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Experimental modelling of drug membrane permeability by capillary electrophoresis using liposomes, micelles and microemulsions

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Abstract

Capillary electrophoresis (CE) was evaluated as an in-vitro format for experimental modelling of membrane permeability using only nanogram quantities of drug compounds. The rationale for the CE technique emanates from emulation of a lipid-like pseudo-stationary phase that governs separations mainly as a result of differences in molecular size, lipophilicity, hydrogen bonding and charge, all of which also have a strong influence on in-vivo drug absorption. By means of micellar, microemulsion and liposome electrolytes, the migration behaviour was studied at 37°C for 22 model drug compounds. The generated CE retention factor data were then compared with membrane permeability reference data. Both simple log D and more common Caco-2 cell parameters were evaluated. In addition, permeation through intestinal segments of rat ileum and rat colon was included. An improved correlation was obtained in the order: micellar < microemulsion < liposome systems. Although the correlation for the best liposome CE system was only $R^2 = 0.77$, the evaluation results for all emphasized the strength and flexibility of CE for assessing specific drug–membrane interaction through tailor-made lipophilic media.

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Introduction

Successful drug development requires optimization of both the pharmacological activity of the drug at the target site and its bioavailability. For orally administered drugs bioavailability involves delivery of the drug to the active site, where passive absorption from the gastrointestinal tract is a critical step. For assessing drug compound properties relevant for passive absorption, several non-biological and biological in-vitro and in-vivo methods have been developed. Routinely, data from these methods are used as the basis for prediction of absorption in humans (Ungell 1997).

Common in-vitro methods of predicting gastrointestinal absorption in humans are based on artificial or biological membrane systems, cell monolayers, such as Caco-2 cells, and excised intestinal segments (Ungell 1997). Alternative methods are those based on separation techniques, such as liquid chromatography. Demonstrated examples comprise immobilized artificial membranes, immobilized liposome chromatography (ILC), immobilized biomembrane chromatography and micellar liquid chromatography.

Among new separation techniques, evaluation of capillary electrophoresis (CE) is also of interest for modelling passive drug absorption because it can provide experimental data with high precision and is easy to automate. In addition, only nanogram quantities of drug are needed for analysis, and substances of low purity can be handled because impurities and decomposition products can be separated from the main component. The rationale for using CE with liposomal, micellar and microemulsion electrolytes as tools for physicochemical characterization of drug compounds is that separations are mainly due to solute differences in molecular size lipophilicity, hydrogen bonding and charge. This emphasizes the potential for using CE in biopharmaceutical prediction, based on the importance of these properties for predicting passive in-vivo absorption (Lipinski et al 1997).

So far a majority of CE studies have correlated migration data in micellar (MEKC), microemulsion (MEEKC) and liposome electrolytes (log k′) to the partitioning coefficient determined in 1-octanol/water (log P_{oct}). In this context, there are still a few CE reports that go beyond prediction of log P and investigate correlation to more advanced drug absorption models. Recently Khaledi and co-workers showed high correlation between MEKC log k′ for uncharged corticosteroids and intestinal absorption in rats (Yang et al 1996). Good correlation between MEKC log k′ and inhibition of thrombin for 18 thrombin inhibitors was shown, and these data were also used as an estimate of passive absorption (Linusson et al 2001). Good correlation between MEKC log k′ for six β-blockers to Caco-2 cell permeability was also shown, as was permeation through the intestinal segment of rat ileum and rat colon data (Örnskov et al 2000). Good correlation with permeation across a dodecanol collodium cell membrane system has also been reported (Mrestani et al 2001). MEKC migration data were correlated to Caco-2 cell permeability data for β-blocker model compounds (Detroyer et al 2003). In addition, good correlation between MEEKC log k′ and human skin permeability for acidic non-steroidal anti-inflammatory drugs has been shown (Ishihama et al 1996).

The aim of the present study was to evaluate different CE modes as experimental formats to model membrane permeability. In particular, micelles, microemulsions and liposomes were used here as lipophilic phases in electrolytes. The model compounds comprised neutral and charged substances. Correlations to permeation through monolayers of human intestinal epithelial cell line Caco-2 and permeation through the intestinal segment of rat ileum and rat colon are reported.

