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Interactions between quinolone antibiotics and phospholipid membrane for prediction of alveolar macrophage uptake *in vitro*

SUN Jin[1,2,3], DEGUCHI Yoshiharu[2], CHEN Ji-Min[1], ZHANG Ru-Hua[1], MORIMOTO Kazuhiro[2]
([1]*Department of Pharmaceutics, Shenyang Pharmaceutical University, Shenyang 110016, China*; [2]*Department of Pharmaceutics, Hokkaido College of Pharmacy, 7-1 Katsuraoka-cho, Otaru-city, Hokkaido 047-0264, Japan*)

KEY WORDS artificial membranes; membrane lipids; liposomes; quinolones; alveolar macrophages; high pressure liquid chromatography

ABSTRACT

AIM: To compare the effectiveness of the different parameters for predicting alveolar macrophage (AM) uptake, interactions between quinolones, including two amphipathic bases, and phospholipid membrane were evaluated by three different membrane-like systems. **METHODS**: AM cells were isolated, cultured as confluent monolayers, then incubated with drug solution at 37 ℃. At designated time points, uptake was terminated by aspirating solution, followed by rinsing, cell lysis, and analysis of drug and protein concentrations. Immobilized artificial membrane (IAM) chromatography and liposome/buffer system were used to determine interactions with phospholipid membrane, expressed as lipophilicity indices, lg k_{IAM} and lg $D_{L\,B,7.4}$, respectively. An *n*-octanol/buffer system was also employed as the reference hydrophobicity, lg $D_{O\,B,7.4}$. **RESULTS**: For the tested set, lg k_{IAM} correlated more significantly with lg $D_{L/B,7.4}$ ($r^2 = 0.93$) than with lg$D_{O\,B,7.4}$ ($r^2 = 0.65$). There were better correlations between either lg k_{IAM} or lg $D_{L/B,7.4}$ and the extent of accumulation in AM than did lg $D_{O/B,7.4}$ ($r^2 = 0.89$, 0.92, and 0.67, respectively). Correlations obtained using lg k_{IAM}, lg $D_{L\,B,7.4}$, and lg $D_{O/B,7.4}$ were comparable when regressed against the logarithm of influx rate into AM for a set consisting of five amphoteric quinolones and quinidine. **CONCLUSION**: Liposome/buffer system and IAM chromatography could provide nearly similar scale of lipophilicity measurement, both distinct from *n*-octanol/buffer system. Accumulation by AM was better described by lg k_{IAM} or lg $D_{L\,B,7.4}$ than lg $D_{O\,B,7.4}$, and the passive diffusion was principal form during drugs transported across AM membrane.

INTRODUCTION

Lipophilicity of a solute, expressed by its partition or distribution coefficients between the lipophilic and hydrophilic phases, represents the interactions between the solute and phospholipid membrane. It has been found that lipophilicity is associated with the transport of solutes across biological membrane and exerts a key role in controlling drug absorption, distribution, and elimination. The optimally evaluative systems of lipophilicity or membrane interactions have been the objectives of intense studies. An *n*-octanol/buffer system has been widely accepted as a model partition system. But unfortunately, bulky *n*-octanol solvent is not a realistic model for the liquid crystalline phospholipid membrane, because membrane consists of ordered hydrophilic and lipophilic regions with anisotropic properties, also because membrane interactions are the sum of diverse intermolecular forces.

Recently, the alternative membrane-like systems have appeared, resulting in eliciting the desired lipophilicity, such as liposome/buffer system and immobilized artificial membrane (IAM) chromatography. Liquid liposome possesses the most structural similarity to fluid bilayer cellular plasma membrane. IAM chromatography introduces immobilized artificial membrane as high pressure liquid chromatography column packing material and mimics the lipid environment of the fluid biological membrane on a solid matrix. Both systems have been shown to outperform *n*-octanol/buffer system in predicting drug-membrane interactions, membrane transport, and biological activity[1-3].

The currently developed quinolones, such as

[3] Correspondence to Dr SUN Jin. Phn 86-24-2395-3006. Fax 86-24-8389-0024. E-mail sunjin66@21cn.com
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grepafloxacin (GPFX) and HSR-903, were designed to treat lower respiratory tract infections. In order to achieve ideally therapeutical efficacy, it is crucial of these quinolones to penetrate well into AM and to accumulate highly within AM enough to effectively destruct the facultative intracellular bacteria[4]. Therefore, it is essential to elucidate the underlying factors accounting for penetration and accumulation in AM for quinolones.

