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KINETIC BIOPHARMACEUTICAL STUDIES OF A NEW PARACETAMOL–GLUCOSAMINE ANALGETIC DRUG

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Background: Intercomponent drug interactions could play important role for drug release, membrane permeability and membranotropic action. Therefore, newly developed drugs need for checking their biopharmaceutical characteristics. A new analgetic drug based on paracetamol (Actimask® Acetaminoprofen) and a hepatoprotector N-acetyl-D-glucosamine has been developed, with increased safety and potentiation of the analgesic effect *(Ruban O., 2022)*. Multibilayer lipid membranes were chosen as promising testing medium due to their proved appropriation and sensitivity for study multi-compound drug-membrane interactions. It is the basis for a kinetic approach allowing elucidation of biopharmaceutical interactions in model membrane medium.

Objectives: Revealing changes of paracetamol release and membrane penetration in the new paracetamol-glucosamine analgetic drug as well as estimation the rationale of the approach developed to trace biopharmaceutical interactions in model membrane medium.

Materials and Methods: *L*-α-dimyristoyl phosphatidylcholine (DMPC) multibilayer membrane was used as a model biomimetic testing medium. Differential scanning calorimetry (DSC) was applicated to trace kinetics of drug-membrane interactions.

Results: Gelatin as a part of Actimask® increased the characteristic time of paracetamol diffusion about threefold, but it had no pronounced effect on the equilibrium paracetamol penetration into the membrane. Sole glucosamine manifested no membranotropic effect under the experimental conditions, however, in combination with gelatin, it sufficiently reduced equilibrium paracetamol penetration while paracetamol diffusion remained within the experimental error. The full drug formulation increased membrantoropic effect by 34 % in compared with sole paracetamol.

Conclusions: Glucosamine and gelatin can affect both kinetic and equilibrium parameters of paracetamol-membrane interactions, while the full set of the drug components is able to increase the effect which correlates well with the previously established enhancement of analgetic effect of the drugs. The approach developed allows accurate tracing of drug release and membrane penetration depending on a set of drug components. Generally, the results obtained prove the rationale of applying the approach to pre-clinical drug examination.

KEY WORDS: nanostructured materials; model lipid membranes; paracetamol; N-acetyl-D-glucosamine; biopharmaceutical interactions; differential scanning calorimetry.

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Paracetamol is known as a worldwide analgesic that and the first-line drug for the treatment of pain and fever in patients of all ages. It is belonged to the group of nonsteroidal anti-inflammatory drugs (NSAIDs), together with aspirin, ibuprofen, diclofenac and a number of other broadly used analgetic substances. However, a side effect of paracetamol is hepatotoxicity. To avoid it, N-acetyl-D-glucosamine (NAG) was used in a drug formulation as a hepatoprotector. It was established that the paracetamol–NAG combination leads to increased safety and potentiation of the analgesic effect of the drug [1]. Microgranules of paracetamol in a gelatin shell (Actimask® Acetaminoprofen) was used in order to create the drug in the form of orally disintegrating tablet, which provides greater compliance for treatment and contributes to the onset of an analgesic effect; besides, covering paracetamol with a gelatin shell is due to the improvement of its organoleptic properties.

However, it is well known that any changes in tablet formulation could significantly affect drug bioavailability, so relevant question is to explore biopharmaceutical properties of the new drug. This issue, in turn, refers to the common problem of drug-excipient interactions [2], which should be discussed in more details.

An excipient is a natural or synthetic material added to dosage forms along with the active pharmaceutical ingredient (API) as either functional or non-functional agents [3]. Generally, excipients can exert multiple roles in a dosage form, so the selection of drug compounds is considered as crucial in any drug formulation design [3, 4]. Though excipients are considered as (therapeutically) inert, they are able to interact with reactive functional groups of an API in different ways [4]. It is commonly accepted that any form of physicochemical interaction involving drug molecules will potentially affect drugs' stability and bioavailability [4]. Last decades, the interest to drug-excipient interactions arises due to establishing of its ability to impact on drug effectiveness and, hence, to be a significant for drug adsorption by organism tissues [2, 5]. For example, ionic interaction between cationic drugs and anionic superdisintegrants resulted in the delayed release and poor dissolution of drugs [6].

