Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pharmaceutics and Biopharmaceutics 67 (2007) 293–299
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Handling of computational in vitro/in vivo correlation problems by Microsoft Excel: V. Predictive absorbability models

Frieder Langenbucher *

BioVista LLC, Riehen, Switzerland

Received 21 August 2006; accepted in revised form 29 January 2007
Available online 8 February 2007

Abstract

This paper discusses Excel applications related to the prediction of drug absorbability from physicochemical constants. PHDISSOC provides a generalized model for pH profiles of electrolytic dissociation, water solubility, and partition coefficient. SKMODEL predicts drug absorbability, based on a log–log plot of water solubility and O/W partitioning; augmented by additional features such as electrolytic dissociation, melting point, and the dose administered. GIABS presents a mechanistic model of g.i. drug absorption. BIODATCO presents a database compiling relevant drug data to be used for quantitative predictions.

Keywords: IVIVC; QSAR; Excel; Access; Absorption potential; Biopharmaceutics Classification System; BCS; Prediction; Solubility; Partitioning; Dissociation; pH profile; Database

1. Introduction

Continuing a series of previous papers [1], this last communication discusses predictive absorption models as another IVIVC application of Excel worksheets. A summary of some simple predictions of activity properties, based on the molecular structure, is followed by three elaborated models: PHDISSOC presents a consistent model for a drug's electrolytic dissociation and its effect on solubility and partitioning; SOLUPART uses these two characteristics to predict the absorption potential; GIABS is a mechanistic model simulating drug transport through the g.i. tract and absorption from there.

BIODATCO sketches a database for IVIVC-relevant data of drug compounds as well as formulated products, covering the literature of generics as well as company-specific information. Although, all data could be stored in a common Excel workbook, Access provides important advantages with respect to data consistency and ease of handling by multiple users. E.g., fixed relationships between tables, defined by key fields, permit to store all information once and in a unique location, thus avoiding any duplication. The value of such a database for successful IVIVC work increases with the number of users, which contribute and use the data pool; ideally it should be run on a worldwide basis, under the auspices of an established private or official organization.

In summarizing, the present series of review papers demonstrates the usefulness of Microsoft Excel/Access as generally available tools, capable to handle most tasks without need for costly commercial software. Necessarily, the discussion is rudimentary and should be regarded as stimulus for further elaboration.. A more detailed documentation is available from the author upon request.

2. Model descriptions

Three predictive models related to drug absorbability are discussed below, with emphasis on their realization by means of Excel worksheets. Background are Quantitative Structure-Activity Relationships (QSAR). These

* Correspondence address: BioVista LLC, Ruechligweg 101, CH-4125 Riehen, Switzerland. Tel.: +41 61603 3474; fax: +41 61601 2738.
E-mail address: langenbucher.fr@bluewin.ch.

0939-6411/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2007.01.019

estimate fundamental properties from structure parameters such as molecular weight, functional groups, and melting point, which are known at the time of synthesis [2–6]. Typical examples are listed below.

- *Functional groups* of the molecule permit to predict important properties. A well known task is the prediction of pK_a values from tabulated data of analogous compounds. O/W partition coefficient is a classical case of predictions based on the presence of functional groups.
- From the *molecular weight*, molecular radius and aqueous diffusivity are estimated according to Fig. 1, with these predictions:

$$\log(R/\text{Å}) = 0.41\log(M) - 0.32$$

$$\log\{D/(\text{cm}^2/\text{s})\} = -0.46\log(M) - 4.1$$

- *Melting point*: a fundamental relationship, derived from thermodynamic laws and verified by 126 neutral substances belonging to six chemical classes, correlates water solubility S_0, partition coefficient K_0 and melting point θ_m:

$$\log S_0\ [\text{mol/L}] = -1.0\log K_0 - 0.01\theta_m\ [^\circ\text{C}] + 1.05$$

Fig. 2 verifies the usefulness of this relationship in the S–K plot, where experimental and estimated solubilities are shown by open and filled symbols, respectively. While experimental data spread over four decades, estimations concentrate within roughly one decade.