In the present study, we evaluated and compared drug-membrane interactions by three different membrane model systems for a structurally diverse set consisting of ampholytes, acids, and cases. The effectiveness of the different parameters for predicting AM uptake, was assessed by comparison of correlation coefficients derived from correlation of either influx rate into AM or ratio of intracellular to extracellular concentrations (C_i/C_e) by AM, with respective lipophilicity parameters.

MATERIALS AND METHODS

Materials GPFX, ciprofloxacin (CPFX), levofloxacin (LVFX), and OPC-17203 (internal standard for HPLC assay) were provided from Otsuka Pharma Co Ltd (Tokyo, Japan). HSR-903 and NR-762 (internal standard) were supplied by Hokuriku Pharma Co Ltd (Fukui, Japan). Quinidine (QUD), propranolol (PROP), nalidixic acid (NDA), oxolinic acid (OXA), and pipemidic acid (PPA) were bought from Wako Chem Co (Osaka, Japan). Egg phosphatidylcholine (EPC) was obtained by Nippon Oil Lipid Co (Tokyo, Japan). IAM PC. MG (4.6 mm × 150 mm) column was purchased from Regis Chem Co (Morton Grove, IL). All other reagents were of analytical grade (Fig 1).

Preparation of the AM monolayer The AM cells were isolated from male Wistar rats (Japan SLC, Shizuoka, Japan) by the bronchoalveolar lavage method[5]. The cells were plated at 2.5×10^5 cells per well in RPMI-1640 medium (Gibco BRL, Life Technologies, Rockville, MD), supplemented with 10 % fetal bovine serum (Gibco BRL), 2-mercaptoethanol 50 μmol/L, and gentamicin 10 mg/L. The non-adherent cells were removed by washing and after 20 h culture AM cells formed confluent monolayers for use in uptake studies.

***In vitro* uptake study** Growth medium was removed and the monolayers were washed twice with serum free medium (SFM, Gibco BRL), supplemented with HEPES 2-[4-(2-hydroxyethyl)-1-piperazinyl] ethanesulfonic acid 10 mmol/L, and then were incubated with the SFM containing studied drugs 500 μmol/L at 37 ℃. At designated time points up to 30 min, the medium was removed and AM monolayers were washed thrice with ice-cold phosphate buffered saline (PBS). The cells were solubilized by NaOH 0.1 mol/L followed by HPLC analysis of drug concentrations and measurement of cell protein with Coomassie protein assay reagent (Pierce Chem Co, Rockford, IL). The intracellular volume of AM was determined by a velocity-gradient centrifugation technique using [^{3}H]-wate[6] and estimated as 4.2 mL·g^{-1} cell protein in this study. Therefore, drug accumulation in AM could be expressed as ratio of intracellular to extracellular concentrations (C_i/C_e). Influx rate (V_0) was calculated as a slope from the linear part of the uptake-time course.

Determination of *n*-octanol/buffer distribution coefficient The distribution coefficient from *n*-octanol/buffer system ($D_{O\,B.7.4}$) was measured by shake-flask technique at *n*-octanol and PBS (pH = 7.4) phases.

Determination of liposome/buffer distribution coefficient The distribution coefficient from liposome/buffer system ($D_{L\,B.7.4}$) was measured by ultra-centrifugation method[7]. Multilamellar liposome was prepared by EPC using film-dispersion method and suspended in PBS (pH = 7.4). The EPC content in liposome (about 1.5 g/L) was determined by the enzymatic choline quantification kit (Wako Chem Co, Osaka, Japan). Drug stock solution (2 mmol/L) was added to blank liposome suspension to reach final concentration (2 μmol/L). The resultant liposome suspension was equilibrated in 37 ℃ incubator for 5 h, and then 5 mL was ultra-centrifuged (280 000 × *g*, Himac CP-65β, Hitachi Koki Co Ltd, Japan) for 40 min to obtain 150 μL supernatant (free drug fraction). The distribution coefficient, $D_{L\,B.7.4}$, is calculated by $D_{L\,B.7.4} = [(C_t - C_f) \times W_1]/(C_f \times W_2)$, where C_t and C_f are original total, free drug concentrations, respectively; W_1 and W_2 are weights of aqueous and lipidic phases, respectively[7].