Literature suggested numerous examples of physicochemical drugs interactions and each of them is of high importance for treatment processes. So, emerging trends in the design and development of drug products indicate ever greater need for in-depth understanding of the roles of drug compound in drug delivery applications [3]. Naturally, the phenomenon is not only limited by drug-excipient interactions but could equally be applicated to API-API interactions (in the case when several APIs are formulated in the same product), so it might be generally referred as intercomponent drug interactions.

Nowadays, this issue is considered in several aspects [2–4, 6–8]: (i) intercomponent interactions within a dosage from, or pharmaceutical incomparability; (ii) affecting drug release, solubility and bioavailability from the dosage form as well as its biopharmaceutical interactions; (iii) usage of excipients as drug delivery systems. The vast majority of the works on this matter is devoted to physicochemical interactions between certain drug components during the processes of API release/dissolution from a dosage form into water medium. Meanwhile, the next step of drug delivery, namely, drug-membrane interactions, is just as essential for bioavailability [4]. It is important that API penetration is usually carried out by passive diffusion through the lipid bilayer of cells [9]. The interaction of drugs with the lipid bilayer of biomembranes is inevitable, since a route of API administration (penetration into the systemic bloodstream, entry into the target cell, metabolism, etc.) is accompanied by interactions with a large number of cells barriers. Drug-membrane interactions seem to be of essential importance when dissolution is not the rate-limiting step of drug administration [2]. Moreover, improvement of membrane permeability by an excipient is thought to be a direct reason to improve drug bioavailability [4].

Generally, drug-membrane interaction is a complex and mutual process. Indeed, on the one hand, it affects the pharmacokinetic properties of pharmaceuticals, and on the other, it impacts on the structural and functional properties of the membranes themselves [10–12]. Besides, it could be an intrinsic part of biological effect of a drug, as it was shown for API of various classes. In particular, NSAIDs are characterized by strong drug-lipid interactions [13] being extended between the polar and hydrophobic segments of lipid bilayers [14]. Their membranotropic effect was established as detergent-like [15] or decreasing membrane melting transition point, thus enhancing the permeability of the membrane [16]. For a number of NSAIDs, it was shown that disruption of the cell membrane barrier is an important component in the drugs pathogenesis [8]. It was also established that NSAID toxicity is associated with the ability of the drug to modify the gastroenteric surface hydrophobic barrier through interaction with endogenous phosphatidylcholines [8]. These findings have indeed been providing evidences that the effect of NSAIDs at membrane level may be an additional mechanism of action and toxicity of NSAIDs [17] and highlight deep relationship between their membranotropic action and pharmacological activity (both therapeutic and negative side effects).

Up to date, a set of data has gained which evidence that the presence of foreign molecules could affect drug-membrane interactions [18, 19]. For example, as it was established for a large group of anti-inflammatory drugs, their transdermal permeability is elevated in the presence of lauric acid [19]. In spite of this, there are comparatively small number of works elucidating drug-excipient interactions in membrane medium, probably due to lack of proper methods and approaches.

As it was shown in our previous works, a set of excipients could serve as a modulating factor for API-membrane interactions [11, 20, 21]. In particular, azithromycin distribution into dipalmitoylphosphatidilcholine membrane varied depending on drug formulation [21]. Here, it should be noted that such modulation could either result from direct intercomponent interactions or appear explicitly at the stage of drug–membrane interactions. The former type of intercomponent interactions may be referred as membrane-mediated interactions; it was actually exemplified in [22–27]. The matter is just starting to develop but seems powerful and promising from practical viewpoint. For example, reduction of drug release by magnesium stearate is canonically attributed to generation of barrier to the aqueous environment [28], however another reason could be formation of drug-excipient complexes in membrane medium, as it was shown in [20].

