ISSN 1027-5495. Functional Materials, 28, No.3 (2021), p. 525-532.
doi:https://doi.org/10.15407/fm28.03.525

A microscopic model of drugs penetration into lipid membranes

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Received February 1, 2021

The problem of interactions between complex ordered media and admixture molecules is a challenge of modern material science. In the case of interactions between lipid membrane medium and drugs, the problem gains important biological sense. The present work is aimed to develop a microscopic model for characterization drug penetration into lipid bilayer membrane. The model considers the balance between elastic ("drowing out") and dispersion ("drowing in") components of "membrane — drug" interactions which defines the equilibrium depth of drug penetration and describes properly such features as penetration to a certain depth, accumulation of drug molecules at the center of the membrane, as well as the absence of penetration. It helps to establish common physical basis of a set of experimental results obtained for these systems, including V-shape dependences "membrane melting temperature vs. the depth of penetration" as well as "specific membranotropic effect of a drug molecule vs. its lipophilicity", etc.

Keywords: mathematic model, lipid membranes, drugs, elastic interactions, dispersion interactions.

Мікроскопічна модель проникнення лікарської речовини у ліпідну мембрану. *Р.Є.Бродський, О.В.Ващенко*

Взаємодія комплексних впорядкованих середовищ з молекулами домішок є складною проблемою сучасного матеріалознавства. У випадку взаємодії ліпідних мембран з лікарськими речовинами ця проблема набуває важливого медико-біологічного значення. Задача даної роботи полягає у розробці мікроскопічної моделі, яка описує проникнення лікарських речовин у ліпідну мембрану. Модель розглядає рівновагу між пружною (виштовхувальною) та дисперсійною (втягувальною) складовими міжмолекулярних взаємодій, яка визначає глибину проникнення лікарської речовини у мембрану, а також адекватно описує випадки накопичення лікарської речовини всередині мембрани та відсутності проникнення. Модель дозволяє встановити загальні фізичні засади низки експериментальних результатів, отриманих для таких систем, у томі числі V-образні залежності температури плавлення мембрани від глибини проникнення домішки, а також питомого мембранотропного ефекту від ліпофільності лікарської речовини.

Взаимодействие комплексных упорядоченных сред с молекулами примеси является сложной проблемой современного материаловедения. В случае взаимодействия липидных мембран с лекарственными веществами эта проблема приобретает важный медико-биологический смысл. Задача настоящей работы состоит в разработке микроскопической модели, описывающей проникновение лекарственных веществ в липидную мембрану. Модель рассматривает равновесие между упругой (выталкивающей) и дисперсионной (втягивающей) составляющими межмолекулярного взаимодействия, оп-

ределяющее равновесную глубину проникновения лекарственного вещества в мембрану, а также адекватно описывает случаи накопления лекарственного вещества внутри мембраны и отсутствия проникновения. Модель позволяет установить общие физические основы ряда экспериментальных результатов, полученных для таких систем, в том числе объяснить V-образные зависимости температуры плавления мембраны от глубины проникновения примеси, а также удельного мембранотропного эффекта от липофильности лекарственного вещества.

1. Introduction

Lipid membranes are highly ordered quasi-bidimentional complex structures which are of general importance for various life processes. They are commonly represented as double layers (or bilayers) consisted of two monolayers of lipid molecules with opposite orientation (Fig. 1).

Generally, the lipid membrane is a carefully balanced environment and any changes inflicted upon its structure must be considered in conjunction with the overall effect that this may have on the function and integrity of the membrane [1]. Many foreign molecules, including drugs, can cross or bind to lipid membranes and potentially modulate their physical properties [1, 2].

Depending on their parameters, drug molecules (admixtures) could localize at the polar membrane surface or penetrate into its non-polar interior. A phenomenological model of drugs effects under their binding to the membrane surface has been suggested in [3]. The present paper considers the effects of admixtures penetration into non-polar (hydrophobic) part of the membrane. The most important feature of this type of interaction is the dependence of membranotropic effects on the depth of admixture localization which stimulates transfer from 2-dimensional to 3-dimensional membrane model.