2.1. PHDISSOC: consistent pH profiles

PHDISSOC provides a generalized model of electrolytic dissociation, including pK_a values and the pH profiles of dissociation fractions f, apparent water solubility S'' and apparent O/W partition coefficient K''. The model is illustrated in Fig. 3 for benazepril. On the pH scale, $n+1$ regions are defined according to the n pK values. Fractions of dissociation species are shown as straight lines with slopes of 0, ±1, ±2, …, intersecting at corresponding pK values. Model consistency may be checked by a GLM analysis, for best agreement between observed and calculated profiles.

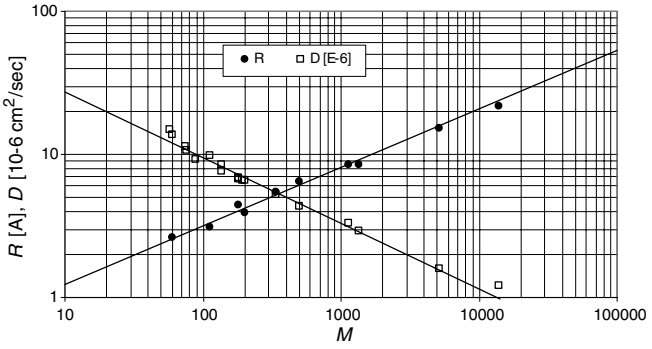


Fig. 1. Prediction of molecule radius R and aqueous diffusivity D from molecular weight M.

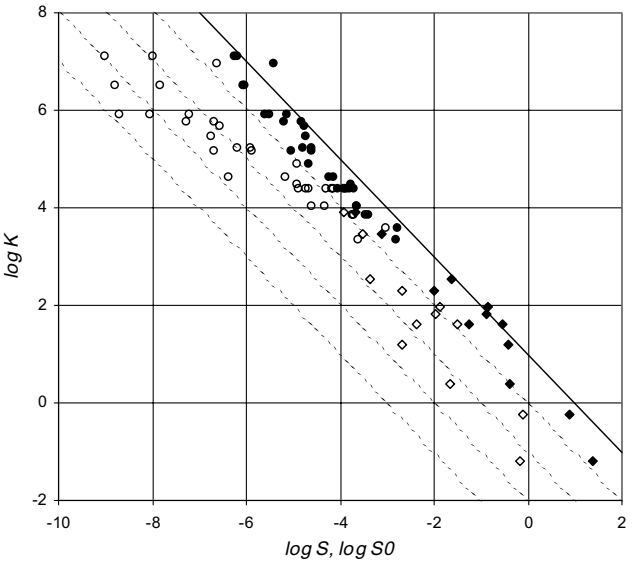


Fig. 2. S/K plot, showing experimental (○) and estimated solubilities (●) as abscissa. Diagonals represent melting points, starting with liquids ($\theta_m = 0$) on top, and increasing toward the lower-left with one decade per 100 °C.

2.1.1. pK values, dissociation species

Each dissociating functional group is characterized by a pK_a value, i.e., a pH value where the group changes its charge. An acidic group is neutral at pH < pK and dissociates at pH > pK, where its charge decreases by 1 U; a basic group is neutral at pH > pK and dissociates at pH < pK, where its charge increases by 1 U.

For the illustration case of benazepril, model parameters are supplied in the worksheet as follows:

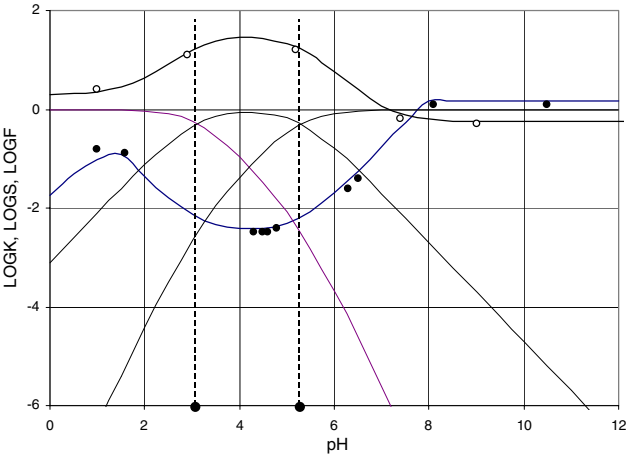


Fig. 3. pH profiles of electrolytic dissociation, water solubility, and partition coefficient. Data are for benazepril with $n = 2$ dissociation constants, corresponding to an acid (p$K_1 = 3.1$) and a basic (p$K_2 = 5.3$) functional group.