One of the most appropriated techniques to explore this matter is differential scanning calorimetry (DSC). On the one hand, it is known as a powerful and high selective tool to study drug-membrane interactions [29, 30] and on the other hand, it is widely used to predict various types of physicochemical drug–excipients interactions [4]. Our previous works involving DSC to drug-membrane interactions demonstrated effectiveness of kinetic regime to exploring membranotropic effect of various drugs combinations [31]. To this end, in the present work, we focused on investigation of kinetic effects of drug components on paracetamol release and distribution over model membrane medium. The aim of the work is to demonstrate possibilities of using kinetic DSC approach to explore changes of biopharmaceutical interactions depending on drug formulation, namely (1) reveal changes of paracetamol release and membrane penetration in the new paracetamol–glucosamine analgetic drug and (2) estimate the rationale of the approach developed to trace biopharmaceutical interactions in model membrane medium.

MATERIALS AND METHODS

Pharmaceutical composition of paracetamol with N-acetyl-D-glucosamine

To create the pharmaceutical composition we used: Paracetamol (Anqiu Lu`an

Pharmaceutical Co., China) or gelatin-coated paracetamol (Actimask® Acetaminophen, SPI Pharma, USA), N-acetyl-D-glucosamine (Zhejiang Candorly Pharmaceutical, China), Plasdone S-630 (ISP, Switzerland), Kolidon CL (BASF, Germany), citric acid (Merck, Germany), sodium bicarbonate (Merck, Germany), Lubripharm (SPI Pharma, USA), Aspartame (Hyet Sweet, France), Orange flavor (Kerry, Italy).

Taken together, NAG and Actimask® consisted 63 % of tablet mass.

Lipid membrane preparation

L-α-dimyristoylphosphatidylcholine (DMPC) membranes were prepared on the basis of DMPC of high purity (Avanti Polar Lipids) using Mettler XP 26 microbalance (Mettler Toledo). 70 % wt/wt hydrated samples were obtained by adding a corresponding amount of bidistilled water. Then, the samples were incubated at 275-278 K for several days in order to provide water – lipid equilibrium. Additionally, regular agitations and heating above 320 K were applicated. The initial value of water content was maintained by addition of bidistilled water in proper amount.

Kinetic studies

Differential scanning calorimetry (DSC) technique was involved to treat the process of drug-membrane interactions. Original DSC profiles were obtained using a DSC 1 microcalorimeter (Mettler Toledo). Sample mass was 10 to 15 mg. Paracetamol content was 6 % wt/wt in all the samples. The ratios of other compound were the same as in the tablet-mass.

Before the procedure of DSC profiles recording, the necessary drugs amount was placed into a 40 μl standard aluminum crucible, then it was covered by neat DMPC membrane. This moment was count as time zero. Then a sample was placed into the measurement cell and underwent consequence heating scans in temperature diapason 273 to 308 K at scanning rate 0.3 K/s.

The procedure of DSC profiles recording has been performed until system equilibrium was reached (i.e. until no further changes of DSC profiles were observed). For each sample, 15 to 20 repeated DSC scans were performed during 120 to 170 hrs. of sample treatment. Neat DMPC membrane was examined under the same conditions as a control. Between the scans, the samples were stored at room conditions. Original DSC data were further processed by means of Star^{e} SW 11.0 software.