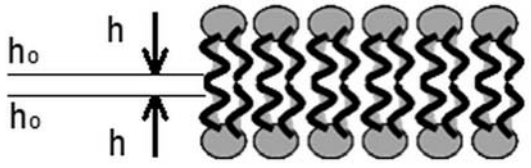

Fig. 1. Simplified structure of a lipid membrane in water medium. Polar moieties of lipids (grey ovals) form the surfaces, non-polar hydrocarbon chains (black lines) constitute the membrane interior; h_o is the equilibrium depth of admixture penetration into the membrane.

Lipid membranes possess a set of specific features, which should be briefly described before moving to the results.

a. Polar moieties of lipids form hydrophilic (polar) membrane surfaces and non-polar lipid chains form its lipophilic (non-polar) inner core [2, 4] (see Fig. 1). Stabilization of the membrane is provided by fine balance between hydrophilic and hydrophobic interactions [2, 5, 6].

b. Properties of hydrophilcity and lipophilsity of individual substances are commonly characterized by their partition coefficient log$P$. The value of log$P$ reflects distribution of a substance between water and octanol; it is positive for hydrophilic substances and it is negative for hydrophobic ones. As to the lipid membrane, transbilayer lipophilicity gradient exists across its polar and non-polar moieties. As it evidenced by EPR data [7] in non-polar interior this gradient is linear at least to the center of lipid chains in each monolayer.

c. Water molecules mainly present at the polar surfaces of membrane, but also distribute, in some degree, into its non-polar interior, to the depth of about 1 nm from the membrane center [8]. This factor also contributes into the above mentioned gradient of lipophilicity.

d. The lipid membrane is characterized by complex transbilayer density profiles [9, 10]. For example, in dipalminoylphosphatidylcholine (DPPC) membrane, maximal density is registered at the distance of about 1 nm from the center [11], i.e. near the middle of lipid chains of each monolayer. As one can conclude from data [12], in all membranes formed by long-chain lipids (12 to 24 groups) the first 9–10 methylene groups of the lipid chains are packed most tightly.

e. Packing density defines fluctuation of cross-section of proper lipid fragment [13] and is closely related to membrane free volume (V_{free}). Generally, V_{free} is defined as difference between the volume of lipid molecules in the membrane and the sum of their Van-der-Vaals volumes [14].

f. One of fine-tuned parameters of lipid membranes is melting temperature (T_m), which characterizes a 1st order phase transi-

tion phase transition from more ordered gel phase to more disordered liquid crystalline phase [2]. It is a complex parameter which is related to electronic and geometrical structure of lipids, as well as to their packing density and a number of other parameters [2, 15]. At other conditions being equal, T_m diminishing indicates lowering of packing density of lipids, and *vise versa* [2, 16].

Keeping in mind these features, one could find interesting the results obtained in [17] for membranes formed by equisized lipids containing double bond C=C in various positions along lipid tails. (In this case, –C=C– fragment could be considered as a kind of admixture which penetrates to various depth into the membrane. Principal difference of this fragment from an admixture molecule consists in its structurally predeterminated localization.) Results [17] evidence vast and essentially linear T_m diminishing (–60°C) under –C=C– fragment moving from position 1 (near the surface) to position 9, and equal T_m elevation (+60°C) under C=C moving from position 9 to the end of the lipid tails (i.e. to the membrane center). So, V-shape dependence $T_m(h)$ was observed for these systems. As far as we know, these results have not been interpreted yet from physical point of view.

Thus, on admixture penetration into the lipid membrane, there is an intriguing interplay between lipid density profiles, T_m values and, as it will be shown in Sec. 2, lipophilicity of admixture. Elucidation of physical basis of this phenomenon with developing of a proper microscopic model is the aim of the present work.

2. Experimental

Melting temperature of model lipid membrane T_m (see Sec. 1, f) could be properly determined using differential scanning calorimetry technique (DSC) [18–21]. Admixture introduction into model lipid membrane predominantly results in T_m shift, this or other way. This shift (ΔT_m) depends, in general, on the type of membrane, on admixture nature and concentration as well as on environment conditions. For the purpose of elucidation the effect of admixture nature at different admixture concentrations (c_{wt}) at other conditions be equal, it is convenient to use the value of $a_{wt} = \Delta T_m / c_{wt}$ [22], i.e. specific membranotropic effect of admixture.