Table 1
Computation of pH profiles for benazepril, according to Fig. 3

PH	Q_W	FRAC1	FRAC2	FRAC3	SOLU1	SOLU2	SOLU3	SOLU*	PART
0	−1.00E+00	9.99E−01	7.94E−04	3.98E−09	1.77E−02	4.16E+00	2.58E+08	1.77E−02	2.02E+00
1	−1.00E−01	9.92E−01	7.88E−03	3.95E−07	9.38E−02	4.19E−01	3.52E+06	9.38E−02	2.24E+00
2	−1.00E−02	9.26E−01	7.36E−02	3.69E−05	1.39E−01	4.48E−02	3.89E+04	4.48E−02	4.25E+00
3	−1.00E−03	5.56E−01	4.42E−01	2.21E−03	2.40E−01	7.47E−03	6.50E+02	7.47E−03	1.55E+01
4	−1.00E−04	1.07E−01	8.50E−01	4.26E−02	1.25E+00	3.88E−03	3.38E+01	3.88E−03	2.80E+01
5	−1.00E−05	8.32E−03	6.61E−01	3.31E−01	1.61E+01	5.00E−03	4.35E+00	5.00E−03	2.17E+01
6	−9.90E−07	2.09E−04	1.66E−01	8.33E−01	6.40E+02	1.98E−02	1.73E+00	1.98E−02	5.89E+00
7	0.00E+00	2.46E−06	1.96E−02	9.80E−01	5.44E+04	1.69E−01	1.47E+00	1.69E−01	1.19E+00
8	9.90E−07	2.51E−08	1.99E−03	9.98E−01	5.35E+06	1.66E+00	1.44E+00	1.44E+00	6.28E−01
9	1.00E−05	2.51E−10	1.99E−04	1.00E+00	5.34E+08	1.65E+01	1.44E+00	1.44E+00	5.70E−01
10	1.00E−04	2.51E−12	2.00E−05	1.00E+00	5.34E+10	1.65E+02	1.44E+00	1.44E+00	5.65E−01

	PK1	*PK2*			
	3.1	*-5.3*			
	CHARGE		*SUM*	*S*	*K*
#1	0	1	1	*0.134*	*2.0*
#2	-1	1	0	*3.3E-3*	*32.6*
#3	-1	0	-1	*1.44*	*0.564*

pK_a values are supplied in the sequence from lowest to highest; for convenience basic values are coded as negative. Charge describes the charge of the n dissociating groups in the $n+1$ species, Sum the overall charge; species #2 is neutral, representing a zwitterion where charges compensate to zero. Vectors S and K list estimated solubilities and partition coefficients of the species; for charged species the value of S depends on the counter-ion.

2.1.2. pH profiles

Table 1 computes pH profiles for a vector PH, according to general principles [7]. With $K_w = 1.0 \times 10^{-14}$ mol^2/L^2 for the ion product of water, the general titration behavior is computed in Q_W:

$$Q_w = [OH^-] - [H^+] = K_w/[H^+] - [H^+]$$

Fractions of the electrolytic species are computed from $(N+1)$ simultaneous linear equations, corresponding to a matrix product $\mathbf{c} = \mathbf{Pf}$ according to this Falk scheme:

N=3			**f**	f_1
				f_2
				f_3
P			**c**	f_4
1	1	1	1	1
$-K_1$	$[H^+]$	0	0	0
0	$-K_2$	$[H^+]$	0	0
0	0	$-K_3$	$[H^+]$	0

The matrix solution $\mathbf{f} = \mathbf{P}^{-1}\mathbf{c}$ is found by the Excel function $F = $ MMULT(MINVERSE(P);C).

