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DRUG MEMBRANE TRANSPORT ENHANCEMENT USING HIGH ENERGY DRUG POLYVINYLPYRROLIDONE (PVP) CO-PRECIPITATES

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SUMMARY

Dissolution rate data obtained with sulfathiazole–povidone(PVP) co-precipitates and hydrocortisone–povidone co-precipitates were compared to cellophane membrane diffusion data obtained with the co-precipitates. The hypothesis, that the rate-limiting drug phases in the co-precipitate dissolution experiments were high energy amorphous phases of the drug, was tested. In regions of the dissolution rate studies where the carrier effects due to the PVP–drug complexes were small, the dissolution rates for the two PVP–drug systems agreed well with the results of the membrane diffusion experiments. The normalized fluxes were found to be about 3.5 for the high energy phase of sulfathiazole and 14–18 for that of hydrocortisone.

INTRODUCTION

Previous reports from this laboratory have shown that co-precipitation of drugs with povidone (PVP) can significantly increase drug dissolution (Simonelli et al., 1969a and 1969b). In addition, extensive solubility studies using the PVP–sulfathiazole system provided strong evidence to support the original postulate; that an amorphous form of drug is the controlling sulfathiazole phase promoting the enhanced dissolution observed in these systems (Simonelli et al., 1976). The latter study also indicated that the co-precipitation technique, in addition to enhancing dissolution may also permit the formulator to increase the apparent solubility of a given drug. If the increased solubility of a drug achieved on co-precipitation is due to the formation of a high energy amorphous phase rather than to complex formation, then the enhancement should be reflected in an increased membrane transport of the drug above unit activity. The potential to improve biological drug activity through enhanced membrane transport achieved by utilizing high

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energy drug phases could be considerable, particularly in the case of topically administered drugs. The purpose of this report therefore was to explore the potential of the co-precipitation technique to enhance the membrane transport of sulfathiazole and hydrocortisone.

In order to quantitatively study drug membrane transport, a cell utilizing a synthetic model membrane was developed, which allowed the mechanism of drug membrane transport from solutions of co-precipitates to be studied under well defined conditions.

THEORETICAL

When two well stirred primarily aqueous compartments are separated by a semi-permeable membrane (Fig. 1) the rate of transport (G), assuming drug binding is negligible, in the steady-state will be given by

$$G = AP_e(C_D - C_R) \tag{1}$$

where A is the surface area of the membrane, P_e is the effective permeability coefficient and C_D and C_R are the drug concentrations in the donor and receptor compartments, respectively. In the case of transport across a porous membrane (Ho et al., 1980) P_e is given by Eqn. 2:

$$P_e = \frac{1}{\frac{2}{P_{aq}} + \frac{1}{P_m}} \tag{2}$$

where P_{aq} and P_m are the permeability coefficients due to the aqueous diffusion layer and the membrane respectively.

When drug is present in bound and unbound form then Eqn. 1 may be written as

$$G = \frac{AP_e}{1 + KC_p}(C_{TD} - C_{TR}) \tag{3}$$

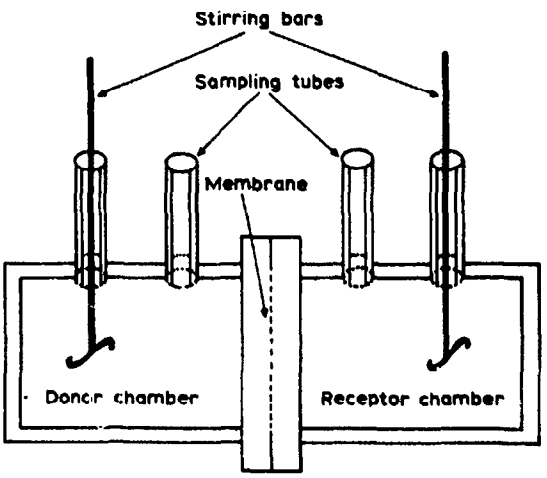

Fig. 1. Schematic diagram of the Lucite diffusion cell.

