FRACTAL DIMENSION OF TRANSDERMAL-DELIVERY DRUG MODELS

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(Received 30 January 2003 - Accepted 2 February 2004)

ABSTRACT

Fractal percolating paths that exist in porous membranes are used to deliver drugs. For a homologous series of phenyl alcohols, the fractal dimension D is calculated as a model for transdermal-delivery drugs. Our program TOPO is used for the calculation of the solvent-accessible surface A_s, which is denoted by the centre of a probe, which is allowed to roll on the outside while maintaining contact with the bare molecular surface S. A_s depends on the probe radius R. D is calculated as $D = 2 - d(\log A_S)/d(\log R)$. For the phenyl alcohols, the quadrupole moment Θ is trebled. The hydrophobic contribution to A_s is doubled while its hydrophilic part remains constant. D increases 12%. The values of all the geometric descriptors and topological indices are in agreement with reference calculations. The 1-octanol-water partition coefficient $\log P$ increases. The molar concentration of organic compounds necessary to produce a 1:1 complex with bovine serum albumin via equilibrium dialysis, $\log 1/C$ increases. The hydrophile-lipophile balance (HLB) decreases. These results are in line with reference calculations. The linear correlation between D and Θ, and various non-linear correlations between D, $\log P$, $\log 1/C$ and HLB point not only to a homogeneous molecular structure of the phenyl alcohols but to the ability to predict and tailor drug properties. The latter is nontrivial in pharmacology.

Keywords: fractal dimension, percutaneous absorption, percutaneous enhancer, transdermal drug delivery, phenyl alcohol, QSAR

INTRODUCTION

Chronic diseases and pathological medical conditions requiring the administration of long-term pharmaceutical dosages have in the past been treated by oral administrations of tablets, pills and capsules or through the use of creams and ointments, suppositories, aerosols and injectables. Although some therapeutic techniques such as the administration of injectables inside the eyeball are rather annoying, the number of punctures could be minimized if the release of the drug is retarded.

On the other hand, medicinal plasters containing natural herbs have been used around the world for centuries to treat multiple ailments, both topical and systemic. Ointments, gels and creams have historically constituted major staples in the pharmacist's arsenal of weapons for the treatment of everything, from insect bites to arthritis to cardiovascular disease. However, it was not until the late 1970s or early 1980s that the first of the modern-day commercial transdermal drug-delivery systems was introduced into the market. Subsequent to this first commercial introduction, many pharmaceutical companies joined the race to develop transdermal drug-delivery systems containing nitroglycerin for the treatment of angina pectoris. As a result of this race, the basic elements of each of the present-day configurations for passive transdermal systems were developed and launched commercially for the first time. The first reservoir technology utilized a rate-controlling membrane. The second reservoir technology used a solid matrix system. Finally, the third reservoir technology employed a drug-in-adhesive system. As one of the most rapidly growing sectors in the pharmaceutical industry, transdermal drug delivery has seen a veritable explosion of interest by the larger pharmaceutical corporations since 1980. As the technology has developed, larger molecules previously thought to be unsuitable for transdermal delivery are commonly being incorporated in state-of-the-art patches capable of delivering systematically effective doses. The larger, more cumbersome patches of the early 1980s have been replaced by more elegant drug-in-adhesive systems, capable of delivering larger quantities of drug from smaller patches without the wear and skin irritation issues associated with the earlier systems.

Given that the skin offers an excellent barrier to molecular transport, the rationale for transdermal drug delivery needs to be carefully identified (Naik *et al*., 2000). During the last decades, there has been great interest in developing systems for controlled delivery of drugs and other bioactive substances (Baker, 1980; Langer, 1983). A suggested technique was to join a specialized patch on the skin, which will deliver pre-specified and reproducible dosages over a wide spectrum of conditions and required durations of therapeutic treatment. The simplest devised scheme utilized uncoated polymer matrices containing the embedded drug (Langer and Folkman, 1976). Other techniques involved covering most of the matrix with an impermeable material that acts as a barrier to diffusion, and the active substance escapes through surface pores or cavities that are left uncoated (Langer, 1980). Percolating paths that exist in porous membranes are used to deliver drugs over a continuous period (Kaye, 1994). The pathways available for the delivery of the medication are usually fractal structures (Bunde *et al*., 1985; Kaye, 1987).