Water solubility: the effective (total) water solubility S'' is determined by the fractions of the species present in solution. At any pH the solubilities are computed individually for each species, and S'' is determined by the species with lowest solubility. Profiles are computed in columns SOLU1, SOLU2, and SOLU3 for each of the $(n+1)$ species. SEFF computes S'' as the minimum of all species.

Partitioning: since each species partitions individually according to its fraction and specific partition coefficient, the pH profile of O/W partitioning is described by

$$K_{eff} = (f^0 K^0) + (f^+ K^+) + (f^- K^-)$$

The uncharged species (neutral or zwitterion) contributes most, since K^0 is much higher than either K^+ or K^-.

2.2. SOLUPART: absorption potential

SOLUPART is a graphical model to predict the absorption potential of a drug substance from its water solubility and O/W partitioning. The model is established in medicinal chemistry, environmental toxicology, or human skin absorption. A quantitative approach in IVIVC was the definition of the "Absorption Potential" [8]

$$\Pi = \log\{K'' f^0 S^0 V/m\} = \log\{S^0 K^0 (f^0)^2/(m/V)\}$$

which postulates logarithmic proportionality to S^0 and K^0, and includes a dose–volume factor m/V as well as electrolytic dissociation f^0.

A similar approach is the Biopharmaceutics Classification System (BCS) [9], which reduces the quantitative model to a simplified 2×2 classification:

Low S, High P	High S, High P
Low S, Low P	High S, Low P

The partition coefficient K is replaced by a permeability P; but P may be assumed to be in proportion to K.

2.2.1. Basic S–K plot

A plot of $\log(S_0)$ vs. $\log(K_0)$ is an informative predictive tool. Fig. 4 illustrates the basic S–K plot for selected substances selected from a database discussed later. Predictors S^0 and K^0 for the neutral (undissociated) species of the parent molecule (•) are plotted on log–log scales. Multiplicative effects are represented by shifts along the axes or diagonals.

↗	Absorption potential Π
→	Dosage-adjusted sink number Y
↘	Electrolytic dissociation Z
↙	Melting point

The existence field of actual substances concentrates in a small band covering three decades. Since, solubility of an organic compound in water or any other fluid cannot exceeds a value of $\approx 10^3$g/L, the field is delimited by two upper boundaries: a vertical line delimits water solubility, a diagonal with slope -1 accounts for the limited solubility in organic phases. A lower boundary reflects not more than the actual situation of effective drug substances.

2.2.2. Dose–volume adjustment

If a dose m is administered to an aqueous volume V, a dimensionless "sink number" can defined as $Y = S/(m/V)$. The choice of V is arbitrary: 1 L gives the most simple transformation, but 0.25 L seems more realistic for drug intake with a glass of water. By substitution of Y, the dimensionless predictor becomes

$$Z = SK/(m/V)$$

This transformation is indicated by points (○), shifted horizontally by $-\log(m/V)$. The vertical line at $\log(Y) = 0$ represents the borderline abscissa value $Y = 1$, corresponding to a saturated aqueous solution. In contact with a lipid reservoir of similar volume, the apparent capacity of the system is augmented by a factor $(1 + K)$, as indicated by a diagonal with slope -1 for $K > 1$.