where C_p is the polymer concentration and C_{TD} and C_{TR} are the total bulk drug (free and bound) concentrations in the donor and receptor compartments, respectively; and K is the equilibrium distribution constant of drug to polymer. The amount of drug (W) in the cell at any time is given by

$$W = C_{TD}V_D + C_{TR}V_R = C^0_{TD}V_D \tag{4}$$

where V_D and V_R are the volumes of the donor and receptor compartments, respectively and C^0_{TD} is the concentration at time t = 0 in the donor compartment. Combination of Eqn. 3 and 4, re-arrangement and integration between the limits of t from 0 to t and C, from C^0_{TD} to C_{TD} when $V_D = V_R = V$ gives

$$\log\left(\frac{2C_{TD}}{C^0_{TD}} - 1\right) = \frac{-2AP_et}{2.303V(1 + KC_P)} \tag{5}$$

or in terms of C_R

$$\log\left(1 - \frac{2C_{TR}}{C^0_{TD}}\right) = \frac{-2AP_et}{2.303V(1 + KC_p)} \tag{6}$$

A plot of the left-hand side of either Eqns. 6 or 7 vs time, t, should be linear with a slope of $2AP^*/2.303V$ where $P^* = P_e/(1 + KC_p)$. In addition, if C_p is kept constant this slope should be independent of C_{TD}.

At early sampling times (i.e. when $C_R \approx 0$) the initial transport rate G_i will be given according to Eqns. 1 and 3, by

$$G_i = AP_eC_D \tag{7}$$

$$G_i = \frac{AP_e}{1 + KC_p} C_{TD} \tag{8}$$

Therefore a plot of G/A vs C_{TD} should have a slope of $P_e/(1 + KC_p)$.

EXPERIMENTAL

Preparation of co-precipitates

a. Sulfathiazole–PVP co-precipitates. Co-precipitates of sulfathiazole with PVP 10,000 were prepared by the alcohol evaporation method described previously (Simonelli et al., 1969).

b. Hydrocortisone–PVP coprecipitate. A weighed quantity of hydrocortisone [1], was dissolved in a minimum volume of glass distilled absolute ethanol, in a round-bottom flask. The hydrocortisone had been recrystallized from ethanol prior to use. A measured

[1] The Upjohn Company, Kalamazoo, Mich.

activity of tritium-labeled hydrocortisone [2] was added to this solution. A sufficient quantity of PVP [3] with 10,000 molecular weight, to obtain a 1-to-10 drug–PVP ratio, was further added and dissolved in this solution. The solvent was then flash evaporated in a rotary evaporator. To accelerate the evaporation process, the flask was placed in a 50°C water bath. When the co-precipitate was formed, the flask was then connected to a Cenco vacuum pump [4]. A cold solvent trap was placed between the flask and the vacuum pump. The system was evacuated for about 1 h until a constant weight was reached. Furthermore, this assured removal of residual solvent from the co-precipitate. The flask containing the co-precipitate was placed in a vacuum desiccator for a period of at least 24 h. Then the co-precipitate was scraped off the flask and converted to a fine powder with use of a mortar and pestle. The powder was stored in a vacuum desiccator in a light-free environment for future use.

Membrane transport studies

a. Preparation of membranes. The membranes employed in our experiments were prepared from regenerated cellulose dialysis tubing (Visking membrane) [5] having a flat width of 42 mm, a dry thickness of 21.8 μm and an average pore size of 2.4 nm. The membrane was cut into circles with a diameter of 38 mm, and washed with distilled water to remove the additives, such as glycerol and sulfur compounds, which were added for softening and preservation of the membrane, respectively. Before use, the membrane was soaked in distilled water to allow it to swell.

Design and operation of the diffusion cell

Each cell consisted of two transparent cylindrical Lucite compartments of depth 5.2 cm and with an opening 3.2 cm diameter. The volume of each compartment was 40 ml. Two side tubes of Lucite on each compartment of the cell were provided; one for insertion of a propeller, which was used (50 rpm) with a Hurst model CA synchronous motor, and the other for sampling (schematic diagram of the diffusion cell is illustrated in Fig. 1). The cellulose membrane was placed between the two compartments and a Teflon gasket ring with 3.2 cm i.d. and 0.5 mm thick was placed over the membrane to ensure sealing of the sides of the two compartments when they were screwed together. A Teflon tape was wrapped around the joint on the cell to prevent water penetration from the constant temperature bath. A brass tube was provided to hold the cell and suspend it in a desired position in the constant temperature bath. The donor and receptor compartments were then filled simultaneously with the media prepared for transport experiments.

