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Dissolution of Physical Mixtures of Dimemorfan Phosphate and Dimemorfan

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The aims of the present investigation were to compare the dissolution properties of dimemorfan phosphate and dimemorfan and to control the dissolution of dimemorfan species, which are pharmacologically equivalent, by using suitable mixtures of dimemorfan phosphate and dimemorfan.

The solubility of dimemorfan was studied in solutions of various pH values. It was almost constant at low pH, reached a maximum at pH 6.6, and decreased significantly with further increase of pH.

Dissolution rates were determined in solutions of various pH values. Dissolution rate of dimemorfan phosphate increased gradually with increase of pH of the dissolution medium, whereas that of dimemorfan decreased. It is suggested that in the case of dimemorfan dissolution, the pH value of the saturated layer is influenced profoundly by the nature of the dimemorfan species, though the effect is small in the case of dimemorfan phosphate because of the existence of phosphate ions in the compound.

Based on an analysis of the dissolution properties of dimemorfan species in solutions of different pH values, a method for controlling the release of dimemorfan species was established by the use of mixtures of dimemorfan and dimemorfan phosphate.

Keywords——dimemorfan phosphate; Dimemorfan; physical mixture; dissolution; pH-solubility profile

The dissolution rate of a drug, together with its solubility, is one of the most important factors which might influence bioavailability. Although the dissolution rates of drugs have been well documented,[2] little work has been done on the dissolution behavior of organic salts. Nelson found in a dissolution study of organic salts that the pH of the diffusion layer varied according to the extent of their dissolution.[3] Higuchi *et al.* found that tolazamide acid in phosphate buffer at various pHs showed different dissolution profiles.[4]

The purpose of the present investigation was to predict and control the dissolution of a mixture of an organic base and a salt based upon the pH dependency of the dissolution of each substance.

Experimental

Materials——Dimemorfan Phosphate (see Chart 1) was supplied by Yamanouchi Pharm. Co., Ltd. Dimemorfan was obtained as follows; dimemorfan phosphate crystals (purity 99.6%) were dissolved in 0.1 N HCl solution, then aliquots of 6 N KOH solution were added to give pH 9. The entire solution was filtered on a glass filter, and the precipitate was washed with distilled water to remove chloride ions until the filtrate gave no precipitate upon the addition of aqueous $AgNO_3$ solution. It was transferred into a desiccator and dried in a vacuum in the presence of P_2O_5 for 24 hr. The other chemicals used in this study were of reagent grade.

X-ray Diffraction (Powder Method)——X-ray diffractions of dimemorfan, dimemorfan phosphate, and a mixture of the two were determined using a Rigakudenki RU-200 X-ray diffractometer under the following

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[2] D. Bauerjee and B.K. Gupta, *Can. J. Pharm. Sci.*, **13**, 94 (1978); S.L. Lin, L. Lachman, C.J. Swartz, and G.F. Huebner, *J. Pharm. Sci.*, **61**, 1419 (1972).

[3] E. Nelson, *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 607 (1957).

[4] W.I. Higuchi, N. Mir, A.P. Parker, and W.E. Hamlin, *J. Pharm. Sci.*, **54**, 8 (1965).

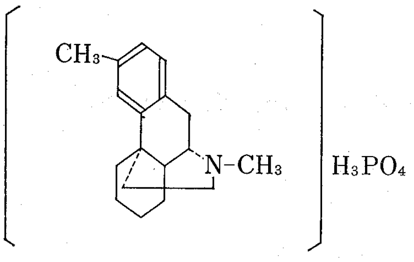

Chart 1. Dimemorfan Phosphate

conditions: Cu target with monochromating filter, voltage 40 kV, current 40 mA, receiving slit 0.15 mm, count range 8000—20000 cps, time constant 0.2 sec, scanning speed 4°/min, chart speed 40 mm/min, scintillation counter detection.

IR Absorption Spectroscopy——A Hitachi EPI-G3 infrared spectrophotometer was used. The measurements were made by the KBr disk method.

Determination of the pK_a of Dimemorfan——The pK_a was determined by a conventional titration method. For the determination of the pH of solutions, an automatic recording titrater (Metrohm. Herisau. model E 536) was employed. A 20 ml aliquot of 0.01 M dimemorfan phosphate was titrated with 0.03 N NaOH under vigorous agitation. The pH change of the solution was monitored automatically using a calomel electrode.