Materials and Methods

Apparatus

Separations were carried out on a model HP^{3D} capillary electrophoresis instrument (Agilent, Waldbronn, Germany) equipped with a UV absorption diode-array detector and HP Chemstation CE software (G1601A, A.06.03). Untreated fused-silica capillaries of 50 μm I.D., 375 μm O.D. from Polymicro Technologies (Phoenix, AZ) were used for these separations. The total capillary length was typically 35.0 cm, with a length to the detection window of 26.5 cm.

Materials

N-Cetyl-N,N,N-trimethyl-ammonium bromide (CTAB, 99%) was purchased from Merck (Darmstadt, Germany). Sodium dodecyl sulfate (SDS, 99%) was from Biochemical BDH, (Poole, UK). Sodium cholate (SC), sodium deoxycholate (SDC), sodium chenodeoxycholate (SCDC), sodium glycochenodeoxycholate (SGCDC), sodium glycocholate (SGC), sodium glycodeoxycholate (SGDC), sodium taurochenodeoxycholate (STCDC), sodium taurocholate (STC) and sodium taurodeoxycholate (STDC) were from Sigma (St Louis, MO), all of minimum 97% purity. 2-Oleoyl-1-palmitoyl-sn-glycero-3-phosphocholine (POPC, 99%) and 1,2-diacyl-sn-glycero-3-phospho-L-serine (PS, 98%) were from Sigma (Steinheim, Germany). Alprenolol, atenolol, metoprolol, practolol, propranolol, H 95/71, H 244/45 and H 216/44 were all made available for the study by AstraZeneca R&D (Mölndal, Sweden). Oxprenolol and pindolol were obtained from Novartis (Basel, Switzerland). Antipyrine was from Sigma-Aldrich (Steinheim, Germany). Ciprofloxacin was from Bayer (Elberfield, Germany). Amiloride, diazepam, cimetidine, hydrocortisone, sulfasalazine and sulpiride were all from Sigma (St Louis, MO). Alfentanil, nordazepam, oxazepam and metolazone were all a generous gift from Professor Per Artursson, Department of Pharmaceutics, Uppsala Biomedical Center, Uppsala University, Sweden. Acetophenone was from Merck (Schurchardt, Germany), propiophenone, butyrophenone and valerophenone were from Aldrich (Steinheim, Germany), and hexanophenone was from Lancaster (Morecambe, UK). All other chemicals were analytical grade (or equivalent) and purchased commercially.

CE procedures and conditions

New fused-silica capillaries were pre-treated by flushing with 0.1 M NaOH (20 min) followed by 10 min rinsing with water. Prior to each run in an analytical separation sequence, the capillary was rinsed consecutively with 0.1 V NaOH (1.5 min), water (0.5 min) and electrolyte (2 min), and finally equilibrated by applying $+300\ V\ cm^{-1}$ for 30 s. Thermostatting of the capillary was carried out with regulated air ($10\ m\ s^{-1}$), which passed through the capillary cartridge at $37.0 \pm 0.1°C$, whereas thermostatting of the autosampler tray to 37°C was carried out using an external water bath. For detection, the absorption was monitored at 230 and 245 nm while complete scans (190–400 nm) were used for peak characterization. Sample solutions were injected hydrodynamically (20 mbar, 5 s over the sample vial; injected volume *c.* 6 nL). All separations were carried out using an applied voltage of $+300\ V\ cm^{-1}$. Standard solutions, typically $1\ mg\ mL^{-1}$, comprised the respective drug compound and a set of five alkylphenones (APK): acetophenone, propiophenone, butyrophenone, valerophenone and hexanophenone. No issues were observed regarding loadability; however, there was an indication that higher analyte concentrations may affect the migration of very hydrophobic compounds in the liposome systems.