Determination of capacity factor for IAM chromatography The eluents were mixtures of acetonitrile and PBS 0.01 mol/L (pH = 7.4) in different acetonitrile percentages [φ, 0 % – 30 % (v/v)] at a flow rate of 1 mL/min. The drugs were dissolved in PBS (200 μmol/L) and 10 μL samples were subjected into HPLC at 35 ℃, monitored at 215 nm with an UV detector. Chromatographic retention was expressed by

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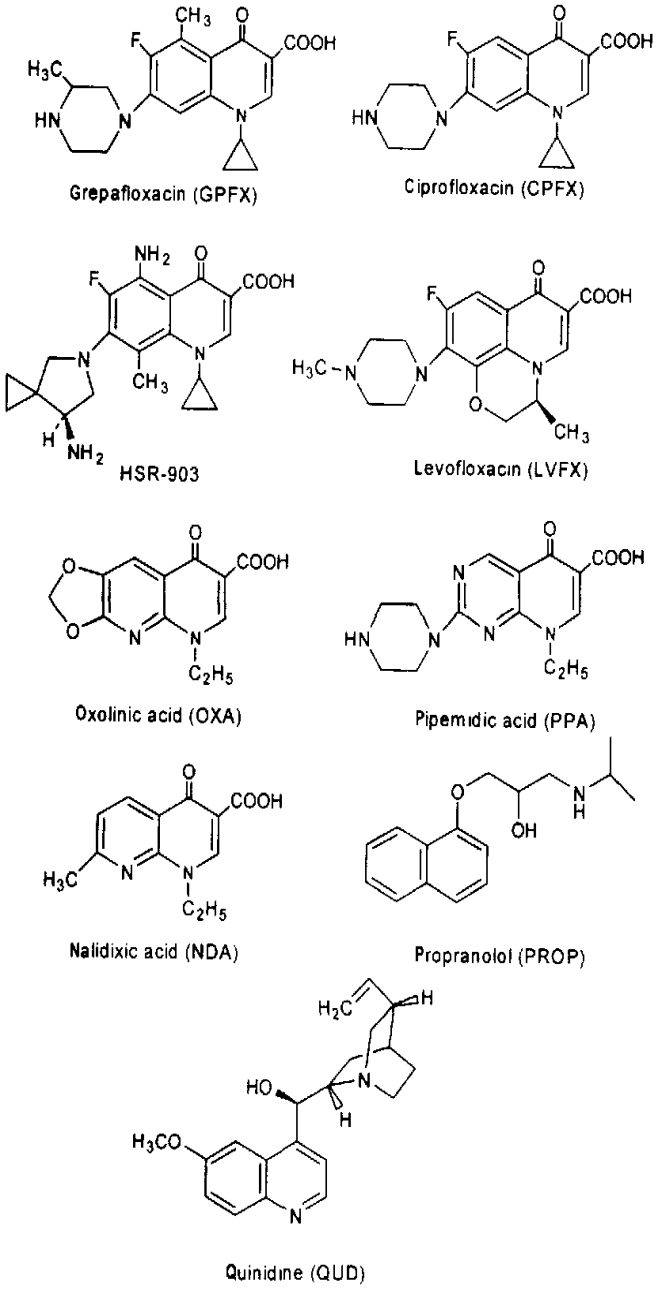

Fig 1. Chemical structures of drugs under investigation.

the logarithm of capacity factor, defined as $\lg k'_{IAM} = \lg [(t_r - t_0)/t_0]$, where t_r and t_0 were the retention times of drugs and a non-retained solute (water), respectively. The logarithm of capacity factor extrapolated to (or measured at) 100 % aqueous phase ($\lg k_{IAM}$) was used to express the membrane affinity of solutes.

All reported values were the average of at least three parallel measurements; the 95 % confidence interval related to each value was not more than 0.07.

Analytical method The concentrations of drugs were determined by an RP-HPLC method. As for AM extraction samples, they were mixed well with five-fold volume methanol for deproteinization and the supernatants were subjected to HPLC. An HPLC system (Shimadazu, Kyoto, Japan) consisted of an LC-10AD pump, RF-10AXL fluorescence or LC-10AD UV detectors, CTO-6A oven, and C-R6A data process integrator, and an STR ODS-Ⅱ column (5 μm, 4.0 mm × 250 mm, Shinwa Chem Co, Kyoto, Japan) was used except for HSR-903. The flow rate was 0.8 mL/min and the