The DSC data on a_{wt} for various drugs (see [23] for details) in DPPC membrane allowed us to obtain a non-monotonous (V-shape) dependence of a_{wt} vs. log$P$ diapason of the admixtures (Fig. 2). As one can see, absolute membranotropic effect ($|a_{wt}|$) grows in the interval of 0 to 6 and reduces at higher log$P$ values. (The result corresponding to log$P \le 0$ relates to drugs interaction with the membrane surfaces and has been described by the model reported in [3].) Growth of $|a_{wt}|$ becomes clear on taking into account the lipophilicity gradient across the membrane (see Sec. 1, b), whereby the larder log$P$ the deeper drug penetration into the membrane interior.

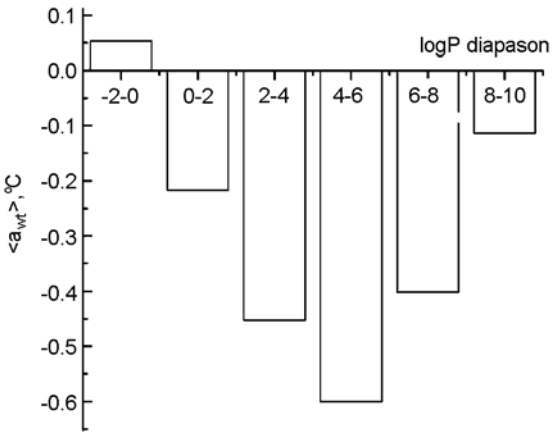

Fig. 2. Mean values of specific membranotropic effect (a_{wt}) at the selected diapasons of admixture lipophilicity.

However, reducing of $|a_{wt}|$ at log$P > 6$ is beyond of the pale of this mechanism. To our mind, this reducing is a direct consequence of non-monotonous lipid chain package across the membrane (see Sec. 1, d) with substantial elevation of V_{free} around the membrane center. Intrinsic $V_{free}(h)$ profile of the lipid membrane provides therefore non-equivalent membranotropic effects of admixtures at various depths of penetration. It is directly confirmed by [24], were a_{wt} was found to be zero for highly lipophilic cholesterol oleyl carbonate (log$P$ 17.4) and could be explained by its accumulation into significantly disordered central moiety of the membrane.

These considerations have moved us to the idea of developing a model describing the above mentioned mechanisms, which is presented in Sec. 3.

3. Model

Penetration of a lipophilic admixture molecule into the membrane to the depth $h = h_o$ (see Fig. 1) is mainly governed by two processes: (1) "drawing in" process occurring

due to passing from the hydrophilic external medium into the region with matching lipophilicity, and (2) "drawing out" process which results from its elastic interactions with lipid tails. If an embedded molecule is smaller than $V_{free}(h_o)$ (see Sec. 1, e), contraction effect could take place. On the contrary, a "repulsive" molecule exceeds $V_{free}(h_o)$. Here, we have restricted ourselves to consideration of relatively small "repulsive" molecules.

We can define h_o from the criterion of potential energy minimum. This energy consists of two above mentioned contributions, namely, dispersion interactions and elastic interactions between admixture molecules and bulk of the lipid tails.

Let's specify the form of each contribution. Energy of dispersion interaction, $U_p(h)$, is defined by lipophilicity of local environment of an admixture molecule, i.e. both of non-polar lipid tails and polar water molecules. It should be taken into account that the tails are, in fact, uniformly lipophilic along their axes, but water content varies essentially [8]. Optimal environment at the dept h_p should evidently have the same polarity as the admixture molecules do. Hence any h deviation form h_p, both positive and negative, leads to U_p elevation.

As it follows from numerous literature data [8, 25–28] water content changes with h essentially linear. This feature, to our mind, is the origin of $\log P(h)$ linearity reported in [7] (see Sec. 1, b). Based on these data, $U_p(h)$ could also be considered as linear, for first approximation. Taking into account the above considerations, we obtain:

$$U_p(h) = C_p \cdot |h - h_p| + K_p, \qquad (1)$$

where h_p is the depth of optimal local environment of the admixture molecule, C_p is a positive constant, K_p is a constant corresponding to $U_p(0)$.

