate, cholate, and glycocholate solutions than in the buffer alone, whereas sodium taurocholate did not have any significant effect on the dissolution of this drug.

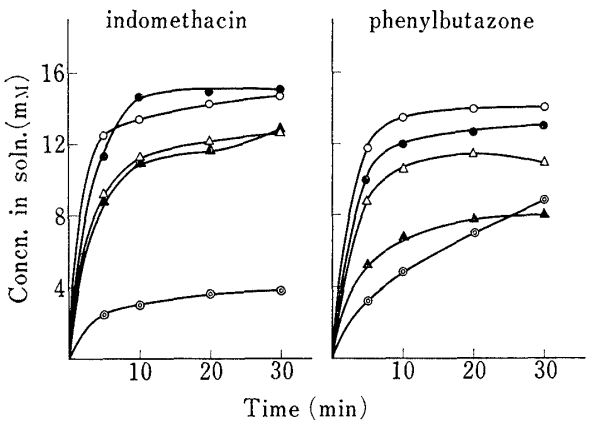

Fig. 1. Effects of Bile Salts on the Dissolution Behavior of Indomethacin and Phenylbutazone in pH 7.3 Phosphate Buffer at 37°

—◎—: control.
—○—: sodium desoxycholate.
—●—: sodium cholate.
—△—: sodium glycocholate.
—▲—: sodium taurocholate.
The concentration of bile salts was 40mM.

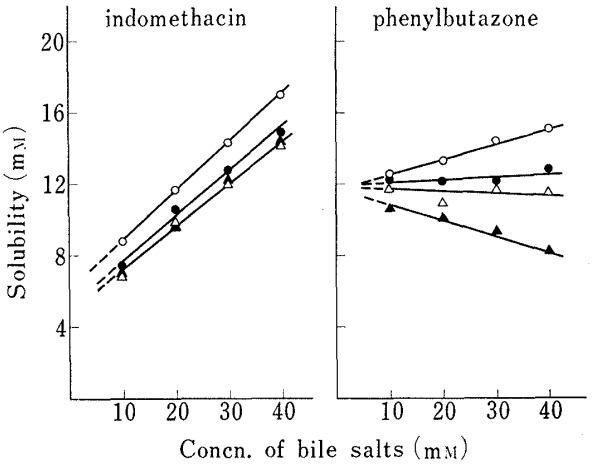

Fig. 2. Effect of Bile Salts Concentration on the Solubilities of Indomethacin and Phenylbutazone in pH 7.3 Phosphate Buffer at 37°

—○—: sodium desoxycholate.
—●—: sodium cholate.
—△—: sodium glycocholate.
—▲—: sodium taurocholate.

13) S. Miyazaki, T. Arita, R. Hori, and K. Ito, *Chem. Pharm. Bull.* (Tokyo), **22**, 638 (1974).
14) R.W. Ashworth and D.D. Heard, *J. Pharm. Pharmacol.*, **18**, *suppl.*, 98S (1966).
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Preliminary studies indicated that after 5 min the ratio of the drug concentration in 40 mM sodium desoxycholate solution to that in water is approximately 440 and 150 for indomethacin and phenylbutazone, respectively.

Interaction of Drugs with Bile Salts

It is known that the effect of bile salts in the dissolution rates of relatively insoluble drugs may involve two mechanisms, *i.e.*, micellar solubilization and wetting effects.[17]

We therefore investigated the mechanisms of action of the bile salts in the case of present drugs. Solubility determinations were carried out to test for appreciable interaction between the drugs and bile salts. The equilibrium solubilities of indomethacin and phenylbutazone in bile salt solutions at various concentrations are shown in Fig. 2. It is clear that the solubility of indomethacin is increased in the presence of the bile salts used. The effect of the bile salts on the solubility was similar to that on the dissolution behavior. Thus, the increase in dissolution rate is mainly due to the increase of solubility. The increase in solubility may be due to micellar solubilization.

Figure 2 also shows the solubility of phenylbutazone in bile salt solutions at 37°. A slight increase in the solubility was observed in the presence of sodium desoxycholate; the effect of the bile salt appeared to be less pronounced than in the case of indomethacin. The solubility of phenylbutazone was not changed by sodium cholate or glycocholate, while the decrease observed in the presence of sodium taurocholate was probably due to slight decreases of the final pH of the solutions.

The slope of the linear portion of the curve represents the ratio of micellar drug to micellar bile salt and is termed the saturation ratio.[10,16] The saturation ratios for the bile salts with the drugs are presented in Table I. The saturation ratios for indomethacin in bile salt solutions are many times greater than those of phenybutazone, indicating that bile salt micelles display a significantly higher affinity for indomethacin.

Table I. Saturation Ratios of Bile Salts for Indomethacin and Phenylbutazone

Bile salts	Saturation ratio[a] $\left(\frac{\text{mol of micellar drug}}{\text{mol of micellar bile salts}}\right)$	
	Indomethacin	Phenylbutazone
Sodium desoxycholate	0.271	0.085
Sodium cholate	0.247	0.023
Sodium glycocholate	0.213	−0.006
Sodium taurocholate	0.234	−0.085

a) Slope of the linear portion of the solubilization curve determined by the least-squares method.