All tested CE electrolytes are listed in Table 1. Phosphate buffer solutions with different pHs were prepared by mixing appropriate volumes of 0.5 M Na_2HPO_4 and 1 M NaH_2PO_4 and subsequently diluting with water to yield an ionic strength of $I = 0.05$. Micellar electrolytes, 100 mM surfactant in sodium phosphate buffer, $I = 0.05$, were prepared on a daily basis. Microemulsion electrolytes consisted of 0.8 w/w% 1-octanol, 3.3 w/w% surfactant (i.e. 115 mM SDS or SDC), 6.6 w/w% 1-butanol and 89.3 w/w% sodium phosphate buffer of pH 7.4, $I = 0.05$. The microemulsion electrolytes were prepared according to Gabel-Jensen et al 2001. Liposome electrolytes, 3 mM

Table 1 CE systems evaluated

Abbreviation	Name and characteristics
Micellar electrolytes (conventional)	
CTAB	N-Cetyl-N,N,N-trimethyl-ammonium bromide, positively charged
SDS	Sodium dodecyl sulfate, negatively charged
Micellar electrolytes (bile acids, negatively charged micellar-like aggregates)	
SC	Sodium cholate
SDC	Sodium deoxycholate
SCDC	Sodium chenodeoxycholate
SGCDC	Sodium glycochenodeoxycholate
SGC	Sodium glycocholate
SGDC	Sodium glycodeoxycholate
STCDC	Sodium taurochenodeoxycholate
STC	Sodium taurocholate
STDC	Sodium taurodeoxycholate
Complex electrolytes (microemulsions, mixed micelles and liposomes)	
SDS	Sodium dodecyl sulfate, microemulsion, negatively charged
SDC	Sodium cholate, microemulsion, negatively charged
POPC/PS	2-Oleoyl-1-palmitoyl-sn-glycero-3-phosphocholine (POPC)/1,2-diacyl-sn-glycero-3-phospho-l-serine (PS), liposomes, negatively charged, 80/20 mole percent
FaSSIF	Fasted state simulated intestinal fluid, mixed micelles, synthetic intestinal media for the fasted state
FeSSIF	Fed state simulated intestinal fluid, mixed micelles, synthetic intestinal media for the fed state

liposomes (80/20 mol% POPC and PS), were prepared according to Wiedmer et al 2000. The average liposome diameter was 116 nm (range 98–137 nm), as verified by dynamic light-scattering measurements using a model BI-200SM Gonimeter (Brookhaven Instruments Co., USA). All liposome electrolytes were stored in a refrigerator and used within 1 week. The electrolytes simulating human intestinal fluid, fasted state simulated intestinal fluid (FaSSIF) and fed state simulated intestinal fluid (FeSSIF) contained 3 mM taurocholate, 0.75 mM lecithin and a buffer of pH *c.* 6.5, FeSSIF contained 15 mM taurocholate, 3 mM lecithin and a buffer of pH *c.* 5.0, respectively. FaSSIF and FeSSIF were prepared as previously described and used on the day of preparation (Galia et al 1998).

Calculation of retention factors

The retention factor k′ was obtained from the electrophoretic mobility of the solute in the lipophilic phase electrolyte μ_S as

$$k' = \frac{\mu_s - \mu_0}{\mu_{lip} - \mu_s} \quad (1)$$

where μ_S is the electrophoretic mobility of the solute in the lipophilic phase electrolyte, μ_0 is the electrophoretic mobility of the solute in the electrolyte in absence of lipophilic phase and μ_{lip} is the mobility of the lipophilic phase. The mobility of the lipophilic phase, μ_{lip}, was calculated by an iterative procedure using the migration data for the five alkylphenones (Muijselaar et al 1994).

Reference absorption data

The reference absorption data are listed in Table 2. The Caco-2 cell, colon and ileum permeability data for the nine β-blockers were from Palm et al (1996, 1998). The colon and ileum permeability data for propranolol were from Ungell et al (1998). The Caco-2 cell permeability data for the set of additional 12 drug compounds were from Stenberg et al (2001).

Calculated descriptors and chemometric modelling

The log D_{calc} values were calculated using the ACD program (Version 6.0 for Windows, Advanced Chemistry Development Inc., Toronto, Canada). The molecular weight, H-bond donors, H-bond acceptors and H-bond sum total descriptors were calculated using an in-house program, SaSA (Version 0.8 for SGI Irix version, AstraZeneca, Mölndal, Sweden). Chemometric modelling was done using the SIMCA-P+ program (Version 10.0, Umetrics AB, Umeå, Sweden).