column temperature was 40 ℃. Mobile phase was composed of 0.01% phosphoric acid (containing sodium sulfate 20 mmol/L)/acetonitrile (3 : 1, v/v) for determination of GPFX, CPFX, LVFX, and PPA (λ_{ex} = 325 nm, λ_{em} = 448 nm for GPFX, CPFX and LVFX, λ_{ex} = 278 nm, λ_{em} = 448 nm for PPA, respectively). An alternative mobile phase, PBS 0.05 mol/L (pH = 3)-acetonitrile-methanol (55:20:25, v:v:v), was used to determine OXA, NDA, QUD, and PROP (λ_{ex} = 325 nm and λ_{em} = 366 nm for OXA and NDA, λ_{ex} = 327 nm and λ_{em} = 382 nm for QUD, and λ_{ex} = 290 nm and λ_{em} = 340 nm for PROP, respectively). HSR-903 was measured by Mightysil RP-18 column (5 μm, 4.6 mm × 150 mm, Kanto Chem Co, Tokyo, Japan) and mobile phase of ammonium phosphate buffer 0.03 mol/L (pH = 2.5)-acetonitrile (3 : 1, v/v). It was monitored by the UV detector at λ_{max} = 308 nm, with a flow rate of 1.2 mL/min at 35 ℃.

RESULTS AND DISCUSSION

Comparison of three membrane-like systems

The chemical structures of drugs under investigation were illustrated in Fig 1, including five amphoteric quinolones, GPFX, HSR-903, CPFX, LVFX, and PPA, two acidic quinolones, NDA and OXA, and two amphipathic bases QUD and PROP.

Lipophilicity was assessed in *n*-octanol/buffer and liposome/buffer systems at pH = 7.4 aqueous phase. As for IAM chromatography, in order to compare the different lipophilicity parameters and to keep experiments close to the physiological environment, lg k'_{IAM} was determined with eluent being PBS 0.01 mol/L (pH = 7.4), but not all compounds can be eluted with 100 % aqueous phase. Therefore, the mobile phases containing various acetonitrile percentages (φ) were prepared to elute the highly lipophilic drugs. Linear relationships between lg k'_{IAM} and φ were confirmed, with all correlation coefficients over 0.995, as shown in Fig 2. Since added acetonitrile showed effects with different extent on lg k'_{IAM}, it was required to normalize lg k'_{IAM} values to 100 % aqueous phase (lg k_{IAM}), not only for data referred to partitioning between phospholipid membrane and aqueous phase, but also to avoid fictitious interaction measuring scales. The resulting values were listed in Tab 1.

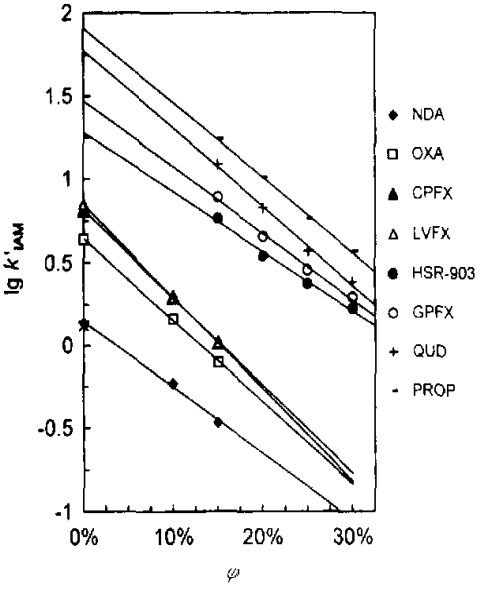

Fig 2. Plots of logarithm of capacity factors determined on IAM PC.MG column (lg k'_{IAM}) at different fractions of acetonitrile (φ).

Tab 1. Various physicochemical parameters and AM uptake. ND means not determined. $n = 4$. $\bar{x} \pm s$.

Drugs	lg $D_{O/B,7.4}$	lg k_{IAM}	lg $D_{L,B,7.4}$	C_i/C_e[1]	V_0[2]
NDA	0.12	0.14	0.90	0.56 ± 0.16	ND
PPA	-1.86	0.12	1.01	5.3 ± 0.4	0.78 ± 0.05
OXA	0.24	0.64	1.33	19.5 ± 0.8	ND
CPFX	-0.78	0.81	1.27	11.7 ± 0.5 (8.1)[3]	4.4 ± 0.6
LVFX	-0.46	0.85	1.78	7.90 ± 0.12 (7.1)[3]	2.5 ± 1.0
HSR-903	0.29	1.28	3.05	38 ± 11 (36.3)[3]	14.73 ± 0.17
GPFX	0.71	1.47	3.63	45.6 ± 1.4 (50.9)[4]	11.4 ± 1.0
QUD	2.13	1.78	3.99	51.8 ± 1.9	13.6 ± 2.2
PROP	1.27	1.91	4.68	49.0 ± 1.3	ND

[1] The extent of accumulation in AM and the ratio of intracellular to extracellular concentrations. [2] Influx rate into AM (μmol · min^{-1} · g^{-1} protein). [3] Came from Ref 16, determined by *in vitro* cultured AM cells. [4] Concentrations ratio of AM to epithelial lining fluid after 4 h oral administration to rats, representing *in vivo* C_i/C_e ratio (unpublished observations).