RESULTS AND DISCUSSION

In the present study, multilamellar model membrane of hydrated L-α-dimyristoylphosphatidylcholine (DMPC) was used as testing medium. Under experimental conditions, this membrane possesses a periodic lamellar structure with interlamellar repeat distance ab. 6–7 nm depending on temperature [32]. DMPC membrane is known to undergo the 1st order phase transition ‘gel to liquid crystal’ (membrane melting) under room temperatures which makes it convenient to explore drug-membrane interactions with a minimum risk of thermal destruction of the substances examined. Kinetics of drug administration into DMPC membrane was monitored using changes of DSC profiles during time of equilibration. Several types of systems were investigated, *viz.*, DMPC membrane containing a selected drug component (paracetamol, NAG), certain drug combinations (e.g., Actimask® + NAG) or the full drug formulation (tablet). Original DSC thermograms of the systems were reported in [1]. Here, we present further data treatment allowing us to obtain quantitative characteristics of drug-membrane interactions.

Taken into account complex character of the DSC peak obtained during equilibration time, it seemed reasonable to perform some fitting procedure to describe the process

quantitatively. For this purpose, a DMPC melting peak was fitted by two ones which reflect existence of membrane portions with different drug content. The fitting procedure and determination of the lower peak fraction (η) are illustrated in Fig. 1. Coefficient of determination $R^2 > 0.98$ was taken as a fitting criterion. All the systems examined met the criterion, except some samples contained the tablet.

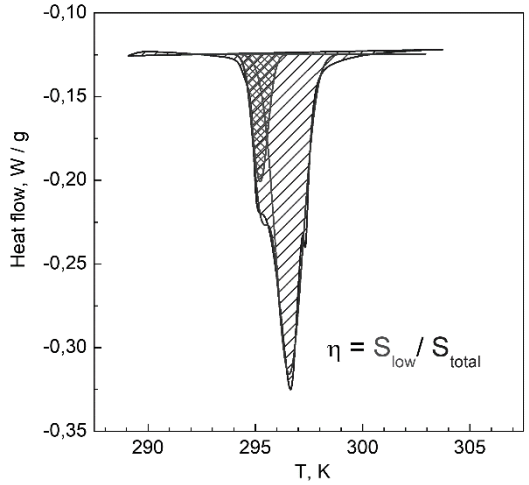

Fig. 1. DSC profile for DMPC membrane containing paracetamol (1st scan, t = 1080 s). Fitting of the melting peak by two Gaussians. The lower peak fraction (η) was determined as the ratio of the lower peak area (S_{low}) to the total original peak area (S_{total}).

The data obtained after the abovementioned processing were plotted as dependences of the lower peak and the upper peak temperatures on equilibration time. Initial steps of equilibration for different systems are depicted in Fig. 2.