Determination of Solubility and pH in the Saturated Solution——The solubility of dimemorfan phosphate in aqueous solution was determined as follows: an excess of dimemorfan phosphate or a mixture of dimemorfan and its phosphate was placed in a 10 ml centrifuge tube, and 9 ml of 1/15 M phosphate buffer or distilled water was added. The tube was heated to 50° for 1 hr, stoppered, sealed further with a wrapping of Sealon film (Fuji Photo. Film Co., Ltd.), and placed in a calibrated constant temperature (37°) water bath for 4 days. The sample was filtered through 0.22 μm Millipore filter, then diluted appropriately, and the concentration of dimemorfan was determined by UV spectrophotometry using a Hitachi 124 UV-VS spectrophotometer at 276.5 nm.

The pH of the saturated solution at 37° was measured using a calomel-glass combination electrode connected to a pH meter (Toa Denpa Kogyo Co., Ltd. model HM-5A).

Dissolution Study——A disk of 13 mm or 16 mm diamter was prepared by compressing approximately 500 mg of powder at about 2.5 ton/cm^2, using an oil press (Miki Seisakusho). It was fixed to a holder with an adhesive (Cemedine Co., Ltd.), and so as to expose only its bottom face to the liquid, the remainder was covered with epoxy resin (Cemedine Co., Ltd.). The dissolution rate study was performed based on the rotating disk method under the following conditions: dissolution medium, 500 ml of buffer solutions (1/15 M phosphate buffer or 0.2 M borate buffer) at various pH values or distilled water at 37°; the rotating velocity of the disk, 150 rpm; USP XIX dissolution test apparatus (Toyama Sangyo Co., Ltd.).

The concentration of dimemorfan and dimemorfan phosphate were determined by UV spectrophotometry using a Hitachi 124 UV-VS spectrophotometer at 276.5 nm.

Results and Discussion

X-ray diffraction patterns (see Chart 2) IR spectra (see Chart 3) and UV absorption spectra of dimemorfan samples were prepared by the methods described in "Experimental", were compared consistently with those of authentic dimemorfan. No changes were observed in the X-ray diffraction patterns and IR spectra of the physical mixtures of dimemorfan and dimemorfan phosphate before and after the compression.

Solubility of Dimemorfan

Solubilities of dimemorfan phosphate or dimemorfan in solution of various pH (final pH) were shown in Fig. 1. Solubility below pH 6.58 was determined by saturating the solution with dimemorfan phosphate, and above pH 6.58 by saturating the solution with dimemorfan. Concentrations of dimemorfan phosphate were converted into equivalent concentrations of dimemorfan, and solubility was defined as that of the sum of dimemorfan species. The solubility was nearly constant at pH 4.8—5.5, started to increase sharply at approximately pH 5.6, reached a maximum at pH 6.58, and then decreased with further increase of pH. The following equilibria for phosphoric acid are known to exist in an aqueous solution.

$$H_3PO_4 \overset{K_{a_1}}{\rightleftarrows} H^+ + H_2PO_4^- \overset{K_{a_2}}{\rightleftarrows} 2H^+ + HPO_4^{2-} \overset{K_{a_3}}{\rightleftarrows} 3H^+ + PO_4^{3-} \qquad (1)$$

$$pK_{a_1}=2.21,\ pK_{a_2}=7.21,\ pK_{a_3}=12.32$$

On the other hand, it is assumed that the following equilibrium for dimemorfan phosphate exists in an aqueous solution.