Preparation and analysis of samples

Sulfathiazole was assayed spectrophotometrically [6] as previously described. Hydrocortisone in PVP solutions was assayed radiometrically [7] and also spectrophotometrically

[2] New England Nuclear, Boston, Mass.
[3] GAF Corp., New York, N.Y.
[4] Central Scientific, Chicago, Ill.
[5] Union Carbide.
[6] Beckman DB, Beckman Instruments, Irvine, Calif.
[7] Beckman Liquid Scintillation Counter, Model LS200, Beckman Instruments, Irvine, Calif.

at 247 nm. Saturated solutions in redistilled water and in PVP solutions were prepared as described by Kabasakalian et al. (1966) and hydrocortisone oxidation was minimized by adopting the procedures outlined by Monder (1968). The experimental temperature was 25°C.

Dissolution procedure

The apparatus used for dissolution rate determinations was similar in design to that previously described by Kwan et al. (1977) and employed a water-jacketed cylinder of internal diameter 3.8 cm. The aqueous dissolution medium volume used was 40 ml and the experimental temperature 25°C. The drug pellet surface area available for dissolution was 1.266 cm^2.

RESULTS AND DISCUSSION

The results of preliminary exploratory studies of the transport of sulfathiazole through a cellophane membrane from a sulfathiazole–PVP (1 : 3) coprecipitate are illustrated in Fig. 2. Previous investigations have established the presence of a stabilized high energy

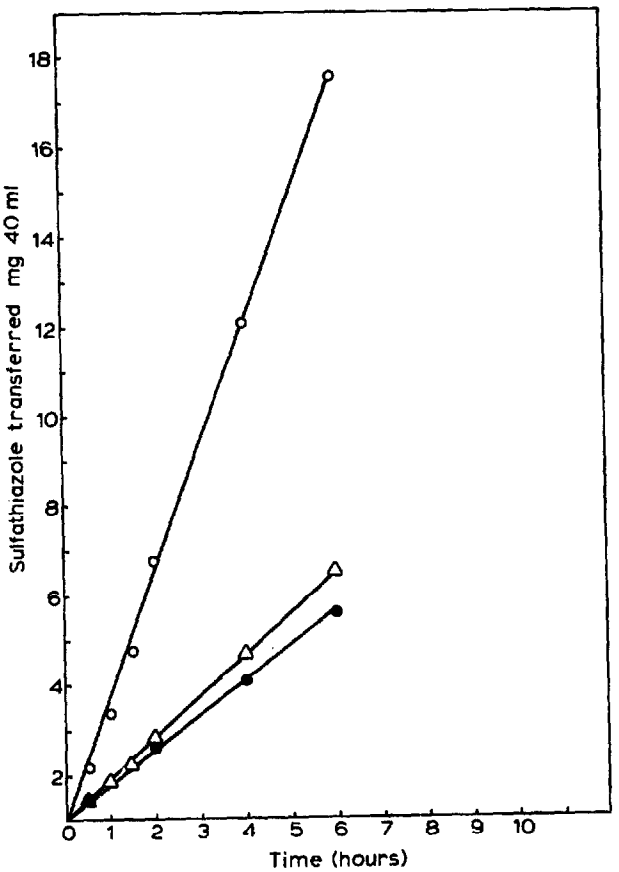

Fig. 2. Fluxes of sulfathiazole obtained in a diffusion cell with a cellophane membrane barrier. Volumes of donor and receptor chambers were 40 ml. Experimental temperature 25°C. Key: ○, saturated solution of 1 : 3 drug–PVP in 5% PVP solution; ●, saturated solution of crystalline drug; △, saturated solution of crystalline drug in 5% PVP.