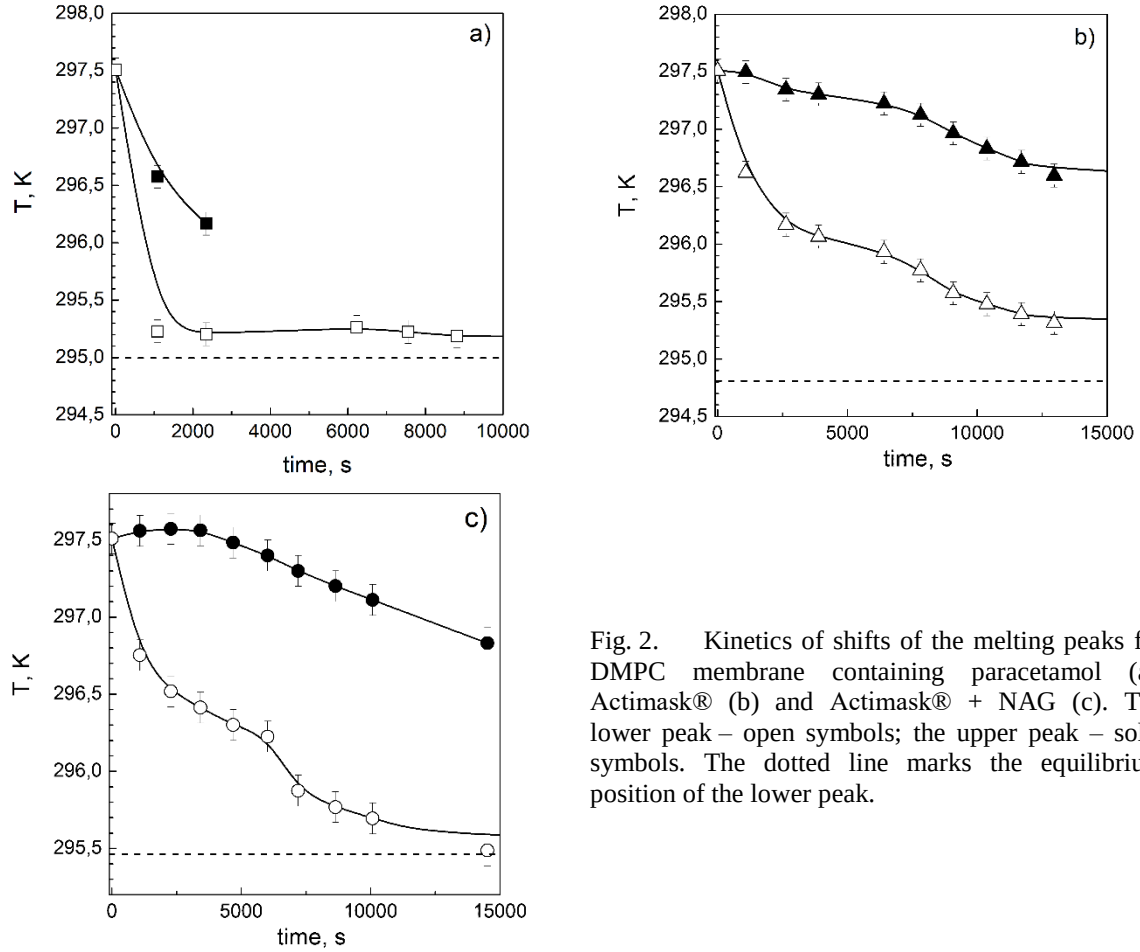

Fig. 2. Kinetics of shifts of the melting peaks for DMPC membrane containing paracetamol (a), Actimask® (b) and Actimask® + NAG (c). The lower peak – open symbols; the upper peak – solid symbols. The dotted line marks the equilibrium position of the lower peak.

As one can see, for the membrane containing sole paracetamol, the lower peak appeared yet in the 1st scan (Fig. 1) and then maintained very close to its equilibrium value (Fig. 2, a). So, one could ascribe it to the portion of membrane saturated with paracetamol. Such rapid paracetamol distribution observed under the experimental conditions is in line both with known high penetrating ability of paracetamol and with the data of MD simulation of paracetamol-DMPC interactions [33]. At the same time, the upper peak decreased much faster and merged the lower peak completely after just the 3rd scan, reflecting equilibrium paracetamol distribution over a sample. Grounding on the above, parameter η seems appropriate to describe kinetics of paracetamol distribution over the membrane medium. For sole paracetamol, the value of η became equal to 1 after approx. $2.5 \cdot 10^3$ s.

The pattern changed significantly with application of Actimask® instead of paracetamol (Fig. 2, b). Here, the lower peak shifts gradually toward its equilibrium position, but does not reach it even within $15 \cdot 10^3$ s. The upper peak exists during the same time period indicating non-homogeneous distribution of paracetamol throughout the membrane. Such effect is most likely evinces hindering of paracetamol release into the membrane medium due to gelatin coating of Actimask® microgranules. Reduced drug release from gelatin-coated capsules is a known effect of drug-excipient interactions, particularly for paracetamol [34, 35] so the effect observed testify in favor of relevance of the approach developed.

As for NAG, there were no visible changes of DSC profiles observed during $6 \cdot 10^5$ s (data are not shown), though it does not generally mean the absence of NAG – membrane interactions. Being taken together with Actimask®, NAG restricts changes of the both peaks and moves the resulting peak temperatures to relatively higher values (Fig. 2, c).