Table 2 Reference absorption data for drug compounds

No	Compound	Caco-2 cell monolayer permeability: P_c ($cm\,s^{-1} \times 10^{-6}$)[a]		Rat intestinal segment permeability: P_{app} ($cm\,s^{-1} \times 10^{-6}$)[b]				Fraction absorbed in humans (%)[c]		Calculated log D for pH 7.4
				Ileum		Colon				
		Mean	Std[d]	Mean	Std[d]	Mean	Std[d]	Mean	Std[d]	
1	Alprenolol	242	14	68	11	116	18	96		1.13
2	Atenolol	1.02	0.1	5.0	1.0	1.92	0.20	54	17	−1.66
3	H 216/44	0.104	0.016							−1.01
4	H 244/45	6.03	0.26							−0.61
5	H 95/71	3.75	0.34							−0.93
6	Metoprolol	91.9	4.0	40.5	9.8	96	22	100	5	0.026
7	Oxprenolol	119.6	6.7	50	25	62	17	97	13	0.57
8	Pindolol	54.7	0.6	24.9	4.5	34.7	9.7	92	11	0.18
9	Practolol	3.46	0.53	5.5	1.3	2.44	0.55	95	3	−1.16
10	Propranolol[e]			41.3	3.8	87.9	22			1.36
11	Alfentanil	310	16.8					Na[f]		1.59
12	Amiloride	0.78	0.064					58	5.0	0.94
13	Antipyrine	215	11					97	7	0.27
14	Cimetidine	1.2	0.087					79		0.11
15	Ciprofloxacin	1.9	0.076					69	7	−1.23
16	Diazepam	756	73					97		2.96
17	Hydrocortisone	41.6	1.25					Na[f]		1.43
18	Metolazone	6.1	0.31					64	23	3.25
19	Nordazepam	307	8.0					99	19	3.15
20	Oxazepam	246	4.4					97	11	2.31
21	Sulfasalazine	0.16	0.021					12	5	0.047
22	Sulpiride	0.39	0.054					36	20	−1.12

[a]Permeability data for the β-blockers from Palm et al (1998) and for the diverse drug compounds from Stenberg et al (2001), n = 3–12. [b]Permeability data from Palm et al (1996). [c]Fraction absorbed in humans after oral administration, data from Stenberg et al (2001). [d]Variability is given as mean ± s.d. [e]Permeability data from Ungell et al (1998). [f]Data not available.

Results and Discussion

Micellar, microemulsion and liposome CE separation

To evaluate the CE format for modelling membrane permeability, the interactions between drugs and different types of electrolyte additives were tested (see Table 1 for details). SDS and CTAB are commonly used anionic and cationic micellar electrolytes. The anionic bile acids, which are native constituents of the fluids in the upper gastrointestinal tract, are also used as lipophilic phases in CE. The microemulsions containing butanol and octanol together with either SDS or the bile acid SDC and the liposome electrolyte have been well characterized in the literature regarding their separation properties. Two sets of model compounds were used in this study: (i) five neutral alkylphenones, (ii) 22 drug compounds. The five alkylphenones were included in the study to enable characterization of model compound CE–media lipophilic interactions. The set of drug compounds is listed in Table 2 and consists of 10 β-blockers and 12 diverse compounds. It represents a wide range of lipophilicity properties, log D spans of almost five orders of magnitude and a diversity regarding molecular size and charge. In addition, these represent a group of drug compounds for which drug absorption data are available.

To mimic conditions of physiological relevance, for example regarding the solvatization of the drug compound in the intestine, simulated intestinal fluid, FeSSIF and FaSSIF were included as electrolytes in this study. Because of the high ionic strength of these electrolytes the voltage was kept low to avoid high current and Joule heating. Moreover, a short analysis time was crucial to minimize peak broadening. This was obtained by applying a low pressure (5 mbar) during separation and using a short effective capillary (length 8.5 cm).