The experimental measurement of transdermal drug permeation is fraught with difficulties, including problems with obtaining human skin samples. Therefore, several groups developed computational methods for predicting fluxes. These include several models based on multiple regression methods (Roberts and Sloan, 2000). Mathematical modelling and computer simulations can be very effective in improving and optimizing the performance of the self-regulating release of therapeutic drugs into specific regions of the body. Further work is required to produce a solution based on simple physicochemical properties alone, which predicts the flux of all molecules, especially hydrophilic, high molecular-weight drugs. However, for the foreseeable future, drug regulators will always demand confirmation of computer predictions from experiments with human skin. Barry (2001) reviewed some selective ways for circumventing the *stratum corneum* barrier, all of which provide areas for future research.

Díez-Sales *et al*. (1991) proposed a drug-delivery system consisting of a specialized patch joined to the skin. The drug can penetrate through the skin by permeability. They tested homologous series of 4-alkylanilines and phenyl alcohols as drug models, measured their permeability and compared it with their molecular volume.

In an earlier publication, the dipole moment and valence topological charge-transfer indices of phenyl alcohols were calculated (Torrens, 2003a). This work presents the calculation of the fractal dimension for a homologous series of phenyl alcohols. It represents a first step for the design of controlled drug-delivery systems. The ultimate goal of the investigation is to provide a reliable design tool for the fabrication of specialized patches on the skin. These patches will deliver pre-specified and reproducible dosages over a wide spectrum of conditions and required durations of therapeutic treatment.

Barry (2001) reviewed novel mechanisms and devices to enable successful transdermal drug delivery. Verma *et al*. (2002) reviewed formulation aspects in the development of osmotically controlled oral drug delivery systems. Norinder and Haeberlein (2002) reviewed the computational approaches to the prediction of the blood-brain distribution. Pardridge (2002) reviewed drug and gene targeting to the brain with molecular Trojan horses. Moss *et al*. (2002) reviewed the quantitative structure-permeability relationships for percutaneous absorption. Xu and Hagler (2002) reviewed chemoinformatics and drug discovery. Boas and Heegaard (2004) reviewed dendrimers in drug research.

METHODS

In our program TOPO (Torrens *et al*., 1991a, 1996, 1998b, 2001a), the molecular surface is represented by the external surface of a set of overlapping spheres with appropriate radii, centred on the atomic nuclei (Meyer, 1985, 1988). The molecule is defined by tracing spheres about the nuclei. It is computationally enclosed in a graduated rectangular box and the geometric descriptors evaluated by counting points within the solid or close to chosen surfaces. The molecular volume is concurrently approximated as $V = P \cdot \mathrm{GRID}^3$, where P is the number of points within the molecular volume and GRID is the size of the mesh grid. As a first approximation, the molecular *bare* surface area should be calculated as $S \approx Q \cdot \mathrm{GRID}^2$, where Q is the number of points close to the bare surface.

Two topological indices of molecular shape can be calculated: G and G'. Consider S_e as the surface area of a sphere whose volume is equal to the molecular volume. The ratio $G = S_e / S$ is interpreted as a descriptor of molecular globularity. The ratio $G' = S / V$ is interpreted as a descriptor of molecular *rugosity*.

The properties of the systems solvated in water are strongly related to the contact surface between solute and water molecules (Hermann, 1972; Wodak and Janin, 1980). The *solvent-accessible surface* A_s was proposed by Lee and Richards (1971). The A_s is defined by means of a probe sphere which is allowed to roll on the outside while maintaining contact with the molecular bare surface S. The A_s can be calculated in the same way as S by means of pseudoatoms, whose van der Waals radii have been increased by the probe radius R (*cf.* Figure 1). *Fractal* surfaces provide a means for characterizing the irregularity of molecular

surfaces (Torrens, 2000a, 2001a, 2002a, b, c, 2003b; Torrens *et al*., 2001b). The area of A_s depends on the value of the probe radius R. The *fractal dimension* D of the molecules may be obtained according to Lewis and Rees (1985) as

$$D = 2 - \frac{d(\log\ A_s)}{d(\log\ R)}$$

The fractal dimension provides a quantitative indication of the degree of surface accessibility toward different solvents. The larger the fractal dimension, the faster the accessible surface area drops with an increase in solvent molecular size.

Figure 1. Molecular surface models for a set of spheres. The contour of the shaded area represents the bare molecular surface and the bold contour defines the solvent-accessible surface. Circles labelled "P" represent probe spheres simulating the solvent.