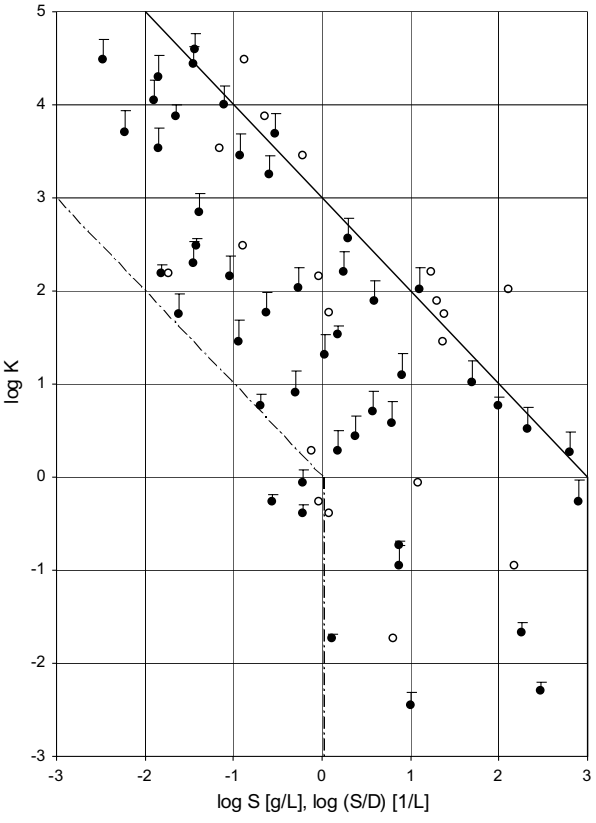


Fig. 4. Log–log S/K plot showing solubility S (•) or $Y = S/(D/V)$ (○) and O/W partition coefficient K. Experimental absorption potentials are indicated by vertical error bars.

For $Y > 1$, all drug is in solution;. for $Y < 1$, only part of it, in proportion to the degree of dissociation. In the same proportion, the effective partitioning decreases, hence the product remains constant and independent of pH.

2.2.3. Electrolytic dissociation

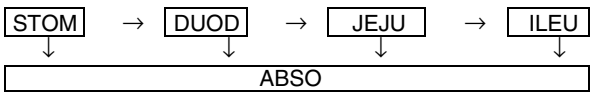
Upon electrolytic dissociation, effective solubility S'' and partitioning K'' vary according to the fraction f^0 of undissociated species. Solubility increases and partitioning decreases with increasing dissociation. Assuming that the neutral species exhibits lowest water solubility and highest partitioning, and disregarding the contribution of charged species, effective values are estimated as $S'' \approx S^0/f^0$ and $K'' \approx K^0 f^0$. In this approximation, both effects compensate to give $K''S'' = K^0 S^0$, hence Z may be generalized to

$$Z = S''K''/(m/V) = S^0K^0/(m/V)$$

In the S–K plot, dissociation is reflected by a ↘ diagonal shift, where solubility increases and partitioning decreases by one decade, for each pH step deviating from the pK value. For an acid this shift occurs with increasing pH, and vice versa for a base; an ampholyte shows two branches.

2.3. GIABS: absorption simulation

GIABS sketches a mechanistic simulation model for g.i. drug absorption. Such *Advanced Compartmental Absorption and Transit* (ACAT) models, originally developed in the 1980s [10–12], were reviewed recently [13], with special attention to commercial software such as [14]. The g.i. tract is modeled by segments, where absorption may occur from any segment:



Initially, a dose m of the drug is contained in the stomach, either as solution or solid, in which case, dissolution profiles may be modeled from theoretical considerations or actual data. From there, the drug is transported through the further segments according to gastric emptying.

2.3.1. Numerical simulation

The main worksheet table simulates the drug transport in columns representing drug amounts in all relevant compartments, in particular the g.i. segments. Additional compartments are defined for the drug absorbed (ABSO), or various states of the substance in these.

Rows correspond to TIME values from 0 to FINTIM, preferably by equidistant time steps. The first row specifies initial conditions. Further rows are computed by solving the underlying linear differential equations by numerical integration methods, e.g., the Euler formula

$$y_i = y_{i-1} + \Delta t f(t,y)$$

where $f(t,y)$ is the product of the initial value y_0 in any donor compartment and a corresponding rate constant k. E.g., an Excel formula

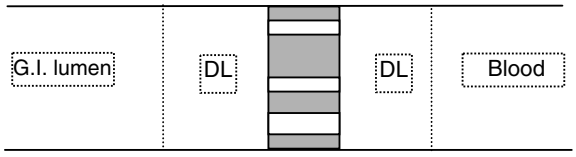
$$\text{JEJU} = \text{K1} * \underline{\text{DUOD}} - \text{K2} * \underline{\text{JEJU}} - \text{KABS} * \underline{\text{JEJU}}$$

updates the jejunum as gain from duodenum minus loss to ileum and via absorption.

