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Erratum

Erratum to "Isolation of drugs from biological fluids by using pH sensitive poly(acrylic acid) grafted poly(vinylidene fluoride) polymer membrane *in vitro*" [Eur. J. Pharm. Biopharm. 67 (2007) 562–568]

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Upon further investigation, the authors of the above article wish to make corrections to sections of their published article, specifically Sections 3.1, 3.2 and 3.3; Table 1 and Refs. [4,20,21,27].

The complete updated Results and discussion section, the revised Table 1 and updated References section have been reproduced below for the convenience of the reader.

3. Results and discussion

In this case, drugs will be absorbed on the PAA-chains through the mechanisms of ion-exchange, i.e. the negatively charged polymer chains will exchange their positively charged counter ion (H+) for preferably a positively charged drug as described in Section 3.1.

However, the amount of absorbed drug (Table 1) is affected by several things: (1) The concentration of the drug in the drug solution; higher drug concentrations give higher amount of adsorbed drug since the ion exchange process is faster. (2) The maximum binding capacity of the membrane; membrane with a higher binding capacity binds drug with a higher rate, for comparable results only membranes with identical binding capacities should be tested. If there are differences in the binding capacities and testing time is predetermined → difference in the amount of drug absorption may exist. (3) The counter ion originally "attached" on each exchange site; the membrane prefers counter ions in a certain order, depending on which counter ion originally attached to the membrane ion-exchange will occur or not. (4) The molecular size and complexity of the drug; complex molecules with high molecular mass (proteins) will occupy more than one binding site → reduced binding capacity. They might also act as "crosslinkers" → reducing drug flux through the membrane.

3.1. Effect of charge of the drug on adsorption onto the 50 wt% grafted PVDF–PAA membrane

Upon further investigation the most of pK_a and log P values in Table 1 are incorrect and I herewith attach correct version. Amounts of model drugs adsorbed onto the membrane (disappearance of the drugs from the sample) are presented in Table 1. The pH of the external adsorption medium affects both the drug and poly(acrylic) acid ionization. At physiological pH PAA is able to dissociate completely (p$K_a \sim 4.0$) due to the surface of the membrane will be negatively charged that assists drug adsorption [18]. Basic antidepressants drugs adsorbed onto the membrane to a considerably greater extent than acidic drugs did. Basic drugs adsorbed onto the membrane approximately doubly more than acidic drugs. However, basic thioridazine adsorbed only weakly (adsorbed amount

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Table 1
Amounts of the drugs adsorbed from spiked serum pool onto the 50 wt% grafted PVDF–PAA membrane