TOPO allows an atom-to-atom analysis of D that is carried out in the way described above on each atom i to obtain an atomic fractal dimension D_i. In order to calculate each D_i, a set of atomic contributions to $A_{s,i}$ are calculated by means of different

probe spheres. The D_i values so obtained can be averaged to obtain a new molecular fractal dimension $D' = \left(\sum_i A_{s,i} D_i\right) / A_s$, where $A_{s,i}$ values are used as weights for D_i values. Notice that if $A_{s,i}$ is zero for any probe, D_i cannot be calculated for atom i and so this atom does not contribute to *D'*. Thus, *D'* represents an average for *non-buried* (solvent-exposed) atoms. For molecules having some buried atoms, *D'* is always greater than *D*. A version of TOPO has been implemented in program AMYR for the theoretical simulation of molecular associations (Rubio *et al*., 1993; Torrens *et al*., 1991b, c, 1998a).

RESULTS AND DISCUSSION

The fractal dimension and other descriptors have been calculated for a homologous series of phenyl alcohols as models for drugs, which can be administrated in a patch joined to the skin. Table 1 shows the dipole $\bar{\mu}$ and tensor quadrupole $\bar{\bar{\Theta}}$ moments for the phenyl alcohols, calculated with our program POLAR (Torrens, 2002d). In the series, the dipole moment increases 57% and the mean quadrupole moment is trebled. The dipole and mean quadrupole moments fluctuate a little with the number of C atoms in the alkyl chain, *n*.

TABLE 1
Dipole and Quadrupole Moments for Phenol and Phenyl Alcohols

Molecule	Number of C atoms in alkyl chain	μ[a]	Θ[b]	Θ_1[c]	Θ_2	Θ_3
phenol	0	1.091	3.043	6.503	3.511	-0.884
1-benzilic alcohol	1	1.697	2.778	7.867	2.073	-1.608
2-phenylethanol	2	1.583	4.588	11.721	1.375	0.668
3-phenylpropanol	3	1.713	6.401	15.153	2.210	1.840
4-phenylbutanol	4	1.590	6.011	15.488	2.729	-0.184
5-phenylpentanol	5	1.710	7.662	18.611	3.425	0.951
6-phenylhexanol	6	1.593	7.418	19.206	4.081	-1.034
7-phenylheptanol	7	1.710	8.952	22.048	4.766	0.040

[a] Dipole moment (D).
[b] Mean quadrupole moment (D·Å).
[c] Quadrupole moment tensor eigenvalues Θ_1, Θ_2 and Θ_3 (D·Å).

Table 2 lists the geometric descriptors for the phenyl alcohols. The results are compared with reference calculations carried out with program GEPOL (Pascual-Ahuir *et al*., 1987) because GEPOL gives rather small errors (<1%) in any molecular surface area. The molecular volume *V* results are in agreement with GEPOL reference calculations (errors *ca*. -0.7%). Although the errors for the molecular surface areas are bigger (*i.e*., -4% for the bare molecular surface area S), this error drops for the water-accessible surface area A_s (-2%) and even for the side-chain accessible surface area A_s' (-0.9%). The comparison between GEPOL and TOPO of special interest because the former does not perform an atom-to-atom analysis of the geometric descriptors of the molecule. For instance, the partition of the accessible surface area A_s shows that its hydrophobic term HBAS is *ca*. 5 times greater than the hydrophilic component part HLAS. In the series, *V* and *S* are doubled, while the side-chain accessible-surface area A_s' increases 55%. The increase in the water accessible-surface area A_s (80%) is due to HBAS, which is doubled, while HLAS remains almost constant.

TABLE 2
Geometric Descriptors for Phenol and Phenyl Alcohols

Molecule	V[a]	V ref.[b]	S[c]	S ref.[b]	A_s[d]	A_s ref.[b]	HBAS[e]	HLAS[f]	A_s'[g]	A_s' rf.[b]
phenol	101.3	101.9	123.47	128.07	249.89	253.47	187.47	62.42	573.20	577.96
1-benzilic alcohol	115.6	116.4	136.91	142.33	267.80	272.59	215.97	51.83	600.32	605.48
2-phenylethanol	133.7	134.6	159.34	166.60	300.88	306.88	239.89	60.99	655.47	660.37
3-phenylpropanol	151.1	152.1	180.86	188.18	330.53	337.40	269.29	61.24	701.82	708.30
4-phenylbutanol	168.4	169.7	201.21	209.74	359.10	367.76	298.02	61.08	748.73	755.67
5-phenylpentanol	185.8	187.1	221.13	231.30	388.89	398.18	327.63	61.26	796.36	803.58
6-phenylhexanol	203.0	204.6	242.59	252.71	418.19	428.31	357.21	60.98	843.68	852.04
7-phenylheptanol	220.5	222.0	262.83	274.30	449.85	458.99	388.28	61.57	890.74	899.79