The high separation power of CE is exemplified in Figure 1 for β-blockers in the SDC electrolyte where compounds that span a wide range of lipophilicities can be separated simultaneously (typical plate numbers = 40 000). This separation power also enables analysis of compounds that are either impure or relatively unstable in aqueous solutions, provided that impurities or decomposition products are separated from the main component (Hilhorst et al 2001; Örnskov et al 2003). With liposomes the resolving power is biased towards small highly lipophilic drugs. Indeed, in this study it was found that hydrophilic compounds such as atenolol only interacted to a minor extent with the liposomes. Typical electropherograms

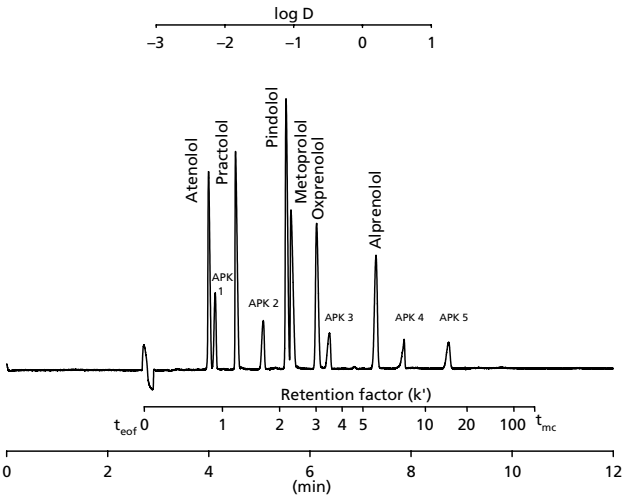

Figure 1 CE separation of six charged β-blockers and five neutral alkylphenones. The retention factor scale is shown together with the migration time scale. The upper scale represents the logarithmic distribution ratio (log D) for the model compounds. APK 1 = acetophenone, APK 2 = propiophenone, APK 3 = butyrophenone, APK 4 = valerophenone and APK 5 = hexanophenone.

for micellar, microemulsion and liposome CE systems are shown in Figure 2.

As expected, CE provided high precision analysis data (Mayer 2001). The reproducibility of CE migration was investigated using different capillaries, electrolytes and sample solutions in experiments carried out on different days. As an example, when using the SDC electrolyte, the reproducibility of CE log k′ for the neutral alkylphenones and charged β-blockers was *c*. 0.8 (% relative standard deviation (RSD), n = 4). A slightly lower reproducibility, 2–11 (% RSD, n = 3), was obtained with the liposome electrolyte for the neutral alkylphenones.

Correlation of CE data to log D and Caco-2 permeability data

The generated CE log k′ data were correlated to two types of parameters used for estimating absorption: log D (distribution coefficient in 1-octanol/water for ionized compounds at a specified pH) and Caco-2 permeability. Figure 3 shows the correlation of five neutral alkylphenones and six congener β-blockers to experimental log D values. The typical correlation value for the neutrals in Figure 3 was 1.00 and for the β-blockers was 0.75–0.99. A comparison of the correlation patterns for the two series of model compounds reveals that the investigated electrolytes can be divided into different classes with respect to their lipid phase functionality. On the other hand, for the alkylphenone model compounds, all systems investigated provide similar interaction mechanisms. For the charged compounds, correlations to log D (Figure 3, β-blockers) show pronounced differences between the different lipophilic phases. The liposomes and FeSSIF systems provide different drug–media interactions compared to all other media. In addition, a non-linear relationship is obtained between log D and CE log k′ for the liposome electrolyte.