Drug	pK_a^{20}	$\log P^{20}$	Adsorbed amount (%)
Alprazolam (A)	2.4	2.12; 2.30 [21]	65.9 ± 6.4
Carbamazepine (A)	7.0	2.45; 1.98	7.8 ± 6.7
Clobazam (A)	<6.0	0.95; 2.65	32.0 ± 17.7
Clonazepam (A)	1.5; 10.5	2.41; 2.84	23.9 ± 3.6
Diazepam (A)	3.3	2.80; 3.18	15.1 ± 2.9
Flunitrazepam (A)	1.8	2.06; 2.36	54.7 ± 17.4
Hydroxycarbazepine (A)			6.1 ± 3.1
Lamotrigine (A)	5.5	2.08	0.4 ± 5.0
Medazepam (A)	6.2	4.41; 4.47	27.2 ± 6.9
Midazolam (A)	6.15	3.37	56.4 ± 14.1
Nitrazepam (A)	3.2; 10.8	2.25; 2.53	13.4 ± 2.4
Norclobazam (A)			38.5 ± 11.3
Nordiazepam (A)	3.5; 12.0	2.93; 3.01 [21]	11.5 ± 2.0
Oxazepam (A)	1.7; 11.3	2.24; 2.1	7.4 ± 1.7
Oxcarbazepine (A)			45.0 ± 18.6
Pentobarbital (A)	8.0	2.07; 2.11	4.9 ± 5.6
Phenobarbital (A)	7.4	1.47; 1.36	ND
Phenytoin (A)	8.3	2.47; 2.09	ND
Primidone (A)	13.0	0.91; 1.74	9.5 ± 7.4
Temazepam (A)	1.6	2.19; 2.4	42.4 ± 18.5
Zopiclone (A)	6.7	0.98	35.0 ± 17.9
Amitriptyline (B)	9.42	5.04; 4.64	94.1 ± 7.5
Chloropramazine (B)	9.3	5.35; 5.20	83.2 ± 18.6
Chloroprotixen (B)	7.6	5.18; 5.30	82.3 ± 3.5
Citalopram (B)	9.5	2.98	98.7 ± 0.2
Clomipramine (B)	9.38	5.19; 5.30	92.6 ± 0.6
Clozapine (B)	8.0	4.30	93.4 ± 0.6
Desipramine (B)	10.44	4.9; 4.09	95.8 ± 0.8
Dm-citalopram (B)			97.5 ± 0.2
Dm-maprotiline (B)			85.7 ± 5.1
Doxepin (B)	9.0	3.88	96.8 ± 0.3
Fluoxetine (B)	8.7	4.05	92.2 ± 1.3
Haloperidol (B)	8.3	3.36; 3.52	96.1 ± 0.6
Imipramine (B)	9.5	4.8; 4.41	95.3 ± 0.9
Levomepromazine (B)	9.2	4.70	89.6 ± 3.8
Maprotiline (B)	10.5	4.22	90.6 ± 3.3
Mianserin (B)	7.05	4.26	95.2 ± 1.4
Norclomipramine (B)			89.8 ± 0.7
Norclozapine (B)			92.4 ± 0.5
Nordoxepin (B)			94.9 ± 0.4
Norfluoxetine (B)			93.4 ± 1.6
Nortrimipramine (B)			92.1 ± 1.3
Nortriptyline (B)	9.7	4.28; 4.32	93.0 ± 0.6
Protriptyline (B)	10.0	4.32	95.5 ± 0.5
Thioridazine (B)	9.5	5.9; 6.42	26.8 ± 15.1
Thiothixen (B)	7.67; 4.8	3.78; 4.80	65.0 ± 10.3
Trazodone (B)	6.14	4.0	75.6 ± 12.8
Trimipramine (B)	8.0	4.73	93.8 ± 1.5

Mean ± SD, $n = 5$. ND, not detectable; (A) behaves like acid, (B) behaves like base, $\log P$, log partition coefficient (oil–water), $^{20}pK_a$ and $^{20}\log P$ values were obtained from Hansch (1990) [20] and Zhao et al. (2001) [21] (see indicated).

26.8 ± 15.1% of the initial drug dose) onto the membrane. Adsorption of basic drugs varied from 26.8% to 98.7% of the initial drug doses (mean adsorbed amount 88.0 ± 14.3%). At pH values greater than two units above pK_a values of basic drugs, they are non-dissociated; and at physiological pH at the pK_a of the drug >7.0, they are fully dissociated and positively charged [19]. Acidic antiepileptic drugs and benzodiazepines adsorbed onto the PVDF–PAA membrane only slightly. Adsorption varied between not detected and 56.4% of the initial drug doses (mean adsorbed amount 27.1 ± 19.8%). At studied pH 7.4, when the pK_a of the drug is <7.0, acidic drugs are dissociated and negatively charged. When pH is equal to the pK_a, all the drug molecules are dissociated exactly 50% [19]. The pK_a values of each studied drugs are given in Table 1 [20,21].

In the present study basic model drugs adsorbed onto the PVDF–PAA membrane considerably to a greater extent than acidic model drugs did. Results of the study clearly indicate that the ionic interaction between a basic positively charged drug molecule and the negatively charged carboxylic acid group of the PAA was the most important factor affecting drug adsorption onto the membrane. In previous studies drug adsorption onto the PVDF–PAA membrane was investigated. Åkerman et al. [5] observed that electrostatic interactions between the basic drugs and the membrane were much stronger than the interactions between acidic and neutral drugs, and the membrane. The formation of complex between the anionic polymer (PAA) and procaine HCl (basic drug) was studied by Govender et al. [22]. They found that non-electrostatic attractions to the interaction of PAA with procaine HCl was greater than those of the electrostatic attractions. Similar electrostatic interactions between drugs and other kind of ion-exchange polymers have been reported [4,22–24]. Our previous published results proposed that acidic drugs adsorbed onto the PVDF–DMAEMA membrane due to positive surface charge via electrostatic interactions [4]. Jenquin et al. [23] have characterized acrylic resin matrix films (Eudragits RL and RS) and mechanisms of drug–polymer interactions. Salicylic acid and chlorpheniramine maleate were used as model drugs. Acidic salicylic acid interacted with these Eudragits polymers (contain quaternary ammonium groups) primarily via ionic electrostatic interactions. Pignatello and co-workers [24] studied the mechanisms of interaction between Eudragit RS100 and RL100 polymers with three nonsteroidal anti-inflammatory drugs: diflunisal, flurbiprofen, and piroxicam. Drugs strongly interacted with the ammonium groups present in polymers with electrostatic interactions. Rodriguez et al. [25] have evaluated the interaction of ibuprofen with cationic polysaccharides in aqueous dispersions and hydrogels. The drug molecules interacted weakly with the polymers through ionic interactions. However, instead of ionic forces, there could be non-ionic interactions like van der Waals forces or hydrophobic interactions that affect on drug adsorption [25,26]. In the present study, adsorption of acidic model drugs onto the membrane may have occurred via non-electrostatic forces.