form of sulfathiazole at this weight fraction (Simonelli et al., 1969a). The flux obtained from a 5% PVP aqueous solution saturated with the sulfathiazole–PVP co-precipitate was significantly greater than that obtained from solutions saturated with crystalline drug. The ratio of the slopes was 3.5 : 1, which is comparable with the 3.8-fold thermodynamic fugacity (or activity) difference between crystalline sulfathiazole and the high energy amorphous phase estimated previously from dissolution (Simonelli et al., 1969a) and solubility experiments (Simonelli et al., 1976). Transport data obtained using solutions saturated with crystalline drug and containing 5% PVP gave fluxes slightly higher (~10–15%) than those obtained in the absence of PVP. Some increase in flux was expected since transport measurements with pure PVP revealed measurable transfer of polymer giving permeability coefficients 0.1–0.05 of those for the drug. In addition, under the experimental conditions employed, the aqueous diffusion layers will contribute to the estimated permeability coefficient and thus the overall effective resistance could be reduced, as predicted by Amidon et al. (1979), in saturated media containing polymer-bound drug. However, as the data show, these effects do not contribute sizeably to the flux data obtained. The sulfathiazole results therefore support the contention that the high energy phase concept is valid and the "carrier" effect of the drug PVP complex in solution is at most an order of magnitude smaller than the thermodynamic effect.

Hydrocortisone–PVP Co-precipitate dissolution

Since previous studies have established that co-precipitation of certain steroids (including hydrocortisone and methylprednisolone) with PVP can increase the relative drug dissolution rate orders of magnitude higher than that observed with sulfathiazole (Mehta et al., 1971), a more detailed investigation of the dissolution and membrane transport properties of hydrocortisone was undertaken to more firmly establish the high energy co-precipitate phase concept.

TABLE 1

EXPERIMENTAL RELEASE RATES OF HYDROCORTISONE AS A FUNCTION OF PVP WEIGHT FRACTION IN COPRECIPITATE

PVP weight fraction	Absolute rates ($G \cdot ml^{-1} \cdot min^{-1} \times 10^5$)		Relative [a] rates	
	Initial	Limiting	Initial	Limiting
0.4 (1 : 1.5)	0.68	0.14	7.39	1.52
0.5 (1 : 1)	1.33	0.22	14.5	2.39
0.6 (1.5 : 1)	1.32	0.60	14.4	6.52
0.7 (2.3 : 1)	6.36	–	69.1	–
0.8 (4 : 1)	5.28	–	57.4	–
0.9 (9 : 1)	2.96	–	32.2	–
0.95 (19 : 1)	2.12	–	23.0	–

[a] Relative to pure hydrocortisone recrystallized from ethanol.

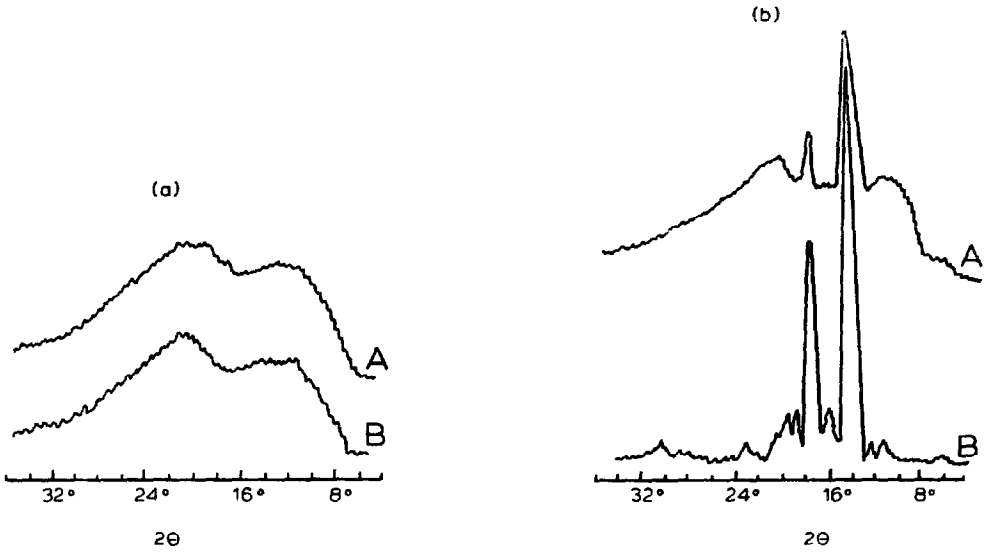

Fig. 3. a: comparison of X-ray diffraction spectra of 1 : 10 hydrocortisone to PVP co-precipitate and PVP (mol. wt. 10,000). Key: A, co-precipitated powder; B, PVP powder. b: comparison of X-ray diffraction spectra of mechanical mixture of 1 : 10 hydrocortisone to PVP powder and crystalline hydrocortisone. Key: A, mechanical mixture; B, crystal powder.