2.3.2. Model details

Geometrically, each segment is defined as a cylinder with length and diameter; the absorbing surface area may be increased by a factor accounting for folds and villi. Each segment is characterized by a typical pH, which defines electrolytic dissociation. Each segment is characterized by a typical transit time. Alternatively, chyme flow may be modeled by first-order gastric emptying, followed by plug flow with constant rate.

Absorption is simulated by a W/O/W membrane model with a lipid membrane and adjacent boundary layers, as illustrated below:



The lipid membrane with thickness HMEM is primarily open to permeation of neutral species. A fractional area FPOR of aqueous pores with radius RPOR, presents a pore pathway for small molecules, even if charged. Pore permeability is governed by the filtration factor FILT = *RMOL*/RPOR. Aqueous boundary-layer PAQU is computed from its effective thickness HLAY, estimated from bulk chyme FLOW. Overall permeability characteristics are computed by these Excel formulas:

PAQU	=DAQU/HLAY	Aqueous
PLIP	=FOLD″(DLIP*LOGP/HMEM)*(1-FPOR)	Lipid
PPOR	=(DAQU/HMEM)*FPOR*FILT	Pore
PMEM	=PLIP+PPOR	Membrane
PEFF	=1/(1/PAQU+1/PMEM)	Effective

3. Access database

Database BIODATCO is designed to store IVIVC-relevant data of drug substances as well as formulated products. Its relational structure is shown in Fig. 5, which compiles tables and relevant fields. Relationships between tables are shown by arrows connecting related fields: "1" marks the primary table where the record is unique; "∞" the related table where several records store relevant data.

3.1. Main table

[MAINTAB] as central table compiles all neutral parent compounds, together with their general characteristics. Table 2 gives an excerpt with a few typical records and these selected fields:

CASNO	Text	Chemical Abstracts reference number
INN	Text	International Nonproprietary Name
MW	[−]	Molecular weight
MELT	[°C]	Melting point
PK1–PK3	[−]	pK_a values (up to three)
SWA	[log, g/L]	Water solubility
KOC	[log]	O/W partitioning
DOSE	[log, g]	Administration dose
S/D	[log, 1/L]	Dose-related solubility
ABS	[log]	Absorption potential

Numerical fields are entered with units, consistent with other fields in the same and other tables. Dissociation constants are ordered by increasing size; in order to distinguish between acidic and basic groups, the latter are coded as negative values. For consistency with models, other numerical fields are entered as logarithmic values. S/D = SWA/DOSE illustrates a computed field, whose values are computed from other fields.

Missing values may be left blank, but special missing values provide useful information. E.g., "-" indicates that no value is applicable for the entry; "#N/A" indicates an entry not yet available but to be supplied later on. In field PK1, "*N*" signifies a neutral substance for which no values are defined. Some missing numerical data can be substituted by standardized USP or Martindale descriptions, as illustrated below:

SWA		ABS	
<−1	≈Insoluble	0	Not
−1 . . . 0	Very slightly	1	Poorly, little
0 . . . 1	Slightly	2	Slow
1 . . . 1.5	Sparingly	3	Incompletely, partly
1.5 . . . 2	Soluble	4	Erratic, irregularly
2 . . . 3	Freely soluble	5	Almost completely, fairly readily
>3	Very soluble	6	Completely, well, rapidly, readily

3.2. Other compound-specific tables

These tables store compound-specific data, the structure of which does not fit into the main table.

- [POLYEXPFUN] tabulates fitted polyexponential parameters, fitted from experimental key applications such as i.v. bolus injection or oral solution.
- [SOLUPART] lists experimental data of solubility and O/W partitioning, obtained from various batches of the drug compound or its salts, but contributing to the pH profile of the compound.