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As shown in Fig 3, lipophilicity derived from different membrane model systems was compared. A reasonable relationship was observed between lg $D_{O/B,7.4}$ and lg k_{IAM} values (Fig 3A):

$$\lg D_{O/B,7.4} = 1.42(\pm 0.40)\lg k_{IAM} - 1.24(\pm 0.47) \quad (1)$$

$n = 9$, $r = 0.80$, $r^2 = 0.65$, $s = 0.69$

In this and following equations, n denotes the number of solutes contained in the regression equation, r denotes correlation coefficient, r^2 denotes squared correlation coefficient, and s denotes standard error of the estimate. Numbers in parentheses account for the standard deviation of regression coefficients. The quality of regression equation is assessed by r^2 and s.

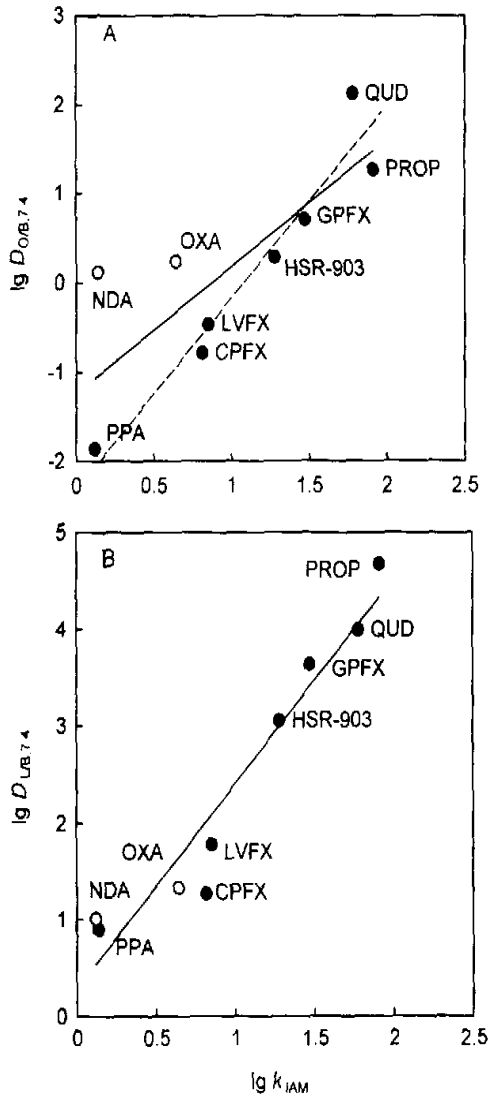

Fig 3. Comparisons of different lipophilicity parameters. lg $D_{O/B,7.4}$, lg k_{IAM}, and lg $D_{L/B,7.4}$ were determined by n-octanol/buffer, IAM chromatography, and liposome/buffer systems at pH = 7.4 aqueous phase, respectively. Panel A: lg $D_{O/B,7.4}$ *vs* lg k_{IAM}, the solid line is the regression line for all studied drugs and dot line for this set excluding NDA and OXA; Panel B: lg $D_{L/B,7.4}$ *vs* lg k_{IAM}.

In the n-octanol/buffer system, the hydrophobic interaction is the predominant force contributing to partitioning of solutes into n-octanol phase, and accordingly lg $D_{O/B,7.4}$ is regarded as hydrophobicity descriptor. The above correlation indicated that the binding to IAM PC.MG surface was in the larger part dependent on the solutes' hydrophobicity. However, owing to inclusion of different types of solutes (acid, base, and ampholyte), the equation showed a lower r^2 and a higher s values, demonstrating much scattered lg $D_{O/B,7.4}$ population (Fig 3A, solid line). After omitting outliers of two acidic quinolones, the quality of regression equation was improved based on r^2 (from 0.64 to 0.93) and s (from 0.69 to 0.33) (Fig 3A, dot line). It implied that IAM chromatography could selectively discriminate two acids from ampholytes and bases on the basis of polar extra-interactions. For example, NDA and HSR-903 showed similar hydrophobicity (lg $D_{O/B,7.4}$), while membrane affinity (lg k_{IAM}) of HSR-903 was far greater than NDA, as shown in Tab 1 and Fig 3A. That is, two acids demonstrated the relatively higher hydrophobicity but lower membrane affinity. It has been found that bases display the higher membrane affinity than expected regarding their hydrophobicity because the ordered phospholipid membrane can accommodate positively charged form of bases resulting in attractive polar extra-interactions[3,8]. We have observed that ampholytes behave similarly to bases, possessing alike extra-interaction with phospholipid (unpublished observation). Therefore, the lipophilicity measuring scale for IAM system differed from that of n-octanol/buffer system.