Hydrocortisone dissolution rates obtained, as a function of PVP weight fraction in co-precipitate are summarized in Table 1. The maximum relative enhancement in dissolution rate was of the order of 70-fold. Dissolution profiles at lower PVP weight fractions were non-linear. The initial rates for the 0.5 and 0.6 weight fraction systems are at a plateau corresponding to a rate of 14–15 times that of the pure drug. Dissolution data for the 0.4, 0.5 and 0.6 PVP weight fraction systems were also obtained in media containing 5% and 10% PVP in an attempt to inhibit nucleation and/or crystal growth which can occur during co-precipitate dissolution (Simonelli et al., 1969a; Mehta et al., 1971). The initial dissolution rates increased in the PVP-containing media for all 3 co-precipitates, the rate for the 0.4 PVP weight fraction system becoming equal to that of the 0.5 and 0.6 weight fraction system. However, the dissolution profiles remained curved. These results suggest that a high energy form of hydrocortisone, with an activity of 14–15 times that of the pure drug is present in PVP co-precipitates and at the lower PVP weight fractions, even in the presence of up to 10% PVP, reconversion to the more stable form occurs during dissolution. In order therefore to minimize this potential for nucleation and crystal growth during membrane transport experiments the 10 : 1 (PVP-drug) co-precipitate system was used. X-ray diffraction data showing the essentially amorphous state of hydrocortisone in this system are shown in Fig. 3.

Hydrocortisone membrane transport

Cellulose membrane transport data for saturated hydrocortisone solutions as well as co-precipitate-containing systems are summarized in Fig. 4. In co-precipitate-containing systems the concentration of PVP was adjusted to 9.5%. The flux from the PVP-contain-

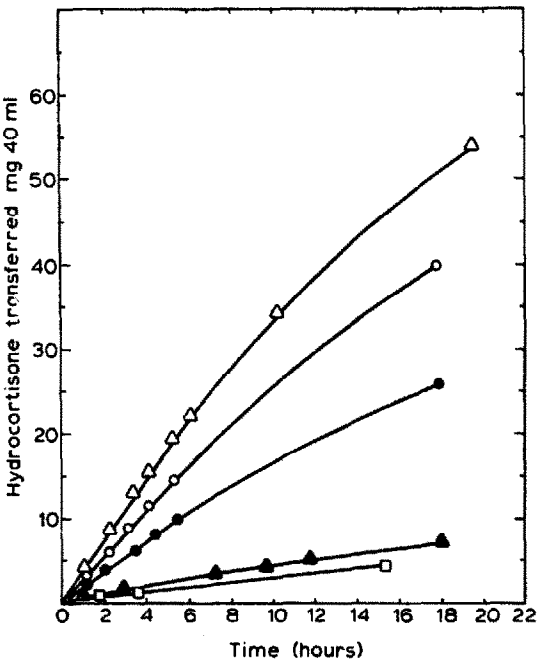

Fig. 4. Fluxes of radioactive labeled hydrocortisone at 25°C obtained experimentally in a diffusion cell with a cellulose membrane barrier. All supersaturated solutions were prepared by dissolving predetermined amounts of a 1 : 10 hydrocortisone–PVP co-precipitate into water and adjusted PVP concentration to 9.5%. Volumes of donor and receptor chambers were 40 ml. Key: △, supersaturated drug solution containing 4.54 mg/ml hydrocortisone and 9.5% PVP; ○, supersaturated drug solution containing 3.41 mg/ml hydrocortisone and 9.5% PVP; ●, supersaturated drug solution containing 2.27 mg/ml hydrocortisone and 0.5% PVP; ▲, saturated solution of hydrocortisone in 9.5% PVP (0.65 mg/ml); □, saturated solution of hydrocortisone in water (0.38 gm/ml).

ing solution, saturated with crystalline hydrocortisone, is about 15% higher than from the aqueous solution, an effect similar to that observed with sulfathiazole. Fluxes obtained from co-precipitate-containing systems were, however, considerably higher, the flux increasing with increasing hydrocortisone content. A comparison of the initial slopes indicates that the highest flux is about 10 times that of unit activity. The data in Fig. 4 are plotted according to Eqn. 6 in Fig. 5. All the data points from PVP-containing systems lie on the same line, indicating good agreement of the data with the proposed model. The greater slope for the hydrocortisone–water system reflects the relationship between P^* and P_m. When the concentration of hydrocortisone was increased above 4.6 mg/ml nucleation was observed in the donor solution and data deviated from the model.