In Fig. 3, time dependences of the lower peaks in various systems are compared. For the system with Actimask®, it can be evident that though the equilibration value is reached much more slowly, it finally matches up (within the experimental error) with that for sole paracetamol. To our mind, such coincidence shows complete paracetamol release from the microgranules. Whilst, under joint Actimask® + NAG application, the equilibrium paracetamol effect appears much slighter, probably reflecting reduction of paracetamol distribution into membrane caused by the presence of NAG. Meanwhile, introduction of the tablet causes additional membrane fluidizing comparative to sole paracetamol. To our mind, such effect could be resulted from both enhancement of paracetamol distribution into membrane and its overlapping with membranotropic effect of other drug components. But anyway, such membrane fluidization correlates well with the previously established enhancement of analgetic effect of the drug [1].

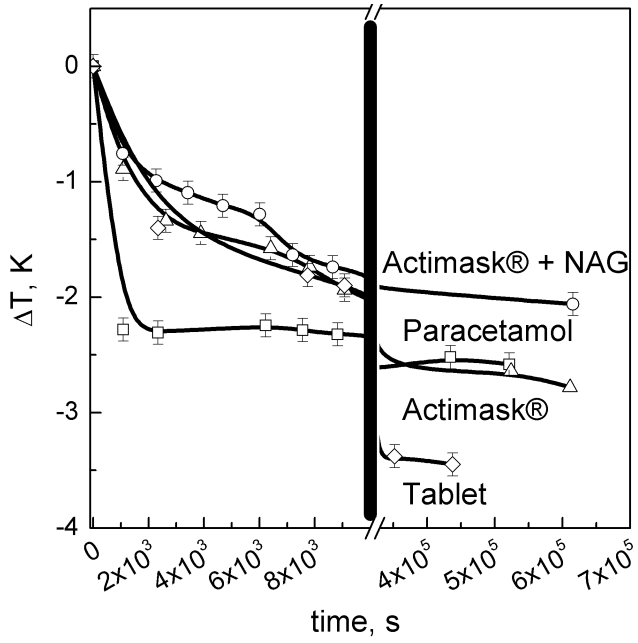

Fig. 3. Kinetics of shift of the lower melting peak for DMPC membrane containing various compounds of the paracetamol-glucosamine drug. The vertical line marks the break region.

Analysis of ΔT(t) dependences (Fig. 3) allowed us to determine some parameters of paracetamol – membrane biopharmaceutical interactions. In particular, the equilibrium paracetamol penetration into the membrane (D_{eq}) was determined as shift of the lower peak corresponding to equilibration time. The characteristic time of paracetamol diffusion (τ) was obtained by approximation of ΔT(t) dependences with descending exponents. Paracetamol distribution over the membrane during the first 100 min of observation (η_{100}) reflect its diffusion through water-lipid barriers.

The obtained parameters of biopharmaceutical interactions are collected in Table 1. They indicate that gelatin as a compound of Actimask® increases τ about threefold, but has no obvious effect on D_{eq}. Combination Actimask® + NAG hinders paracetamol diffusion (lowering of η_{100}) and diminishes D_{eq} by 20 %. However, the tablet increases D_{eq} by a third (34 %) relative to the sole paracetamol.

Table 1. Parameters of biopharmaceutical interactions.