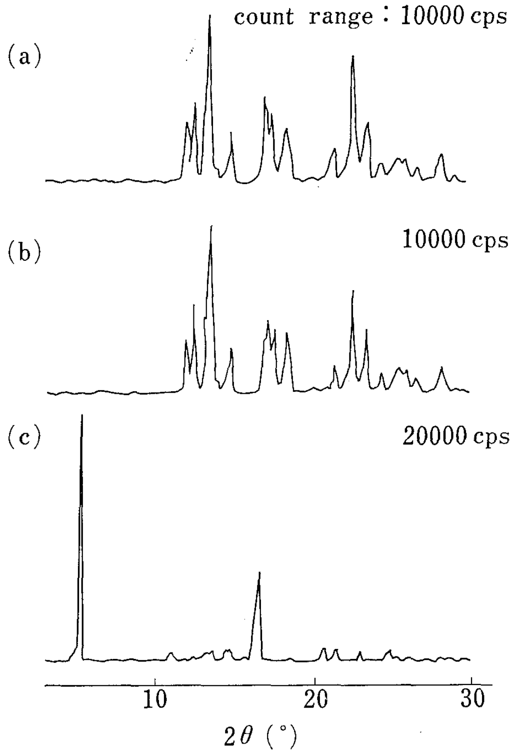

Chart 2. X-ray Diffraction Patterns of Dimemorfan prepared by the Method Described in "Experimental" (a), Authentic Dimemorfan (b), and Dimemorfan Phosphate (c)

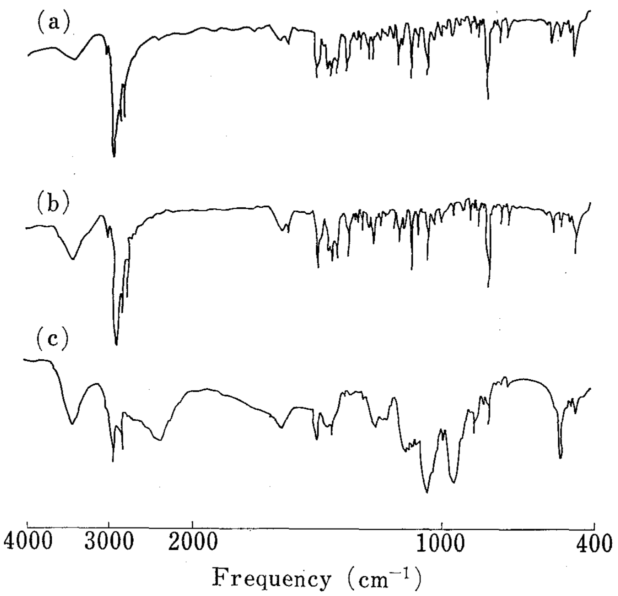

Chart 3. IR Spectra of Dimemorfan prepared by the Method described in "Experimental" (a), Authentic Dimemorfan (b), and Dimemorfan Phosphate (c)

$$\mathrm{BH^+} \overset{K_1}{\rightleftarrows} \mathrm{B} + \mathrm{H^+} \qquad (2)$$

$$\mathrm{BH^+ \cdot H_2PO_4^-} \overset{K_2}{\rightleftarrows} \mathrm{BH^+} + \mathrm{H_2PO_4^-} \qquad (3)$$

$$\mathrm{(BH^+)_2HPO_4^{2-}} \overset{K_3}{\rightleftarrows} \mathrm{2BH^+} + \mathrm{HPO_4^{2-}} \qquad (4)$$

B: dimemorfan

Clearly, from equation (1), the phosphate ion around the protonated dimemorfan in the pH range of 4.5—5.5 is predominantly $H_2PO_4^-$. Further, with an increase of pH the equilibrium in equation (1) moves to the right, and thus the equilibria in equations (2—4) move to the right at the pH values larger than 6.58. Therefore dissolution of protonated dimemorfan is facilitated. Finally the solubility converges on that of uncharged dimemorfan. Previously Friberger *et al.* reported that the solubility of local anesthetic compounds was constant in the acidic pH range, but decreased with an increase of pH from a specific pH value.[5] Recently Kramer *et al.* described the pH dependency of the solubility of anesthetic compounds and stated that the solubility changed from that of the ionic form to that of the base form with an increase of pH.[6] The turning point was defined as $\mathrm{pH_{max}}$. The $\mathrm{p}K_a$ of dimemorfan was calculated based on Kramer's equation,[6]

$$[\mathrm{BH^+}]_s(K_a)^2/[\mathrm{H_3O^+}]_{max} + ([\mathrm{BH^+}]_s - [\mathrm{B}]_s)K_a - [\mathrm{B}]_s[\mathrm{H_3O^+}]_{max} = 0$$

where the subscript s indicates a saturated species. The calcuated value was 7.92 at 37°, which is very close to the empirical $\mathrm{p}K_{a2}$ of 7.14 at room temperature obtained by potentiometric

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5) P. Friberger and G. Äberg, *Acta. Pharm. Sueci.*, **8**, 361 (1971).
6) S.F. Kramer and G.L. Flynn, *J. Pharm. Sci.*, **61**, 1896 (1972).