Energy of elastic interactions, $U_e(h)$, is defined by the extent of deformation of hydrophobic moiety resulted from admixture molecules accommodation, i.e. both from the size of the molecule and from $V_{free}(h)$. Transbilayer profiles of $V_{free}(h)$ are known from literature [26, 29]. Actually, the local value of $V_{free}(h)$ is a local accessible cross-area of lipid tails $a_{free}(h)$ multiplied by a certain characteristic depth interval. Let us assume that this interval is equal to the thickness of an admixture molecule embedded into the membrane (even if it is different, the corresponding values of $V_{free}(h)$ would differ by a constant, but general shape of the dependence remains unchanged).

Let V and a are the volume and the cross-area of the embedded molecule, correspondingly. Then, additional (produced) free volume (ΔV_{free}) arises in those regions of non-polar membrane interior where lipid chains push one from another. It is proportional to $V - V_{free}(h)$ or $a - a_{free}(h)$. In the case of a small number of admixture molecules (when they penetrate independently and localize far enough one from another) ΔV_{free} is proportional to the total amount of admixture. Similarly, elastic energy in this case is also proportional to admixture amount as far as each molecule contributes equally in this value. Hence, U_e value is proportional to ΔV_{free} and, therefore, to $V - V_{free}(h)$.

According to [25], $V_{free}(h)$ profile has a minimum in the middle of lipid tails (which corresponds to a maximum of close-packed lipid cross-sectional area), and the shape of this dependence is roughly linear in the regions beyond this minimum. It means that the general shape of $V - V_{free}(h)$, as well as of $U_e(h)$, is similar to above mentioned $U_p(h)$, but is specularly reflected (with maximum instead of minimum).

Below, we will consider two types of curves which fit well the model under consideration, beginning with a simpler linear one (where $U_p(h)$ and $U_e(h)$ are linear relative to $|h - h_e|$) and then moving to a model with smooth extremes.

Within the linear model,

$$U_e(h) = -C_e \cdot |h - h_e| + K_e, \qquad (2)$$

where the sense of h, C and K is similar to that in Eq. (1). According to [12], h_e localizes in the proximity of 9^{th} methylene group (see Sec. 1, d).

So, total energy of a molecule embedded into the membrane is

$$U(h) = U_p + U_e = \qquad (3)$$
$$= C_p \cdot |h - h_p| - C_e \cdot |h - h_e| + K_p - K_e.$$

As it clear from Fig. 3, dependence (3) consists of 3 linear regions and may have a single minimum (when $C_p > C_e$, see Fig. 3a, b) or a single maximum (when $C_p < C_e$, see Fig. 3c, d). Thus, admixture molecules could behave in following ways:

1) An admixture molecule are hindered to penetrate into non-polar membrane interior (Fig. 3c, d) as far $U(h)$ has a maximum.