The interactions of drugs with bile salts were also studied by the molecular sieve method.[14] Figure 3 shows the micellar interaction between the drugs and sodium desoxycholate. Since sodium desoxycholate had the greatest effects on the solubility and dissolution rate of both drugs, it was selected for further study. As might be expected, indomethacin formed a micellar complex, and the fraction of this increased as the concentration of sodium desoxycholate increased. On the other hand, phenylbutazone forms a micellar complex with the bile salt to only a small extent. The difference between indomethacin and phenylbutazone in micellar interaction may be considered to depend on the molecular size of the

17) M. Gibaldi and S. Feldman, *J. Pharm. Sci.*, **59**, 579 (1970).

ionized drugs, since both drugs are almost completely ionized at pH 7.3. However, further studies are required.

These results indicate that the increase in the solubility of indomethacin in the presence of sodium desoxycholate is due to micellar solubilization. This may also be the case for other bile salt systems.

It appears that the increased dissolution rates of phenylbutazone in the presence of sodium desoxycholate, cholate, and glycocholate are probably due to the wetting effect,[18] *i.e.*, a reduction of the interfacial tension between the drug and the dissolution medium. The dissolution behavior of drugs was also investigated at a low concentration of bile salts, since the wetting effect is observed even in dilute surfactant solutions below the critical micelle concentration (CMC).[19]

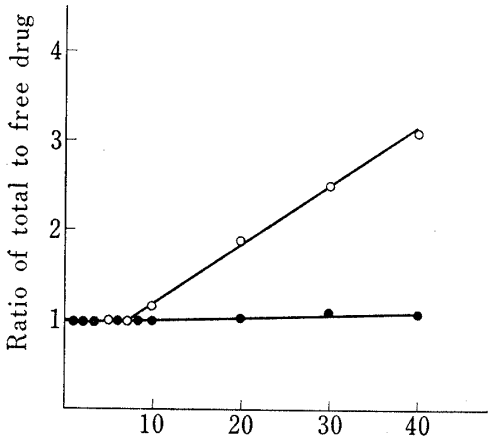

Fig. 3. Plots showing the Ratio of Total to Free Drug in pH 7.3 Phosphate Buffer containing Various Concentrations of Sodium Desoxycholate at 37°

—○—: indomethacin.
—●—: phenylbutazone.
The concentration range of the bile salt was 1 to 40 mM.

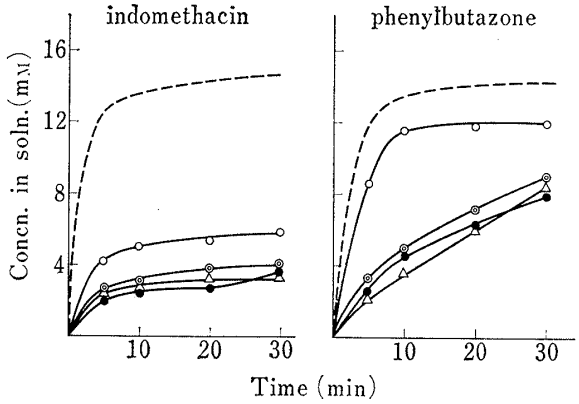

Fig. 4. Effect of Bile Salts on the Dissolution Behavior of Indomethacin and Phenylbutazone in pH 7.3 Phosphate Buffer at 37°

—◎—: control.
—○—: sodium desoxycholate.
—●—: sodium cholate and sodium taurocholate.
—△—: sodium glycocholate.
The concentration of bile salts was 2 mM.
The dotted lines show the dissolution curves of drugs in 40 mM sodium desoxycholate.

The results obtained by the molecular sieve method showed that the CMC of sodium desoxycholate was approximately 7 mM. The dissolution properties of indomethacin and phenylbutazone in 2 mM bile salt solutions were compared, as shown in Fig. 4. It can be seen that the dissolution rate of indomethacin was increased in 40 mM bile salt solution (above the CMC), but that there was little increment at 2 mM (below the CMC). On the other hand, the presence of the lower level of sodium desoxycholate was sufficient to enhance the dissolution of phenylbutazone. No effect was observed in the cases of other bile salts. This was to be expected, since sodium desoxycholate has a higher surface tension than the other salts at 2 mM.[20]

These results confirmed that the enhancement of the dissolution characteristics of indomethacin in the presence of bile salts is mainly due to micellar solubilization. On the other hand, the mechanism by which bile salts enhanced the dissolution of phenylbutazone probably involves enhanced wetting and increased effective surface area of the solid. This is consistent with the finding that phenylbutazone is strongly hydrophobic.[21] The contact angles of a

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19) M. Gibaldi, "Introduction to Biopharmaceutics," Lea and Febiger, Philadelphia, 1971, p. 36.
20) S. Miyazaki, H. Inoue, T. Yamahira, and T. Nadai, unpublished data.
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drop of water formed on compacted drug powder were approximately 28° and 90° for indomethacin and phenylbutazone, respectively.[20]

From the viewpoint of drug bioavailability, these findings indicate that bile salts may enhance the dissolution rates of indomethacin and phenylbutazone *in vivo* and thereby promote intestinal absorption of the drugs. Studies are now in progress on the effect of bile salts on drug bioavailability.