[a] Molecular volume (Å^3).
[b] Reference: calculations carried out with program GEPOL.
[c] Molecular surface area (Å^2).
[d] Water-accessible surface area (Å^2).
[e] Hydrophobic accessible surface area (Å^2).
[f] Hydrophilic accessible surface area (Å^2).
[g] Side-chain accessible surface area (Å^2).

Table 3 reports the topological indices for the phenyl alcohols. In the series, the molecular globularity G decreases 21%, molecular rugosity G' remains almost constant, fractal dimension D increases 12% and fractal dimension averaged for non-buried (solvent-exposed) atoms D' increases 14%. On going from D to D', the $D' - D$ increment rises from 2% to 4% in the series. The corresponding interpretation is the presence of some atoms in 7-phenylheptanol that are more buried than in phenol.

TABLE 3
Topological Indices for Phenol and Phenyl Alcohols

Molecule	G[a]	G ref.[b]	G'[c]	G' ref.[b]	D[d]	D ref.[b]	D'[e]
phenol	0.851	0.824	1.218	1.257	1.194	1.200	1.220
1-benzilic alcohol	0.838	0.810	1.184	1.223	1.216	1.226	1.251
2-phenylethanol	0.794	0.763	1.191	1.237	1.244	1.257	1.288
3-phenylpropanol	0.759	0.732	1.197	1.237	1.269	1.281	1.310
4-phenylbutanol	0.733	0.707	1.195	1.236	1.286	1.301	1.333
5-phenylpentanol	0.712	0.684	1.190	1.236	1.305	1.319	1.353
6-phenylhexanol	0.689	0.664	1.195	1.235	1.320	1.333	1.369
7-phenylheptanol	0.672	0.646	1.192	1.235	1.335	1.347	1.386

[a] Molecular globularity.
[b] Reference: calculations carried out with program GEPOL (Pascual-Ahuir *et al*., 1987).
[c] Molecular rugosity (Å^{-1}).
[d] Fractal dimension of the solvent-accessible surface.
[e] Fractal dimension of the solvent-accessible surface averaged for non-buried atoms.

Table 4 summarizes solvation descriptors for the phenyl alcohols calculated with SCAP (Torrens, 2000b, 2001b,c, 2002e; Torrens *et al*., 1998c). In the series, minus Gibbs free energy of solvation in water $\Delta G^o_{\text{solv,w}}$ decreases and minus $\Delta G^o_{\text{solv,o}}$ in 1-octanol

increases. Therefore, the 1-octanol-water partition coefficient $\log P$ increases. This is related to the augmentation of HBAS through Table 2. Notice that for values of $\log P > 3$, more than 99.9% of the solute is in the organic phase. For that reason, some results predict a negligible quantity of solute in the aqueous phase. In the series, the molar concentration of organic compounds necessary to produce a 1:1 complex with bovine serum albumin (BSA) *via* equilibrium dialysis, $\log 1/C$ increases. On the other hand, the hydrophile-lipophile balance (HLB) decreases in the series. These trends are in line with reference calculations carried out with a method by Kantola *et al*. (1991). Experimental data are not available for all the series.

TABLE 4
Solvation Descriptors for Phenol and Phenyl Alcohols

Molecule	$\Delta G^{o}_{\text{solv,w}}$ [a]	$\Delta G^{o}_{\text{solv,o}}$ [b]	log P[c]	log P ref.[d]	log 1/C[e]	log 1/C ref.[d]	HLB[f]	HLB ref.[d]
phenol	-19.29	-22.77	0.61	1.40	2.76	3.35	6.49	5.84
1-benzilic alcohol	-17.80	-27.12	1.64	0.69	3.53	2.82	5.64	6.43
2-phenylethanol	-16.51	-31.68	2.67	1.02	4.30	3.07	4.79	6.15
3-phenylpropanol	-15.04	-36.10	3.70	1.24	5.08	3.23	3.93	5.97
4-phenylbutanol	-13.57	-40.57	4.74	1.48	5.86	3.41	3.07	5.77
5-phenylpentanol	-12.14	-45.08	5.79	1.63	6.64	3.53	2.20	5.65
6-phenylhexanol	-10.66	-49.53	6.83	1.84	7.42	3.68	1.34	5.48
7-phenylheptanol	-9.26	-54.05	7.87	2.08	8.20	3.86	0.48	5.28