In view of IAM and liposome/buffer systems, the more significant relationship between lg $D_{L/B,7.4}$ and lg k_{IAM} values was established:

$$\lg D_{L/B,7.4} = 2.12(\pm 0.23)\lg k_{IAM} + 0.29(\pm 0.27) \quad (2)$$

$n = 9$, $r = 0.96$, $r^2 = 0.93$, $s = 0.39$

Taking r^2 and s values into account, the quality of equation was notably high for structurally diverse solutes, with no scattered lg $D_{L/B,7.4}$ population (Fig 3B). This indicated that IAM and liposome/buffer systems provided a similar lipophilicity measurement scale and gave comparable information. Liquid crystalline liposomal membrane is the fluid, dynamic, and ordered bilayer

lipid membrane, the most representative artificial membrane model, and can describe the drug-membrane interactions accurately. From ^{31}P NMR and molecular dynamics simulation studies, IAM surface demonstrated many properties in interfacial motional characteristics and distributions of interfacial functional groups, similar to those in liquid liposomal membrane[9,10]. Ong *et al* found that there existed a good relationship of lipophilicity from IAM and liposome/buffer systems for 23 structurally unrelated compounds[11]. Moreover, seen from intermolecular forces, the partitioning of solutes into IAM and liposomal membrane is associated with hydrophobic and hydrophilic as well as electrostatic forces, while only hydrophobic force occurs in *n*-octanol phase. Taken all together, IAM chromatography can model the partitioning process of solutes into fluid liposomal membrane.

Prediction of AM accumulation and penetration The AM uptake was investigated using *in vitro* cultured AM monolayers. In the preliminary uptake studies, AM uptake reached a steady state after 30 min incubation, and then accumulation of drugs was determined at 30 min, expressed as C_i/C_e ratio. The results were in a good agreement with the reference or *in vivo* values, by which *in vitro* AM model was validated (Tab 1). GPFX and HSR-903 showed concentrative uptake in AM, with C_i/C_e ratio being 45.6 and 38. In conjunction with their excellent antibacterial spectra and activity[12,13], they may be effective in killing the facultative intracellular bacteria, contributable to good efficacy in the treatment of pneumonia. The uptake of NDA was lowest, and its C_i/C_e value (0.59) was below 1, displaying a very inefficient accumulation by AM.

When AM uptake reached the steady state, the influx rate into AM equaled the efflux rate from AM. C_i/C_e ratio truly represented the extent of accumulation within AM and strength of binding to intracellular AM components. The relationships between C_i/C_e values and different lipophilicity parameters were investigated, as demonstrated in Fig 4 and the following regression equations:

$$C_i/C_e = 14.45(\pm 3.85)\ \lg D_{O/B,7.4} + 22.81(\pm 4.27) \quad (3)$$
$$n=9,\ r=0.82,\ r^2=0.67,\ s=11.81$$
$$C_i/C_e = 13.61(\pm 1.56)\ \lg D_{L/B,7.4} 7.25(\pm 4.30) \quad (4)$$
$$n=9,\ r=0.96,\ r^2=0.92,\ s=5.95$$
$$C_i/C_e = 29.51(\pm 3.94)\ \lg k_{IAM} 4.06(\pm 4.63) \quad (5)$$
$$n=9,\ r=0.94,\ r^2=0.89,\ s=6.83$$

Evidently, $\lg D_{L/B,7.4}$ and $\lg k_{IAM}$ better predicted drugs accumulation within AM than did $\lg D_{O/B,7.4}$. This