Effect of nucleation inhibitors on transport

Since attainment of higher transport rates seemed to be limited by recrystallization, a number of nucleation and crystal growth inhibitors were screened for hydrocortisone crystal growth inhibition. As a result, Clayton yellow and dodecylamine hydrochloride were selected for use in membrane flux experiments.

In the presence of 0.05% Clayton yellow, co-precipitate solutions, containing up to 6.5 mg ml^{-1} of hydrocortisone, could be prepared in aqueous solution of 9.5% PVP without visible cloudiness developing during the membrane transport studies. Data from these experiments are also included in Fig. 5 and are co-incidental with data obtained at lower drug concentrations in the absence of inhibitor. These results suggest that Clayton yellow does not influence the membrane permeability but enhances hydrocortisone transport by preventing crystallization in the donor compartment. At higher hydrocortisone concentrations visible nucleation did occur and the transport rate declined rapidly with time.

Estimates were made of the hydrocortisone initial transport rates. The actual and normalized values obtained are plotted, together with those estimated in the absence of Clayton yellow, vs hydrocortisone total concentration in Fig. 6. The good linear relationship which includes the data from solutions which became cloudy is evident thus supporting the presence of a high energy phase in co-precipitate systems. The relative maximum enhancement in membrane transport brought about by co-precipitate was 18–19-fold and in systems in which no nucleation was observed, 14–15-fold. These values are similar

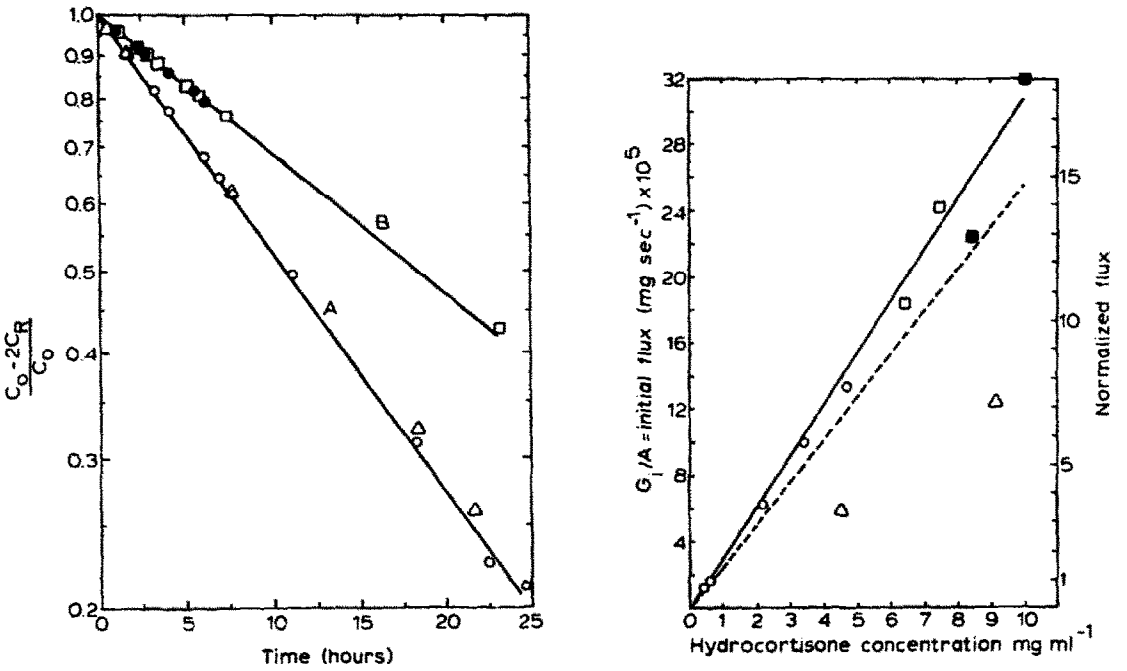

Fig. 5. Semi-log plot of $(C_0 - 2C_R)/C_0$ vs time for transport of hydrocortisone across dialysis membrane. Key: A – ▲, saturated solution of crystalline hydrocortisone in water; and ⊙, saturated solution of crystalline hydrocortisone in 0.05% Clayton yellow. B – ●, coprecipitate of hydrocortisone dissolved in water; and ⊡, in 0.05% Clayton yellow.