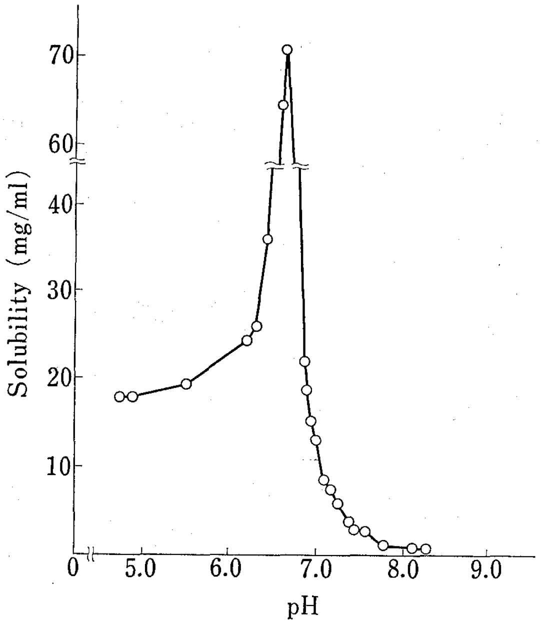

Fig. 1. The Solubility Profile of Dimemorfan Species in 1/15 M Phosphate Buffer Solution at 37°

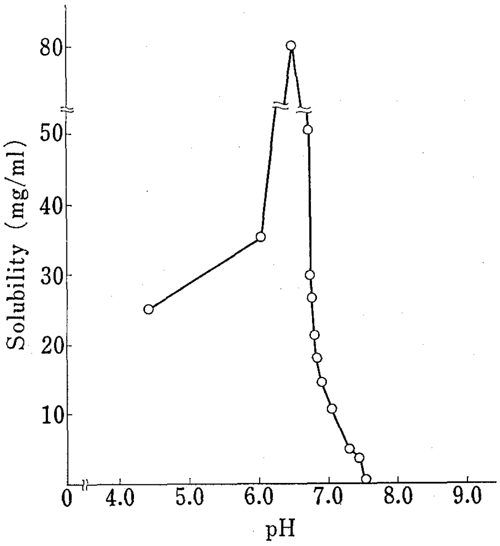

Fig. 2. The Sclubility Profile of Dimemorfan Species in Distilled Water at 37°

titration in this study. The small difference between these pK_a values is presumably due to temperature, which affects the protonation of species in the solution. In addition, the existence of phosphoric acid may affect the equilibrium between dimemorfan and protonated dimemorfan because the pK_{a2} of phosphoric acid is 7.21, and the solubility of dimemorfan phosphate in phosphate buffer solution may be modified by the common ion effect. Fig. 2 shows the pH-solubility profile of dimemorfan in distilled water at various ratios of the physical mixture of dimemorfan and its phosphate, the ends of the plot corresponding to dimemorfan phosphate alone and dimemorfan alone. The solubility increased gradually between pH 4.46 and pH_{max} 6.5, and then decreased sharply with increase of pH. The solubility in distilled water was larger than that in phosphate buffer solution. Further, in terms of the final pH of dimemorfan phosphate in the distilled water, it was smaller than that in phosphoric acid solution.

The results mentioned above indicate that the solubility of dimemorfan in phosphate buffer solution is modified by the common ion effect of phosphoric acid. At pH higher than 6.5 the solubilities of dimemorfan in both solutions were almost equal. In this pH range the common ion effect is eliminated and only the dissociation of the dimemorfan cation is facilitated by a decrease of hydrogen ion concentration.

pH Dependency of Dissolution Rate

The dissolution behavior of dimemorfan phosphate in solutions of different pH values is shown in Fig. 3. Initial dissolution rates at pHs 6, 7, and 8 increased in this order. The solubilities determined at various pHs values are shown in Table I. It is clear that the solubility of dimemorfan is pH-dependent. Therefore, it is suggested that the saturated layer which is formed at the surface of the crystals is pH-dependent. The final pH of borate buffer solution had a tendency to fall with the dissolution of dimemorfan phosphate. This is because the phosphate ions generated by the dissolution of dimemorfan phosphate overcome the buffer capacity and produce a new equilibrium to give a lower pH. The solubility in borate buffer solution was larger than that in phosphate buffer solution, suggesting that the solubility of dimemorfan phosphate is influenced by the common ion effect of phosphate ions.