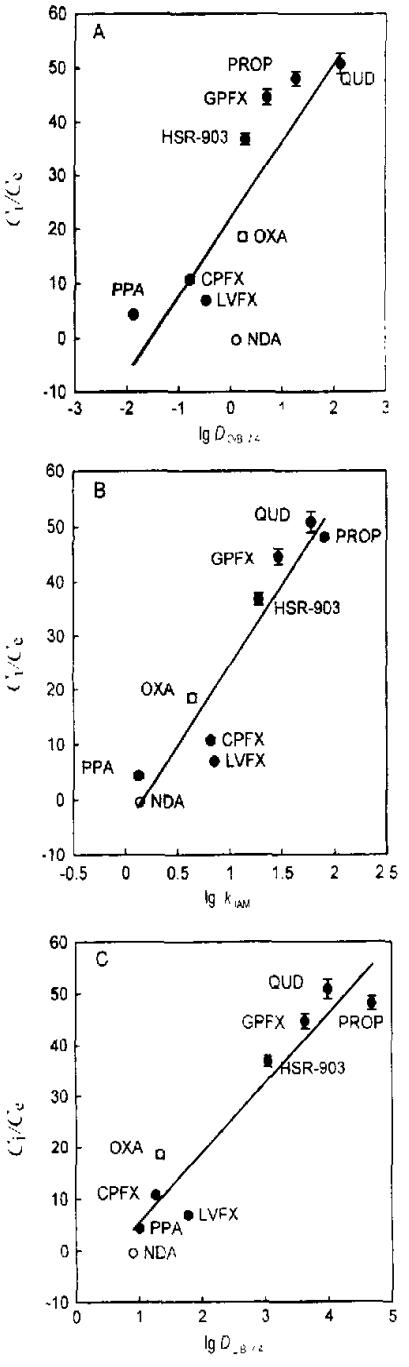

Fig 4. Correlations between C_i/C_e and different lipophilicity parameters. C_i/C_e defined as the ratio of intracellular to extracellular concentrations, described the extent of accumulation in AM and was determined after AM uptake reached equilibrium. Panel A: C_i/C_e – lg $D_{O/B,7.4}$, solutes hydrophobicity; Panel B: C_i/C_e – lg k_{IAM}, solutes binding to IAM PC.MG membrane; Panel C: C_i/C_e – lg $D_{L/B,7.4}$, solutes binding to EPC bilayer fluid liposomal membrane.

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suggested that not only hydrophobicity but also other forces determining the binding to IAM and liposomal membranes, ascribed to the binding process within AM. In other word, the membrane affinity quantified by IAM and liposome/buffer systems was a more efficient predicator of AM intracellular binding than hydrophobicity from *n*-octanol/buffer system. In effect, NDA and OXA showed relatively higher hydrophobicity as outliers in Fig 4A but lower membrane affinity and poorer AM intracellular accumulation in Fig 4B and 4C. Furthermore, the existence of attractive polar extra-interaction between phosphate group of the head-group of the ordered membrane with positively charged amino group, probably exerted an essential action during drugs interacting with AM intracellular components.

To elucidate the underlying mechanism of transport across AM membrane, we measured AM uptake time-course within short intervals up to 3 min. Because of short uptake period, the intracellular free amount of drugs was minor so that the efflux rate was negligible compared with influx rate. AM uptake was mainly decided by influx process and proportional to time (Fig 5A). The initial uptake rate (V_0) accordingly represented influx rate into AM and was calculated as a slope from the linear part of the uptake time-course (Tab 1). The tested group included five amphoteric quinolones and quinidine. The positive relationships were established between V_0 and their respective lipophilicity, as shown in Fig 5B. Correlation coefficients obtained using lg k_{IAM}, lg $D_{L\,B,7.4}$, and lg $D_{O/B,7.4}$ were comparable when regressed against lg V_0, with r^2 values being 0.89, 0.76, and 0.74, possibly due to composition for this set, the most being the structurally homogenous amphoteric quinolones. It had been pointed out that there were similar results derived from lg k_{IAM} and lg $D_{O/B,7.4}$ as for structurally related solutes, but lg k_{IAM} usually gave more precise results for structurally diverse compounds[11,14]. In the case of passive diffusion, the membrane permeability coefficient (P_m) is positively proportional to lipophilicity and diffusion coefficient that is related to molecular weight[15]. Since the molecular weight spanned a narrow range for tested drugs, P_m was principally controlled by lipophilicity. Therefore, based on the above results, the passive diffusion was to a greater extent involved in the process of transporting studing drugs across AM membrane.