Components	**Kinetic**		**Equilibrium**	
	τ, min	***η₁₀₀ ****	***D_eq*, K**	***δD_eq*, %**
Paracetamol	0.10	1.0	-2.6	0
Actimask®	0.37	0.9	-2.8	+8
Actimask® + NAG	0.32	0.7	-2.1	-20
Tablet	–	–	-3.5	+34

* Lower peak fraction after 100 min of equlibration

Equilibrium profiles of specific heat capacity (C_p) were obtained from corresponding DSC thermograms (Fig. 4). The temperature regime of thermal analysis of DMPC membrane was chosen so that to obtain information about two its intrinsic phase transitions around physiological temperatures [36, 37] as well as to avoid peak distortion due to non-optimal scanning rate [38]. The resulting C_p profile of the neat membrane contains two peaks. The sharp peak at 297.5 K reflects the membrane melting and was taken as a reference. Another one, at 288.6 K, corresponds to so-called pre-transition [36]. It disappears completely under drugs introduction. As one can see, C_p profiles of almost all systems contains a single sharp melting peak a few degrees below the reference. It suggests that in equilibrium state paracetamol distributes homogeneously over the DMPC membrane both in combinations with

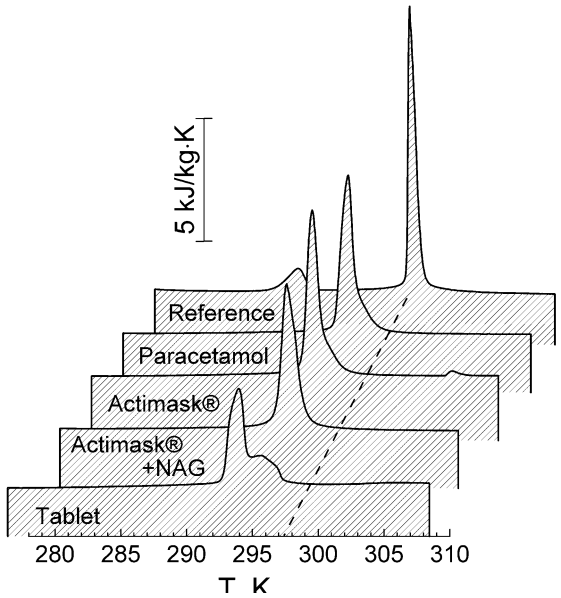

Fig. 4. Equilibrium profiles of specific heat capacity (C_p) for DMPC membrane containing various compounds of the paracetamol-glucosamine drug. The dotted line marks position of the reference peak (melting of neat DMPC membrane).

gelatin and with NAG. The only exception is C_p profile for membrane with the tablet which contains an additional broad peak above the paracetamol one. It obviously indicates individual interactions of other compounds of the drug with DMPC membrane. A small high-temperature thermal event observed for the membrane with Actimask® may be attributed to a membrane portion bound to sole gelatin.

The spectrum of possible underlying mechanisms of intercomponent interactions in the tablet is rather wide [2]. Generally, it could be relay to the rate and extent of drug dissolution and release, changes in the permeability of the membrane or in the stability of the drug. As for paracetamol, there are literature data concerning its pharmacological interactions with mannitol, vanillin and methylparaben [39, 40]. Besides, reducing paracetamol activity relative to hepatocyte membranes were reported for its combinations with acetylcysteine and Ca-pantothenate [41]. However, none of the substances listed is present in the composition of the drug examined, so there is insufficient basis for further speculations about the effects observed.

Thus, revealing of specific mechanisms of biopharmaceutical interactions for the paracetamol-glucosamine drug obviously requires more detailed studies. Meanwhile, the approach developed seems appropriate and instructive for exploring such kind of problems.

CONCLUSIONS

A new approach was developed allowing to elucidate biopharmaceutical intercomponent interactions in drug formulations and their impact on drug-membrane interactions. It was exemplified in a new paracetamol–glucosamine analgetic drug with reduced negative side hepatotoxic effect of paracetamol. Series of DSC profiles obtained for phase transitions of DMPC membrane allowed us to trace paracetamol release and distribution.

Paracetamol was established to be capable of fast and homogeneous distribution throughout the membrane in full accordance with its known high membrane permeability. As a part of Actimask® Acetaminophen (gelatin-coated paracetamol microgranules), paracetamol saturated the membrane three times slower, though the equilibrium paracetamol penetration into the membrane was the same as for the sole paracetamol within experimental error. Such effect could be most likely attributed to hindered paracetamol release from the microgranules.