When the initial pH of the medium was 9.0, the amount dissolved reached a maximum within about 30 min, and then decreased gradually. As shown in Table I, the saturated con-

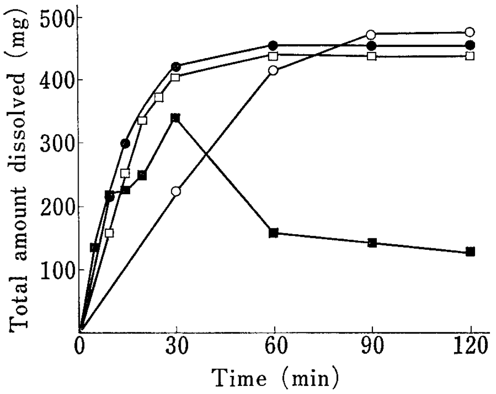

Fig. 3. Dissolution of Dimemorfan Phosphate in 500 ml of Various Buffer Solutions as a Function of Time

Key: —○—; pH 6.00, —□—; pH 7.00, —●—; pH 8.00, —■—; pH 9.00.

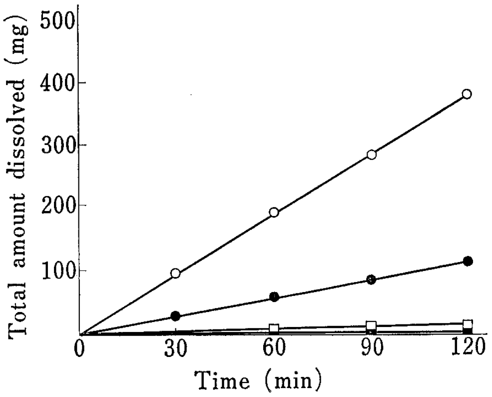

Fig. 4. Dissolution of Dimemorfan in 500 ml of Various Buffer Solutions as a Function of Time

Key: —○—; pH 6.00, —●—; pH 7.00, —□—; pH 8.00, —■—; pH 9.00.

Table I. Solubility of Dimemorfan Phosphate in Various Buffer Solutions

Medium	Initial pH	Solubility (mg/ml)	Final pH
1/15 M Phosphate	6.00	25.99	5.64
buffer solution	7.00	34.17	6.20
0.2 M Borate	8.00	41.47	5.53
buffer solution	9.00	44.57	5.92

centration of dimemorfan in the solution of starting pH 9.0 is comparatively high, so the initial diffusional concentration gradient between the surface of the crystal and the bulk solution might be rather high. However, the pH of the bulk solution is maintained at pH 9.0 because of the buffer effect. Therefore dissolved dimemorfan phosphate may undergo recrystallization as the concentration builds up in the bulk solution.

Table II. Solubility of Dimemorfan in Various Buffer Solutions

Medium	Initial pH	Solubility (mg/ml)	Final pH
1/15 M Phosphate	6.00	8.363	7.15
buffer solution	7.00	3.421	7.50
0.2 M Borate	8.00	0.6145	8.35
buffer solution	9.00	0.1441	9.02

The dissolution of dimemorfan is shown in Fig. 4. The dissolution rate of dimemorfan increased with an increase of pH of the dissolution medium at pH 8.0 and pH 9.0. Table II shows the solubility of dimemorfan. It increased with decrease of pH and at pH 8.0 and pH 9.0, which are above the pK_a of dimemorfan, approached that of the molecular form of dimemorfan. This supports the view that the dissolution rate of a species is proportional to the concentration gradient between the saturated layer formed at the surface of the crystal and the bulk solution.