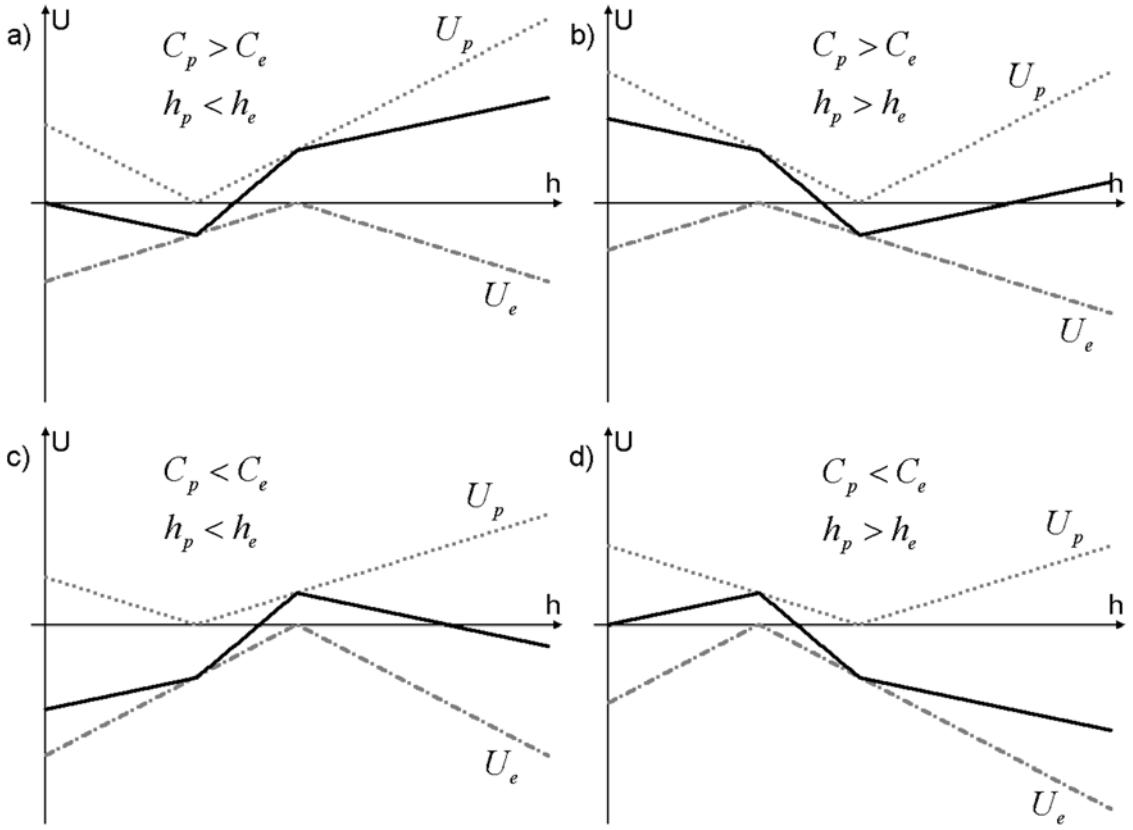

Fig. 3. General shape of linear $U(h)$ dependences (Eq. 3) for various ratios between the constants: $U_p(h)$ (dotted lines); $U_e(h)$ (dot-dash lines); envelope curves (solid lines).

Whilst, certain part of admixture molecules could overcome the potential barrier and permeate deeper than $U(h)$ maximum, trapping to the region of $U(h)$ decreasing. Such molecules have an opportunity to accumulate at the center of bilayer, though their number is rather small as compared with the total amount of admixture.

2) An admixture molecule do penetrate into the membrane and localize at the depth h_o corresponding to $U(h)$ minimum, which is equal to h_p in both cases, $h_p < h_e$ and $h_p > h_e$ (Fig. 3a, b). It actually means that the value of h_e has no effects on the admixture localization (this is an intrinsic feature of just the linear model which will be retuned to below).

3) An admixture molecule is able to localize at the center of the membrane and accumulate in there if h_o value (corresponding to $U(h)$ minimum) is larger than the monolayer thickness. This case realizes if optimal lipophilicity of microenvironment for a given molecule is larger than local lipophilicity in any point across the membrane (as it reported in [24]). This case of drug — membrane interactions is worth special attention, as far as drug accumulation into the membrane is known to have enormous influence on their efficacy [30].

So, the linear model reflects all the effects observed under drug — membrane interactions and allows one to predict the optimal depth of drug localization in the lipid membrane (naturally, drug molecules balance around the optimal depth due to thermal motion).

The main features of the linear model:

1. This model describes all basic effects of drug — membrane interactions, namely, penetration of a drug molecule into bilayer at a certain depth, its localization into the center of the membrane, as well as the absence of penetration.

2. Linearity of $U_p(h)$ and $U_e(h)$ dependences beyond extreme points follows from numerous experimental data and simulations.

3. This model allows one to obtain analytically the equilibrium (optimal) depth of drug localization h_o. However h_o appears to coincide with h_p in all cases, meaning that drug — membrane interactions is only governed by lipophilicity of admixture, which seems queerly.