Fig. 6. Initial hydrocortisone transport rate vs hydrocortisone concentration in 9.5% PVP prepared from 10 : 1 (PVP–drug) co-precipitate. Also included is the normalized flux which is defined: (flux with coprecipitate)/(flux with saturated solution of crystalline drug in 9.5% PVP). Key: ⊙, PVP 9.5%; ⊡, PVP 9.5% plus Clayton yellow, 0.05%; ▲, PVP 9.5% plus dodecylamine HCl 1%; ■, systems in which visible nucleation occurred during the experiment; - - - - - -, includes contribution from aqueous diffusion layers; ———, assumes only membrane control.

in magnitude to the relative enhancements observed in the dissolution rate experiments. Also included in Fig. 6 are data obtained using dodecylamine HCl (1%) as nucleation inhibitor. In the presence of dodecylamine a much lower effective permeability coefficient (P_e) was obtained, indicating possible solubilization of the drug by dodecylamine HCl. As a result, for a given hydrocortisone concentration a much lower membrane flux was observed (Fig. 6). With this agent solutions containing as high as 18 mg/ml of hydrocortisone were required before visible nucleation occurred in the donor chamber. However, in these systems the limiting hydrocortisone transport rates were still only 15–16 times unit activity.

In Fig. 6 the expected relationship (Eqn. 7) between G_i/A and C_{TD} using P_e calculated from Fig. 5 is included (dotted line), K being estimated from the solubility data. In addition the relationship expected if $P_e = P_m$ is also shown (upper line). P_m was estimated from Eqn. 2 using P_{aq} determined from previous base line studies of the limiting stirring rate-dependent transport of benzoic acid in the same cell. The data in Fig. 6 lie closer to the "P_m" line, suggesting, as predicted by Amidon (1979), that the presence of bound drug in the system can eliminate the effect of the aqueous diffusion layer, and this also contributes to the enhanced membrane transport.

REFERENCES

Amidon, G.E., Thesis, The University of Michigan, 1979.

Ho, N.F.H., Park, J.Y., Amidon, G.E., Ni, P.F. and Higuchi, W.I., Methods for interrelating in vitro, animal and human absorption studies. In Aguiar, A.J. (Ed.), Gastrointestinal Absorption of Drugs, American Pharmacetuical Association, Academy of Pharmaceutical Sciences, Washington, D.C., 1980, in press.

Kabasakalian, P., Britt, E. and Yudis, M.D., Solubility of some steroids in water. J. Pharm. Sci., 55 (1966) 643.

Kwan, K.H., Higuchi, W.I., Molokhia, A.M. and Hofmann, A.F., Dissolution kinetics of cholesterol in simulated bile I: Influence of bile acid–lecithin ratio and added electrolyte, J. Pharm. Sci., 66 (1977) 1094–1101.

Mehta, S.C., Simonelli, A.P. and Higuchi, W.I., High energy solids coprecipitate methylprednisolone polyvinylpyrrolidone (PVP). Presented at the APhA Academy of Pharmaceutical Sciences, San Francisco meeting, March–April 1971.

Monder, C., Stability of corticosteroids in aqueous solutions. Endocrinology, 82 (1968) 318–326.

Simonelli, A.P., Mehta, S.C. and Higuchi, W.I., Dissolution rates of high energy polyvinylpyrrolidone (PVP)-sulfathiazole coprecipitates, J. Pharm. Sci., 58 (1969a) 538–549.

Simonelli, A.P., Mehta, S.C. and Higuchi, W.I., Mechanisms of solubilization and drug release rates from metastable (high-energy) drug–polyvinylpyrrolidone coprecipitates. Presented at the APhA Academy of Pharmaceutical Sciences. Montreal meeting, May 1969b.

Simonelli, A.P., Mehta, S.C. and Higuchi, W.I., Dissolution rates of high energy sulfathiazole–povidone coprecipitate II: Characterization of form of drug controlling its dissolution rate via solubility studies, J. Pharm. Sci., 65 (1976) 355–361.