The Noyes-Nernst equation can be written as follows:

$$\frac{\mathrm{d}C}{\mathrm{d}t} = k\frac{S}{V}(C_{\mathrm{o}} - C) \qquad (5)$$

or

$$-\ln\left(1-\frac{C}{C_0}\right) = k\frac{S}{V}t \tag{6}$$

C: concentration at time t
C_0: concentration in the saturated layer
S: effective surface area for diffusion
V: volume of the bulk solution
k: dissolution rate constant

Table III. Dissolution Rates of Dimemorfan Phosphate and Dimemorfan in Various Buffer Solutions

Dissolution medium	pH	Dimemorfan phosphate (cm/sec)	Dimemorfan (cm/sec)
1/15 M Phosphate	6.00	2.20×10^{-3}	3.27×10^{-3}
buffer solution	7.00	3.05×10^{-3}	2.67×10^{-3}
0.2 M Borate	8.00	3.60×10^{-3}	1.19×10^{-3}
buffer solution	9.00	—	0.966×10^{-3}

The dissolution rate constant, which was calculated based on Eq. (6), are listed in Table III. It was found that the dissolution rate constants of dimemorfan were inversely proportional to the initial pH of the dissolution media, although those of dimemorfan phosphate were proportional to it. This indicates that the dissolution of dimemorfan phosphate is greatly influenced by the extent of dissociation of phosphate, and that the dissolution of dimemorfan is directly influenced by the hydrogen ion concentration of the solution.

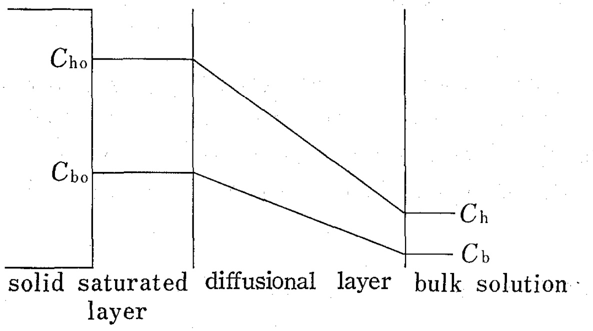

Fig. 5. A Schematic Model of the Dissolution of Mixtures of Dimemorfan and Dimemorfan Phosphate

C_{ho}: saturated concentration of dimemorfan phosphate
C_{bo}: saturated concentration of dimemorfan
C_h: bulk concentration of dimemorfan phosphate
C_b: bulk concentration of dimemorfan

Dissolution of Physical Mixtures of Dimemorfan and Its Phosphate

A schematic model of the dissolution of a mixture of dimemorfan and dimemorfan phosphate is shown Fig. 5. For the dissolution of physical mixtures, the following assumptions are made.

(1) Dimemorfan and its phosphate diffuse independently.

(2) The existing ratio of dimemorfan and its phosphate in the saturated layer at the crystal surface and in the bulk solution follows the Henderson-Hasselbach equation.

Based on these assumptions, the dissolution of a physical mixture of dimemorfan and dimemorfan phosphate can be described by the following equations:

$$V\frac{\mathrm{d}C_h}{\mathrm{d}t} = k_h S_h (C_{ho} - C_h) \tag{7}$$

$$V\frac{\mathrm{d}C_b}{\mathrm{d}t} = k_b S_b (C_{bo} - C_b) \tag{8}$$

From Eqs. (7) and (8),

$$V\frac{\mathrm{d}}{\mathrm{d}t}(C_h - C_b) = k_h S_h C_{ho} + k_b S_b C_{bo} - k_h S_h C_h - k_b S_b C_b \tag{9}$$

From the Henderson-Hasselbach equation,

$$C_{\mathrm{h}} = C_{\mathrm{b}}K,\ K = 10^{(\mathrm{p}K\mathrm{a}-\mathrm{pH})} \tag{10}$$

Inserting Eq. (10) into Eq. (9)

$$V\frac{\mathrm{d}}{\mathrm{d}t}(K+1)C_{\mathrm{b}} = k_{\mathrm{h}}S_{\mathrm{h}}C_{\mathrm{ho}} + k_{\mathrm{b}}S_{\mathrm{b}}C_{\mathrm{bo}} - C_{\mathrm{b}}(Kk_{\mathrm{h}}S_{\mathrm{h}}+k_{\mathrm{b}}S_{\mathrm{b}}) \tag{11}$$