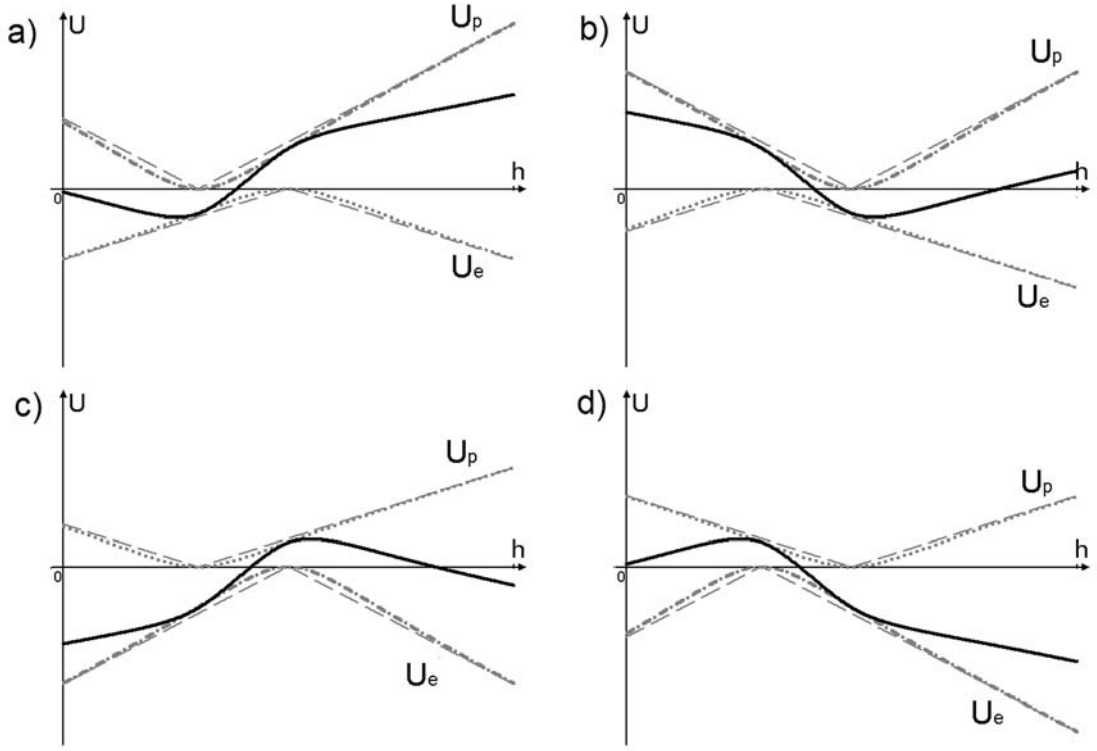

Fig. 4. General shape of non-linear $U(h)$ dependences (Eqs. 4) for various ratios between the constants: non-linear $U_p(h)$ and $U_e(h)$ are marked with dashed lines; other legends are characterized in Fig. 3.

The last feature caused necessity of moving towards non-linear model. It is possible to simulate some kind of dependences with a smooth extreme and linear shape beyond of it by function $f(x) = C \cdot |x| \cdot (1 - \exp(-\alpha|x|))$, where $\alpha > 0$ is a coefficient which regulates the degree of smoothing. Thus, Eqs. (1)–(3) become to:

$$U_p(h) = C_p \cdot |h - h_p| \cdot (1 - \exp(-\alpha|h - h_p|)) \quad (4)$$
$$U_e(h) = -C_e \cdot |h - h_e| \cdot (1 - \exp(-\alpha|h - h_e|))$$
$$U(h) = C_p \cdot |h - h_p| \cdot (1 - \exp(-\alpha|h - h_p|)) - C_e \cdot |h - h_e| \cdot (1 - \exp(-\alpha|h - h_e|)).$$

Here, k_p and k_e coefficients are absent because they are uns uffisient for the extremums position.

Examples of these functions at $\alpha = 10$ are depicted in Fig. 4 for the same ratios between the other constants as in Fig. 3. As one can see, the general shape of the dependences (existence of extremes and their mutual positions) remains unchanged compared with the linear model that confirms maintaining of the system's behavior. The main divergence from the linear model consists in influence of the elastic component on the depth of admixture localization, i.e. on the minimum of $U(h)$ at $C_p > C_e$ (Fig. 4a, b). Indeed, within a framework of non-linear model, despite of the linear one, h_o does not coincide with h_p, but is shifted this or other way.