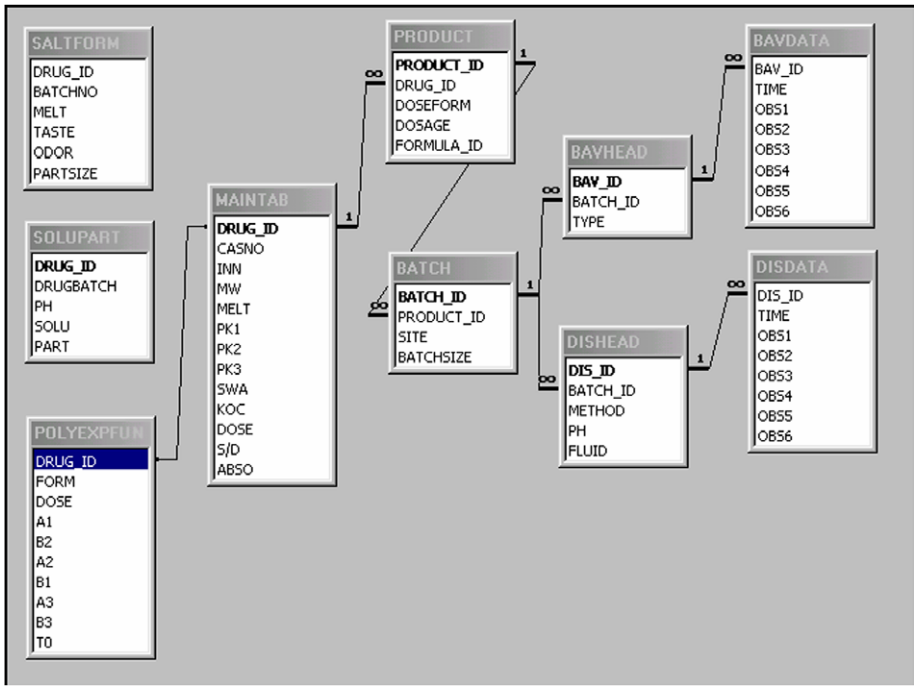


Fig. 5. BIODATCO tables and relations, as indicated by arrows between related fields.

Table 2
Table [MAINTAB] of BIODATCO.MDB database, compiling relevant information for neutral parent compounds

CASNO	INN	MW	MELT	PK1	PK2	PK3	SWA	KOC	DOSE	S/D	ABS
1134-47-0	Baclofen	214	208	3.9	−9.6	–	0.87	−0.96	−1.30	2.17	0.23
#N/A	Benazepril	425	#N/A	3.1	−5.3	–	0.18	1.53	#N/A	#N/A	0.10
298-46-4	Carbamazepine	236	206	N	–	–	−0.62	1.76	−0.70	0.08	0.23
58-94-6	Chlorothiazide	296	343	6.7	–	–	−0.56	−0.27	−0.52	−0.04	0.08
57-62-5	Chlortetracycline	479	169	3.3	7.4	−9.3	−0.22	−0.39	−0.30	0.08	0.10
15307-86-5	Diclofenac	296	158	4.1	–	–	−2.48	4.48	−1.60	−0.88	0.23
20830-75-5	Digoxin	781	265	N	–	–	−1.62	1.75	−3.00	1.38	0.23
126-07-8	Griseofulvin	353	224	N	–	–	−1.82	2.18	−0.10	−1.72	0.10
58-93-5	Hydrochlorothiazide	298	274	8.8	10.4	–	−0.22	−0.07	−1.30	1.08	0.15
37350-58-6	Metoprolol	267	60	−9.6	–	–	1.11	2.02	−1.00	2.11	0.23
6452-71-7	Oxprenolol	265	80	−9.5	–	–	0.24	2.20	−1.00	1.24	0.23
57-83-0	Progesterone	315	131	N	–	–	−1.65	3.87	−1.00	0.65	0.13
23031-25-6	Terbutaline	225	122	−8.8	10.0	11.0	2.00	0.76	−2.30	4.30	0.10
	...										

- [SALTFORM] identifies and describes salts of parent compounds, and compiles their relevant properties (melting point, taste/odor, particle size, etc.).

3.3. Product-specific tables

These tables store information of formulated products. In the context of IVIVC, interest focuses on dissolution data in vitro and bioavailability in vivo.

- [PRODUCT] identifies the drug product by PRODUCT_ID, and provides a general product description (dosage form, dosage, composition, etc.).
- [BATCH] identifies a specific batch, together with manufacturing conditions (site, date, size, etc.).
- [DISHEAD] and [BAVHEAD], as overhead tables for experimental data of in-vitro dissolution tests and in-vivo plasma/urine studies, identify the test or study number and link it with the batch investigated and all relevant testing conditions.
- [DISDATA] and [BAVDATA] store experimental data, where each record is identified by BAV_ID or DIS_ID, respectively. Further fields list the observation TIME together with replications OBS1–OBS12, eventually split into groups of 6 or 12.