where $C=0$ at $t=0$

$$\ln\left(1-\frac{Kk_{\mathrm{h}}S_{\mathrm{h}}+k_{\mathrm{b}}S_{\mathrm{b}}}{k_{\mathrm{h}}S_{\mathrm{h}}C_{\mathrm{ho}}+k_{\mathrm{b}}S_{\mathrm{b}}C_{\mathrm{bo}}}C_{\mathrm{b}}\right) = -\frac{Kk_{\mathrm{h}}S_{\mathrm{h}}+k_{\mathrm{b}}S_{\mathrm{b}}}{(K+1)V}t \tag{12}$$

substituting $S_{\mathrm{h}}/S_{\mathrm{b}}$ for r, we have

$$\ln\left(1-\frac{Krk_{\mathrm{h}}+k_{\mathrm{b}}}{rk_{\mathrm{h}}C_{\mathrm{ho}}+k_{\mathrm{b}}C_{\mathrm{bo}}}C_{\mathrm{b}}\right) = -\frac{S_{\mathrm{b}}(Krk_{\mathrm{h}}+k_{\mathrm{b}})}{(K+1)V}t \tag{13}$$

Solving Eq. (13) for C_{b},

$$C_{\mathrm{b}} = \frac{rk_{\mathrm{h}}C_{\mathrm{ho}}+k_{\mathrm{b}}C_{\mathrm{bo}}}{Krk_{\mathrm{h}}+k_{\mathrm{b}}}\left[1-\exp\left(-\frac{S_{\mathrm{b}}}{V}\cdot\frac{Krk_{\mathrm{h}}+k_{\mathrm{b}}}{K+1}t\right)\right] \tag{14}$$

Since $C=C_{\mathrm{b}}+C_{\mathrm{h}}$

$$C = \frac{rk_{\mathrm{h}}C_{\mathrm{ho}}+k_{\mathrm{b}}C_{\mathrm{bo}}}{Krk_{\mathrm{h}}+k_{\mathrm{b}}}(K+1)\left[1-\exp\left(-\frac{S_{\mathrm{b}}}{V}\cdot\frac{Krk_{\mathrm{h}}+k_{\mathrm{b}}}{K+1}t\right)\right] \tag{15}$$

k_{b}, k_{h}: dissolution rate constants of the base and its salt, respectively
C_{bo}, C_{ho}: saturated cocentrations of the base and its salt, respectively
V: volume of the dissolution medium

The dissolution of physical mixture of dimemorfan and its phosphate in pH 7.2 phosphate buffer solution is shown as a function of time in Fig. 6. The dissolution of dimemorfan increased with increase of mixing ratio (r) at this pH. The solubility of the physical mixture was determined and the results are listed in Table IV. The solubility increased with increase of the mixing ratio (r). Clearly the dissolution of dimemorfan from physical mixtures is closely related to the solubility of the mixture.

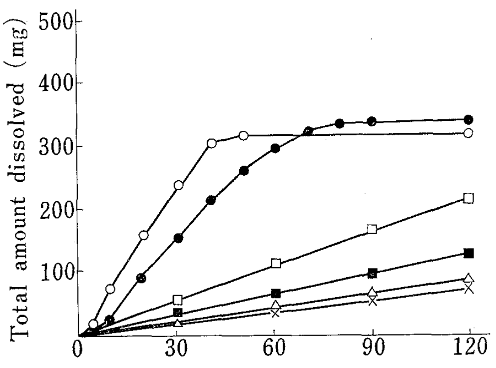

Fig. 6. Dissolution of Physical Mixtures of Dimemorfan Phosphate and Dimemorfan in 500 ml of pH 7.2 Buffer Solution as a Function of Time

Mixing ratio of dimemorfan phosphate and dimemorfan
—○—; 1: 0, —●—; 0.75: 1, —□—; 0.625: 1, —■—; 0.5: 1, —△—; 0.25: 1, —×—; 0: 1.

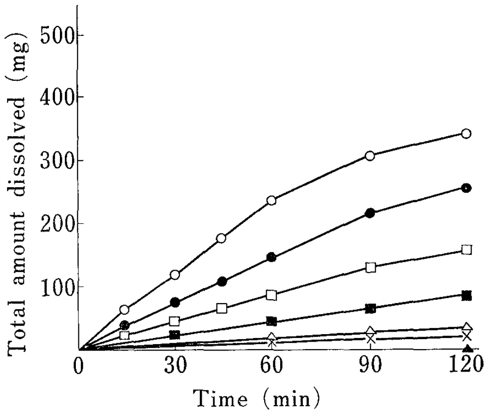

Fig. 7. Dissolution of Physical Mixtures of Dimemorfan Phosphate and Dimemorfan in 500 ml of Distilled Water as a Function of Time

Mixing ratio of dimemorfan phosphate and dimemorfan
—○—; 1:0, —●—; 1:1, —□—; 0.75:1, —■—; 0.625:1, —△—; 0.5:1, —×—; 0.25:1, —▲—; 0:1.