In general, the shift value can be determined none but numerically. Nevertheless, we can give certain analytical estimation for the case when the shift is relatively small, and h_p is separated enough from one h_e. In this case h_p drops into "linear" region of $U_e(h)$. Let $h_p > h_e$. In the proximity of h_p

$$U_e(h) \approx -C_e \cdot (h - h_e)$$
$$U_p(h) \approx C_p\alpha(h - h_p)^2.$$

Then,

$$U(h) \approx C_p\alpha(h - h_p)^2 - C_e \cdot (h - h_e),$$

hence,

$$U'(h) \approx 2C_p\alpha(h - h_p) - C_e. \quad (5)$$

Setting (5) to zero, we obtain $h_{min} = h_p + C_e/2C_p\alpha$. Thus, h_o appeared to be shifted on $C_e/2C_p\alpha$ in the direction of $U_e(h)$ decreasing

in the proximity of h_p, as it is shown in (Fig. 4b).

Taking into account transbilayer profile of lipid tails packing (see Sec. 1, d), a "repulsive" drug molecule which localizes into the lipid membrane at the different depth h generates different $\Delta V_{free}(h)$. Indeed, the tighter is lipid packing, the stronger is repulsion between a drug molecule and neighbouring lipids and, therefore, the larger is ΔV_{free}. Though ΔV_{free} distributes non-uniformly within the membrane, it generally causes elevation of the membrane area. As it was noted in [3], this effect corresponds to exerting effective lateral pressure P_{eff} which is negative (stretching) in the case of a "repulsive" molecule. The value of P_{eff} is proportional to the changes of the membrane area, i.e. to ΔV_{free}. According to Clapeyron-Clausius equation, P_{eff} is directly related to the membrane melting temperature T_m [3]. Namely, when the shift of the melting temperature under drug penetration (ΔT_m) is relatively small, the linear relation between ΔT_m and P_{eff} takes place, as well as it might be between ΔT_m and $\Delta V_{free}(h)$.

This conclusion could be verified with the knowledge of $\Delta T_m(h)$ for an admixture of the fixed size and at the same $V_{free}(h)$, $T_m(h)$ and $V_{free}(h)$ could be of similar shape. However, it is problematically to find a number of admixtures with such properties. A good match for such admixture could be double C=C bond, which is inherent for lipid tails of biological membrane. A double-bond fragment of a lipid chain (–C=C–) is larger than a single-bond one (–C–C–) [2], so it could be considered as a "repulsive" admixture which generates positive $\Delta V_{free}(h)$ in membrane. Then, C=C position along a lipid chain could be considered as the depth of penetration. V-shape dependence between T_m and C=C position was obtained experimentally in [17] (see Sec. 1). The same shape of dependence was obtained in [25] for $a_{free}(h)$. Both of them have a single extreme around the middle of lipid tails and linear shape beyond it. It approves well the correctness of our above considerations about quantitative relation between $V_{free}(h)$ and $\Delta V_{free}(h)$ which we have used for obtaining of $U_e(h)$ (Eq. (2)). Thus, $V_{free}(h)$ dependence appears the physical basis of experimentally observed V-shape dependences like "membrane melting temperature vs. the depth of penetration", "specific membranotropic effect of a drug vs. its lipophilicity", etc.

4. Conclusions

In the present work, a microscopic model is developed for characterization drug penetration into lipid membrane. It consider the balance between elastic ("drowing out") and dispersion ("drowing in") components of membrane — drug interactions which defines the equilibrium depth of drug penetration.

Two types of models were considered, linear and non-linear. Both of them describe adequately such features as drug penetration into a certain depth, its accumulation in the center of the bilayer, as well as absence of penetration. However, non-linear model better fits real system due to taking into account impact of elastic interactions on the equilibrium depth of drug penetration.

Generally, the model developed gives physical basis to experimentally obtained V-shape dependences "membrane melting temperature vs. the depth of penetration" as well as "specific membranotropic effect of a drug vs. its lipophilicity". In perspective, it seems reasonable to take into account anizometry of a drug molecule.

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