Acknowledgements

Models described in this paper were originally developed by the author in SAS language, for use in the former

Ciba-Geigy Ltd. The assistance of M. Deck, J. Mysicka, and H. Rettig, when developing these ideas in the 1980s, as well as for preparing this manuscript, is greatly acknowledged. Special thanks are due to L. Leeson for his persisting encouragement to publish the S-K model.

References

[1] F. Langenbucher, Handling of Computational IVIVC Problems by Microsoft Excel, Eur. J. Pharm. Biopharm. I. Principles Some General Algor. 53 (2002) 1–7;
F. Langenbucher, Handling of Computational IVIVC Problems by Microsoft Excel, Eur. J. Pharm. Biopharm. II. Distrib. Funct. Moments 55 (2003) 77–84;
F. Langenbucher, Handling of Computational IVIVC Problems by Microsoft Excel, Eur. J. Pharm. Biopharm. III. Convol. Deconvol. Algor. 56 (2003) 429–437;
F. Langenbucher, Handling of Computational IVIVC Problems by Microsoft Excel, Eur. J. Pharm. Biopharm. VI. General. Matrix Anal. Linear Compart. Syst. 59 (2005) 229–235.

[2] W.J. Lyman, W.F. Reehl, D.H. Rosenblatt, Handbook of Chemical Property Estimation Methods, McGraw-Hill, New York, 1982.

[3] Y.C. Martin, A practitioner's perspective of the role of quantitative structure–activity analysis in medicinal chemistry, J. Med. Chem. 24 (1981) 229–237.

[4] D.D. Perrin, B. Dempsey, E.P. Serjeant, pK_a Prediction for Organic Acids and Bases, Chapman & Hall, London, 1981.

[5] W.J. Dunn, J.H. Block, R.S. Pearlman, Partition Coefficients: Determination and Estimation, Pergamon Press, New York, 1986.

[6] S.H. Yalkowski, A. A Sinkula, S.C. Valvani, Physical Chemical Properties of Drugs, Marcel Dekker, New York, 1980.

[7] C. Bliefert, pH-Wert-BerechnungenVerlag Chemie, Weinheim, Germany, 1978, Eqs. (5.31) and (7.11).

[8] J.B. Dressman, G.L. Amidon, D. Fleisher, Absorption potential: estimating the fraction absorbed for orally administered compounds, J. Pharm. Sci. 74 (1985) 588–589.

[9] G.L. Amidon, H. Lennernas, V.P. Shah, J.R. Crison, A theoretical basis for a biopharmaceutic drug classification; the correlation of in vitro drug product dissolution and in vivo bioavailability, Pharm. Res. 12 (1995) 413–420.

[10] G.E. Amidon, N.F.H. Ho, A.B. French, W.I. Higuchi, Predicted absorption rates with simultaneous bulk fluid flow in the intestinal tract, J. Theor. Biol. 89 (1981) 195–210.

[11] N.F.H. Ho, H.P. Merkle, W.I. Higuchi, Quantitative, mechanistic and physiologically realistic approach to the biopharmaceutical design of oral drug delivery systems, Drug Dev. Ind. Pharm. 9 (1983) 1111–1184.

[12] N.F.H. Ho, J.Y. Park, G.E. Amidon, P.F. Ni, W.I. Higuchi, Methods for interrelating in vitro, animal, and human absorption studies, in: A.J. Aguiar (Ed.), Gastrointestinal Absorption of Drugs, APhA Academy of Pharmaceutical Sciences, Washington, DC, 1983.

[13] S. Li, H. He, L.J. Parthiban, H. Yin, A.T.M. Serajuddin, IVIVC considerations in the development of immediate-release oral dosage form, J. Pharm. Sci. 94 (2005) 1396–1417.

[14] GastroPlus User Manual, Version 3.1.0a, Simulations Plus Inc., Lancaster, Calif. 2001.