3.2. Effects of proteins and hormones on drug adsorption

Albumin was not adsorbed onto the PVDF–PAA membrane (Table 2). Drug adsorption onto the PVDF–PAA membrane with and without albumin was studied by Åker-

man et al. [5]. It was observed that since albumin binds desipramine and thioridazine at physiological pH, the reduced drug adsorption onto the PVDF–PAA membrane in the presence of albumin at pH 7.0 was most probably due to the distribution of the drug between albumin and the PVDF–PAA membrane. It could be suggested that albumin did not affect the binding capacity of the membrane or reduce the drug adsorption via steric effects. Albumin binds thioridazine very tightly in serum (>99.5%) [3]. It would be suggested that this phenomenon may also explain weak adsorption of thioridazine onto the PVDF–PAA membrane in the present study. Adsorbed amount of IgG varied between not detected and 53.8% (mean adsorbed amount $27.1 \pm 22.9\%$; Table 3). In physiological concentration (reference range: 7.0–16.1 g/l; Laboratory Centre, Kuopio University Hospital, Kuopio, Finland) the adsorbed amount of IgG was $29.2 \pm 2.8\%$ of the initial dose. The highest adsorption was in IgG concentration of 1.0 g/l. Cortisol adsorbed $26.0 \pm 6.0\%$ onto the membrane (Table 4). However, TSH and T_4F were not adsorbed onto the membrane. Reference ranges of studied hormones are given in Table 4. We would propose that cortisol and IgG may decrease drug adsorption onto the PVDF–PAA membrane from serum, but that should be examined further in future studies.

3.3. Effect of lipophilicity of the drug on adsorption

Effect of lipophilicity on adsorption of basic model drugs from serum onto the 50 wt% grafted PVDF–PAA membrane was evaluated. Results of previous study proposed that adsorption of basic drug onto the PVDF–PAA membrane was related to the lipophilicity of the drug [5]. There was much bigger number of basic model drugs in the present study than in previous investigation [5]. Basic model drugs that we have evaluated are all lipophilic ($\log P = 2.98$–5.9), and they adsorbed onto the membrane extensively except for thioridazine that is the most lipophilic basic drug ($\log P = 5.9$). Based on results of present study, it would be proposed that lipophilicity did not enhance the adsorption of basic model drugs onto the PVDF–PAA membrane from serum ($R = 0.1936$, $p = 0.052$). Adsorption of acidic drugs was also not related to drug lipophilicity. Other authors have observed a favourable effect of drug lipophilicity on adsorption to the ion-exchangers [28–30]. Adsorption of clomipramine and viloxazine hydrochlorides in to a new multilayer polyethylene-lined film (Stedim 6) and polyvinyl chloride (PVC) bags was studied by Airaudo et al. [28]. Behavioural differences observed between the two drugs with regard to PVC are explained in terms of differences of lipophilicity of the drugs. Jaskari et al. [29] have observed that the lipophilic drugs, tacrine and propranolol, were adsorbed to the ion-exchange fibers more strongly and for longer than the more hydrophilic nadolol. The highest amount of binding was observed for the most lipophilic salicylate (5-Cl) and the most lipophilic fiber (Smopex®-105pe). In the other report Vuorio et al. [30] found that lipophilic tacrine and propranolol bound into ion-exchange materials consisting of a poly(ethylene) framework more effectively than hydrophilic drugs.

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