IAM chromatography and liposome/buffer system provided results superior or similar to *n*-octanol/buffer system in explaining drug accumulation and penetration by AM. They can model more diverse types of solute-membrane interactions than does *n*-octanol/buffer system. Furthermore, the importance is that IAM and liposome/buffer systems can specially discriminate lipophilicity of structurally diverse solutes by membrane affinity, whereas *n*-octanol/buffer can not by hydrophobicity. In addition, IAM chromatography possesses

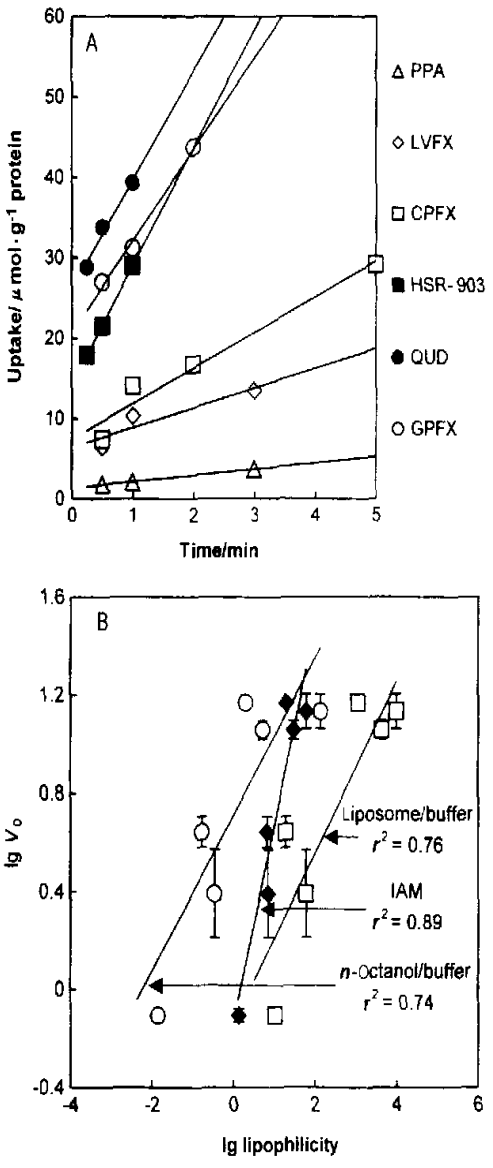

Fig 5. AM uptake time-course and correlations between lg V_0 and lg (lipophilicity). V_0 represented the influx rate into AM (μmol·min^{-1}·g^{-1} protein) and was determined as a slope from the linear part of the uptake time-course. Panel A: AM uptake time-course within short interval; Panel B: correlations of lg V_0 with lg (lipophilicity).

some practical advantages, such as ease of automation, high speed, minimum amount, not high purity and reproducibility, which for sure increase the potential application of IAM chromatography.

In conclusion, liposome/buffer system and IAM chromatography presented similar scale of lipophilicity measurement, both mimicking the biological membrane well and emulating all types of intermolecular forces during membrane interactions, both of which were distinct from *n*-octanol/buffer system. Membrane affinity was a better predictor than hydrophobicity for predicting drugs accumulation by AM and the passive diffusion was associated with transport for studing drugs across AM membrane.

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通过喹诺酮抗生素与磷脂膜的相互作用预测肺泡巨噬细胞单层的体外摄取

孙 进[1,2,3]，出口芳春[2]，陈济民[1]，张汝华[1]，森本一洋[2]（[1]沈阳药科大学药学院药剂研究室，沈阳 110016，中国；[2]北海道药科大学药剂研究室，北海道小樽 047-0264，日本国）

关键词 人工膜；膜脂质类；脂质体；喹诺酮类；肺泡巨噬细胞；高压液相色谱

目的：预测肺泡巨噬细胞单层的体外摄取。**方法**：以培养的肺泡巨噬细胞单层为体外模型，用磷脂膜色谱，脂质体/水系统评价药物与磷脂膜的相互作用，分别表示为 lg k_{IAM}，lg $D_{L\,B,7.4}$，用正辛醇/水系统测定参考的疏水性参数（lg $D_{O\,B,7.4}$）。**结果**：lg $D_{L\,B,7.4}$（$r^2=0.93$）比 lg $D_{O/B,7.4}$（$r^2=0.65$）具有与lg k_{IAM}更显著的相关性。lg k_{IAM}和 lg $D_{L\,B,7.4}$均

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E-mail aps@mail.shcnc.ac.cn Phn/Fax 86-21-6474-2629

比lg $D_{O\,B,7.4}$与细胞内药物的蓄积度有更好的相关性. 但对于由5个两性喹诺酮抗生素和奎尼丁组成的受试集合, 三者均与药物进入细胞内的速度具有相近的显著的正相关性. **结论**: 磷脂膜色谱和脂质体/水系统给出相似的亲脂性测量尺度, 且均与正辛醇/水系统区别有显著性. 与疏水性参数相比, 膜亲和性是更有效的肺泡巨噬细胞内药物蓄积和结合的预测参数.

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