To further evaluate the utility of CE, the correlation to Caco-2 cell permeability data was investigated. The R^2 values for correlation to Caco-2 data for the nine β-blockers in Table 2 were 0.17, 0.18 and 0.58 (n = 9) for micellar, microemulsion and liposome CE systems, respectively. Note that these R^2 values improved to 0.90, 0.89 and 0.88 (n = 8) if the model compound H 216/44 was excluded from the regression. H 216/44 is a larger and more flexible molecule than the other β-blockers, is capable of forming several intra- and intermolecular hydrogen bonds, and has been shown to be an outlier in correlations between log D and Caco-2 cell permeability data (Artursson 1990), log D and immobilized liposome chromatography retention data (Palm et al 1998). Additional biological in-vitro permeability data, available for seven of the 10 β-blockers, was also investigated. The R^2 values for correlation to rat colon permeability were 0.68, 0.74 and 0.76 (n = 7), and to rat ileum were 0.67, 0.74 and 0.78 (n = 7), for micellar, microemulsion and liposome CE systems, respectively. The correlations were statistically significant. The model drug compound set diversity was extended by including 12 additional drug compounds. The R^2 values from the correlation of 21 drug compounds to Caco-2 data were 0.08, 0.26 and 0.53 for micellar, microemulsion and liposome CE systems, respectively. Note that the R^2 values were improved to 0.52, 0.75 and 0.78 if the H 216/44, sulfasalazine and antipyrine compounds were

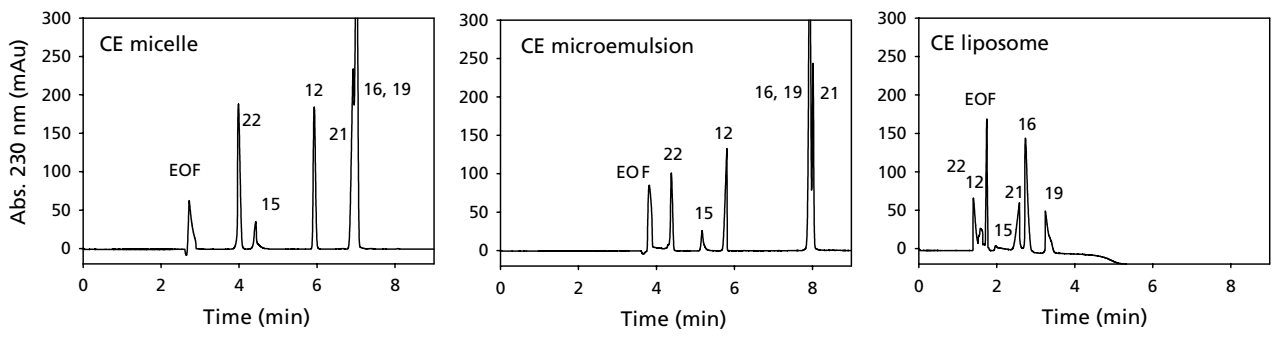

Figure 2 CE separation of drug compounds in micellar, microemulsion and liposome electrolytes. See Table 2 for compound identity.