N-acetyl-D-glucosamine, another API in the drug formulation, had no pronounced effect on DSC profiles. Meanwhile, taken together with Actimask®, it caused diminishing of paracetamol distribution into the membrane. The full drug formulation had slight influence on the initial steps of paracetamol distribution comparing to Actimask® + NAG. Meanwhile, the tablet had increased membranotropic effect in the equilibrium state which correlates well with the previously established enhancement of analgetic effect of the drugs.

Thus, the approach developed allows accurate tracing drug release and membrane penetration depending on a set of excipients. Generally, the results obtained prove the rationale of the approach developed in applying to pre-clinical drug examination.

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CONFLICT OF INTEREST

The authors declare no conflict of interests.

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КІНЕТИЧНІ БІОФАРМАЦЕВТИЧНІ ДОСЛІДЖЕННЯ НОВОГО АНАЛЬГЕТИЧНОГО ПРЕПАРАТУ ПАРАЦЕТАМОЛ–ГЛЮКОЗАМІН

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Актуальність. Міжкомпонентні взаємодії у фармпрепаратах можуть відігравати важливу роль у вивільненні лікарської речовини, її проникненні крізь мембрану та мембранотропній дії. Таким чином, новітні препарати потребують перевірки їх біофармацевтичних характеристик. Розроблений новий анальгетичний препарат на основі парацетамолу (Actimask® Acetaminoprofen) та гепатопротектору N-ацетил-D-глюкозаміну показав підвищену безпечність та підсилення анальгетичного ефекту *(Ruban O., 2022)*. Мультибішарові ліпідні мембрани було обрано як перспективне тестове середовище завдяки їх встановленій доречності та чутливості при вивченні мультикомпонентних взаємодій лікарських речовин з мембраною. Це створило основу для кінетичного підходу, який дозволяє виявляти біофармацевтичні взаємодії у модельному мембранному середовищі.
Метою роботи було виявлення змін вивільнення парацетамолу з нового препарату парацетамол-глюкозамін та його проникнення крізь мембрану, а також оцінка придатності розроблюваного підходу до моніторингу біофармацевтичних взаємодій у мембранному середовищі.
Матеріали і методи. Мультибішарові мембрани *L*-α-диміристоїлфосфатидилхоліну були використані як біомиметичне тестове середовище. Метод диференціальної скануючої калориметрії був застосований для моніторингу кінетики взаємодії лікарських речовин з мембраною.
Результати. Желатин як складова Actimask® підвищує характерний час дифузії парацетамолу майже втричі, але не впливає на його рівноважний розподіл у мембрану. Глюкозамін індивідуально не має вираженого мембранотропного ефекту за умов експерименту, втім у комбінації з желатином суттєво зменшує рівноважний розподіл парацетамолу у мембрану, майже не впливаючи на його дифузію. Повний набір компонентів препарату підвищує мембранотропний ефект на 34% у порівнянні з індивідуальним парацетамолом.
Висновки. Глюкозамін та желатин можуть впливати як на кінетичні, так і на рівноважні параметри взаємодії парацетамолу з ліпідною мембраною, тоді як повний набір компонентів препарату підвищує ефект парацетамолу, що добре корелює з попередньо встановленим підсиленням анальгетичного ефекту препарату. Розроблюваний підхід дозволяє чітко відстежувати вивільнення лікарської речовини та її проникнення крізь мембрану у залежності від набору компонентів препарату. Загалом отримані результати показують придатність даного підходу для застосування у доклінічних дослідженнях фармпрепаратів.
КЛЮЧОВІ СЛОВА: наноструктуровані матеріали; модельні ліпідні мембрани; парацетамол; N-ацетил-D-глюкозамін; біофармацевтичні взаємодії; диференціальна скануюча калориметрія.