[a] Gibbs free energy of solvation in water (kJ·mol^{-1}).
[b] Gibbs free energy of solvation in 1-octanol (kJ·mol^{-1}).
[c] P is the 1-octanol/water partition coefficient.
[d] Reference: calculations carried out with a method developed by Kantola *et al*. (1991).
[e] C is the molar concentration necessary to produce a 1:1 complex with bovine serum albumin *via* equilibrium dialysis.
[f] Hydrophile-lipophile balance.

A linear model for the molecular quadrupole moment of the phenyl alcohols *vs*. fractal dimension gives:

$$\Theta = -49.0 + 43.1D \qquad (r = 0.972) \qquad (1)$$

Non-linear models for $\log P$, $\log 1/C$ and HLB of the phenyl alcohols *vs*. fractal dimension result:

$$\log P = 163 - 302D + 139D^2 \qquad (r = 0.999) \qquad (2)$$

$$\log 1/C = 124 - 225D + 104D^2 \qquad (r = 0.999) \qquad (3)$$

$$\text{HLB} = -128 + 250D - 116D^2 \qquad (r = 0.999) \qquad (4)$$

The best linear model for the fractal dimension of the phenyl alcohols *vs*. a series of physicochemical parameters results:

$$D = 2.51 + 0.000336\Theta - 0.000140M_W - 0.832G - 0.483G \qquad (5)$$

$$n = 8 \quad r = 0.99998 \quad SD = 0.0006 \quad F = 15570.0$$

where M_W is the molecular weight. The mean absolute percentage error (MAPE) is 0.02% and the approximation error variance (AEV) is lower than 0.0001. However, Equation (5) should be taken with care because it includes too many independent variables so that it would not be

statistically significant. The best non-linear model for the fractal dimension does not improve the results.

The correlation coefficient found between *cross-validated* representatives and the property values R_{cv} has been calculated with the leave-*n*-out procedure (Besalú, 2001). The procedure furnishes a new method for selecting the best set of descriptors according to the criterion of maximization of the value of R_{cv}. The R_{cv} calculations for the phenyl alcohols are given in Table 5 for $1 \leq n \leq 5$. In general, R_{cv} decreases with *n*.

TABLE 5
Cross-validation Correlation Coefficient in Leave-*n*-out for Phenyl Alcohols

n	logP vs. D	log1/C vs. D	HLB vs. D	D vs. Θ,M_W,G,G'
1	0.996	0.996	0.996	1.000
2	0.996	0.996	0.996	0.911
3	0.996	0.996	0.996	0.680
4	0.996	0.996	0.996	-
5	0.997	0.997	0.997	-

From the preceding results the following conclusions can be drawn.

1. The method used here offers an accurate, stable, spatially invariant and fast algorithm to obtain the fractal dimension of the solvent-accessible surfaces of molecules.
2. The difference between both fractal indices D' and D increases in the series. The $D' - D$ difference is a sensitive method to elucidate the occurrence of atoms that are hidden to the solvents in the range of sizes used to calculate D and D'.
3. The linear correlation between D and Θ, and various non-linear correlations between D, $\log P$, $\log 1/C$ and HLB point not only to a homogeneous molecular structure of the phenyl alcohols but also to the ability to predict and tailor drug properties. The latter is nontrivial in pharmacology.

Work is in progress on the calculation of $\log P$ maps for the phenyl alcohol molecules. An extension of the present study to a homologous series of 4-alkylanilines would give an insight into a possible generality of these conclusions.

ACKNOWLEDGEMENTS

I wish to thank Dr. E. Besalú for providing me several versions of his full linear leave-many-out program prior to publication. The author acknowledges financial support from the Spanish MCT (Plan Nacional I+D+I, Project No. BQU2001-2935-C02-01) and Generalitat Valenciana (DGEUI Project Nos. INF01-051 and INFRA03-047).

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