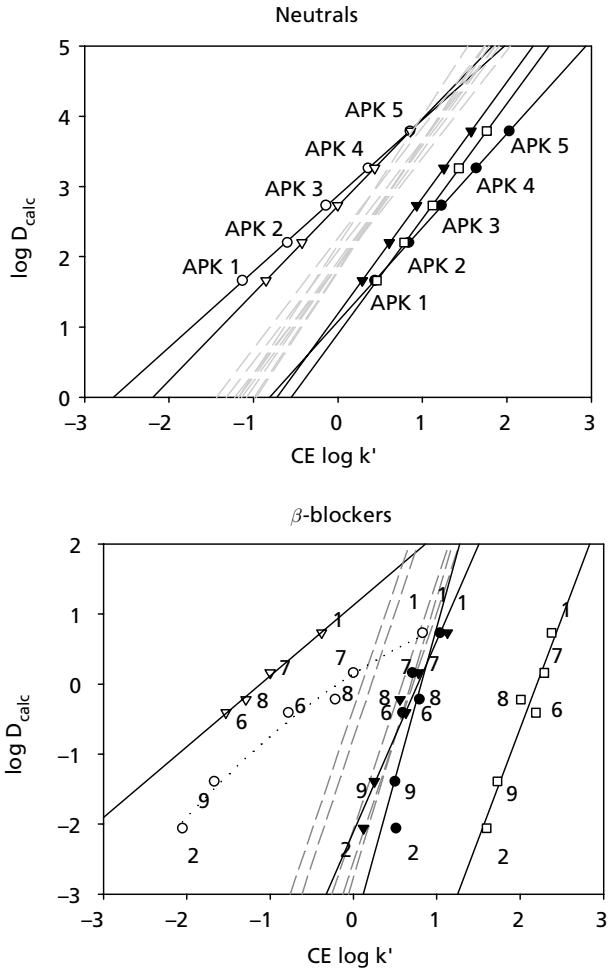

Figure 3 Correlation between CE migration in micellar, microemulsion and liposome electrolytes and log D for neutral alkylphenones and six β-adrenoceptor antagonists. See Table 2 for drug compound identity. CE systems tested: (○) = liposomes (POPC/PS), (▽) = simulated human intestinal fluid BGE at fed state (FeSSIF), i.e. mixed micelles, n = 4, (▼) = microemulsion (deoxycholate/1-octanol/butanol), (●) = micelles (CTAB), (□) = micelles (SDS), dotted grey lines = bile acid micelles (deoxycholic acid, cholic acid, chenodeoxycholic acid, glycodeoxycholic acid and glycocholic acid). Model compound symbols for neutrals as in Figure 1. See Table 2 for drug compound identity.

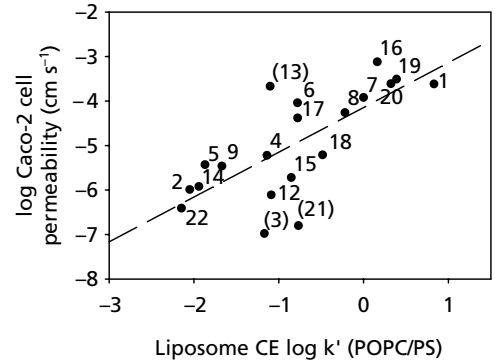

Figure 4 Correlation between CE liposome migration and Caco-2 cell monolayer permeability coefficients for 17 model compounds ($R^2 = 0.77$). Compounds with numbers in brackets (H 216/44, antipyrine and sulfasalazine) were excluded in the regression but are plotted together to display their CE migration behaviour. See Table 2 for compound identity.

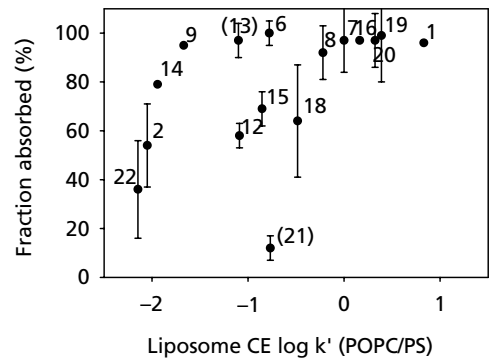

Figure 5 Correlation between CE migration in liposomal electrolyte and fraction absorbed after oral administration to humans (FA%). See Table 2 for compound identity.

excluded from the regression. Sulfasalazine and antipyrine have been identified as outliers in studies of correlation between fraction absorbed (%) and surface plasmon resonance liposome surface data (Danelian et al 2000) and ILC retention data (Liang et al 2000; Österberg et al 2001). The result for the CE liposome correlation to the Caco-2 cell permeability data is shown in Figure 4.

Modelling of fraction absorbed from human intestinal tract

Caco-2 cell permeability is one of the most widespread in-vitro methods used for the assessment of drug absorption. A number of studies have demonstrated good correlation with human absorption data for passively absorbed compounds (Artursson et al 2001). However, some limitations of the Caco-2 cell technique have been raised. For example, it has been questioned how well colon-derived cell lines such as Caco-2 can model human absorption when the majority of drugs are absorbed in the higher gut. In addition, inter-laboratory variability of Caco-2 data is typically high (Artursson et al 2001) therefore all Caco-2 data used in this study were selected from the same laboratory.