Table IV. Solubility of Physical Mixtures of Dimemorfan Phosphate and Dimemorfan in Phosphate Buffer Solution at 37°

Initial pH	Mixing ratio W_b: W_h	Solubility (mg/ml)	Final pH
7.20	0:1	26.64	6.27
	1:0.625	18.57	6.88
	1:0.5	14.92	6.97
	1:0.25	6.093	7.30
	1:0	2.676	7.60

W_b: weight of dimemorfan.
W_h: weight of dimemorfan phosphate.

Table V. Solubility of Physical Mixtures of Dimemorfan Phosphate and Dimemorfan in Distilled Water at 37°

Medium	Mixing ratio W_b: W_h	Solubility (mg/ml)	Final pH
Distilled water	0:1	25.08	4.48
	1:1	22.08	6.80
	1:0.75	19.78	6.82
	1:0.625	18.24	6.85
	1:0.5	14.70	6.90
	1:0.25	4.557	7.33
	1:0	0.06816	7.65

W_b: weight of dimemorfan.
W_h: weight of dimemorfan phosphate.

A similar experiment was done using distilled water as the dissolution medium, and the results are presented in Fig. 7. In the case of distilled water, it was concluded that as phosphate ions were not present initially in the medium, the dissolution rate was directly affected by increasing salt content. The solubility data presented in Table V appear to support this view.

Comparing Eqs. (6) and (13), the following equations are obtained:

$$C_o = \frac{rk_hC_{ho}+k_bC_{bo}}{Krk_h+k_b}(K+1) \tag{16}$$

$$r = \frac{(K+1)C_{bo}-C_o}{KC_o-(K+1)C_{ho}}\cdot\frac{k_b}{k_h} \tag{17}$$

Table VI. Dissolution Rate of Physical Mixtures of Dimemorfan Phosphate and Dimemorfan in 500 ml of Distilled Water or pH 7.2 Buffer Solution at 37°

Mixing ratio W_b: W_h	Distilled water		pH 7.2 Buffer solution	
	Calculated (cm/sec)	Observed (cm/sec)	Calculated (cm/sec)	Observed (cm/sec)
0:1		2.03×10^{-3}		2.70×10^{-3}
1:1	1.25×10^{-3}	1.20×10^{-3}		
1:0.75	0.805×10^{-3}	0.998×10^{-3}		
1:0.625	0.667×10^{-3}	0.593×10^{-3}	0.389×10^{-3}	0.946×10^{-3}
1:0.5	0.486×10^{-3}	0.231×10^{-3}	0.316×10^{-3}	0.716×10^{-3}
1:0.25	0.276×10^{-3}	0.247×10^{-3}	0.217×10^{-3}	1.08×10^{-3}
1:0		0.235×10^{-3}		2.17×10^{-3}

W_b: weight of dimemorfan.
W_h: weight of dimemorfan Phosphate.

where K is the dissociation constant described by Eq. (10); k_h and k_b are the dissolution rate constants of dimemorfan phosphate and dimemorfan, respectively; C_b and C_h are the solubilities of dimemorfan alone and its phosphate alone, respectively. These values are listed in Tables IV and V.

Apparent dissolution rate constants calculated by Eqs. (6) and (15) are listed in Table VI. For the dissolution of dimemorfan species in distilled water, the observed dissolution rate constants were almost equal to those calculated based on Eq. (15), except in the case of the 1: 0.5 (base: salt)mixture. The rate constant increased with increase of phosphate content. However, in the phosphate buffer solution, the observed values differed significantly from the calculated ones. The results suggest that phosphate ions suppress the dissolution of dimemorfan phosphate present in the physical mixture and affect the equilibrium of dissolved species in the saturated layer. In distilled water, which exerts no common ion effect on dimemorfan phosphate, the dissolution is completely controlled by the mixing ratio.