To further evaluate the capability of different CE systems to model passive drug absorption, correlation of migration data to the fraction absorbed after oral administration to humans (FA%) was investigated (see Table 2 for FA% reference data). An improved correlation was obtained if the sulfasalazine and antipyrine drug compounds were excluded from the regression. The results are shown in Figure 5. It is generally understood that in-vivo drug absorption data are strongly dependent on experimental conditions, which is why large differences

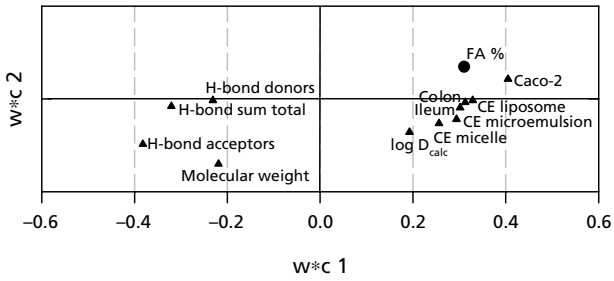

Figure 6 Loading plot from multivariate modelling of six absorption estimates (CE and in-vitro data) together with five theoretical molecular descriptors. Fraction absorbed after oral administration to humans (FA%) used as Y variable. PLS regression: one PLS component, $R^2 = 0.66$, $Q^2 = 0.56$, number of drug compounds (N) = 14. Note that the second PLS component is used only for display purposes (not significant). CE systems: micellar (SDC), microemulsion and liposome. See Table 2 for details on in-vitro (Caco-2, ileum and colon) and in-vivo data.

are often observed between different reports. This variability, exemplified in Figure 5 for the in-vivo data modelled here, makes it difficult to fully validate the predictability of any in-vitro or in-silico model. Still, an attempt was made to compare the in-vivo modelling capability of the CE systems with that of other in-vitro and in-silico methods. Figure 6 shows the loading plot from a multivariate modelling: Caco-2 cell, ileum and colon in-vitro data, and migration data from micellar (SDC), microemulsion and liposome CE. Five theoretical molecular descriptors were also included in the modelling (see Materials and Methods section). One PLS (partial least-squares projections to latent structures) component was significant in the modelling of the fraction absorbed after oral administration to humans (FA%) ($R^2 = 0.66$, $Q^2 = 0.56$, Q^2 = regression coefficient for the cross-validation procedure). The results in Figure 6 show that ileum and colon permeability, CE microemulsion and CE liposome variables are closer to the Y-response, fraction absorbed, than Caco-2 and log D. Variables close to the Y-variable are positively related to Y and to each other. Also related but negatively correlated to the fraction absorbed is the total number hydrogen bonds in the model compounds. This supports the theory that CE is an interesting complement to other in-vitro and in-silico methods, in particular liposome electrolytes. In particular, the flexibility of the CE format enables modelling of partitioning to different biological cell membranes because the pseudo phase can be tailored to exhibit different lipid phase properties. In this way different drug–media interaction mechanisms can be obtained by simply changing the electrolyte, as shown in Figures 3A and B. For both the neutral alkylphenones and the charged β-blockers the type of surfactant was more important than the phase structure for influencing the retention factor. For example, the retention behaviour in the FeSSIF and the liposome electrolytes was similar. This probably emanates from the fact that both these electrolytes contain phospholipids even if the FeSSIF electrolyte is based on mixed micelles. For the alkylphenone model compounds similar retention behaviour was observed in the liposome and CTAB electrolytes. This is in accordance with the fact that liposomes made of dipalmitoyl-L-α-phosphatidylcholine and dipalmitoyl-L-α-phosphatidylglycerol, and cationic micelles, such as tetradecylammonium bromide, exhibit a similar H-bond accepting strength. In addition, SDS and SC electrolytes are stronger H-bond donors than liposomes, and SDS electrolytes exhibit a stronger interaction with H-bonding acceptor model compounds than SC electrolytes (Burns et al 2002).

Conclusions

CE using micellar, microemulsion and liposomal electrolytes was found to be a promising experimental method for early assessment of drug membrane properties when only small quantities of drug compound are available, although only a limited set of drug compounds was investigated in the present study. In particular, when using liposomes in the electrolyte, experimental conditions mimic physiological membranes and thus open up possibilities for predicting drug membrane permeability. A common observation for the different CE electrolytes throughout all these investigations was the improved correlation in the order of micellar < microemulsion < liposome systems. This emphasizes the general potential of liposome CE for biopharmaceutical characterization of drug compounds. Although rough correlations were obtained for all systems, the study emphasized that CE has an interesting potential for assessing specific drug mechanism interactions through tailor-made CE media.

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