Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Pharmaceutics and Biopharmaceutics 58 (2004) 265–278
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Review article

Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system

Marc Lindenberg[a], Sabine Kopp[b], Jennifer B. Dressman[a,*]

[a]*Department of Pharmaceutical Technology, Johann Wolfgang Goethe-University, Frankfurt am Main, Germany*
[b]*Quality and Safety: Medicines, World Health Organization, Geneva, Switzerland*

Received 29 January 2004; accepted in revised form 5 February 2004

Available online 12 April 2004

Abstract

Since its inception in 1995, the biopharmaceutical classification system (BCS) has become an increasingly important tool for regulation of drug products world-wide. Until now, application of the BCS has been partially hindered by the lack of a freely available and accurate database summarising solubility and permeability characteristics of drug substances. In this report, orally administered drugs on the Model list of Essential Medicines of the World Health Organization (WHO) are assigned BCS classifications on the basis of data available in the public domain. Of the 130 orally administered drugs on the WHO list, 61 could be classified with certainty. Twenty-one (84%) of these belong to class I (highly soluble, highly permeable), 10 (17%) to class II (poorly soluble, highly permeable), 24 (39%) to class III (highly soluble, poorly permeable) and 6 (10%) to class IV (poorly soluble, poorly permeable). A further 28 drugs could be provisionally assigned, while for 41 drugs insufficient or conflicting data precluded assignment to a specific BCS class. A total of 32 class I drugs (either certain or provisional classification) were identified. These drugs can be further considered for biowaiver status (drug product approval based on dissolution tests rather than bioequivalence studies in humans).

Keywords: Biopharmaceutical classification system; Permeability; Solubility; Absorption; World Health Organization; Essential Medicines

1. Introduction

Since the biopharmaceutics classification system (BCS) was introduced in 1995, it has had an increasing impact on regulatory practice. The BCS presented a new paradigm in bioequivalence, based on scientific principles. According to the tenets of the BCS, certain drug products can be considered for biowaivers, i.e. approving the product based on in vitro dissolution tests rather than requiring bioequivalence studies in human subjects. At first, biowaivers were only applied to Scale-Up and Postapproval Changes (SUPAC), but later the biowaiver principle was extended to the approval of new generic drug products. As a result, unnecessary human experiments can be avoided and the costs of developing generic products can be significantly lowered.

To classify a drug according to the BCS, the solubility, dose and permeability of the drug must be known. According to the FDA guidance for the industry 'Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system' (August 2000), a biowaiver can currently be requested only for solid, orally administered immediate-release products (>85% release in 30 min), containing drugs with a high solubility over the pH range from 1 to 7.5 (dose/solubility ($D : S$) ratio <250 ml) and a high permeability (fraction absorbed >90%). In addition, only excipients which do not affect the rate or extent of absorption may be used. Further restrictions are that drugs with a narrow therapeutic range and drug products designed to be absorbed in the oral cavity may not be considered for biowaivers.

The possibility of considering biowaivers for drugs assigned to BCS classes other than class I (high solubility/high permeability) is currently being discussed.

* Corresponding author. Department of Pharmaceutical Technology, Johann Wolfgang Goethe-University, Marie-Curie-Str. 9, 60439 Frankfurt am Main, Germany. Tel.: +49-69-7982-9680; fax: +49-69-7982-9724.
E-mail address: dressman@em.uni-frankfurt.de (J.B. Dressman).

0939-6411/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2004.03.001

Thus, the effect of the BCS on regulatory practices is likely to increase even more in the future.

The aim of this work was to search the public domain for all solubility and permeability data relevant to orally administered drugs belonging to the WHO model list of Essential Medicines. According to the quality and consistency of the data, drugs were then assigned to a BCS class (as defined by the FDA), given a provisional assignment or it was determined that data were too inconclusive to assign the drug to a specific BCS class.

2. Materials and methods

The basis for this study was the Essential Medicines WHO Model List, Core List, 12th edition (revised April 2002). The newest edition of the WHO list can be downloaded from the following website: http://www.who.int/medicines/organization/par/edl/eml.shtml. Research on the solubility and permeability of the drugs on the list that are orally administered was carried out using PubMed Central, the general pharmaceutical literature and information obtained from pharmaceutical firms and authorities. All of this information was freely available on the Internet or from other sources. The search in the PubMed Central was conducted using the following keywords in different combinations: absolute, absorption, aqueous, bioavailability, permeability, pharmacokinetics, solubility and the name of the drug.

Whenever possible, original literature was consulted in order to evaluate the quality of the data and to make the classification as transparent as possible. Data from secondary sources were included for completeness or when original literature could not be located.

All guidelines of the FDA, including the one for classification of drugs in the BCS, can be found at the following website: http://www.fda.gov/cder/guidance/. The three parameters needed for classification of drugs according to BCS are the dose, the solubility and the permeability.

According to the biowaiver guidance (August 2000), high solubility drugs are those with a ($D : S$) ratio of <250 ml over the range of pH 1.0–7.5 at 37 °C. The FDA biowaiver guidance states further, that in the absence of evidence suggesting instability in the GI-tract, a drug substance is considered highly permeable when the extent of absorption (as measured by fraction of dose absorbed, rather than systemic bioavailability) in humans is determined to be 90% or more of an administered dose.

The three individual parameters were evaluated as follows.

2.1. Dose

The dose used for calculation of $D : S$ ratio was the highest recommended dose (in mg) stated in the WHO list for that drug. This dose may differ from specifications given in prescribing information, resulting in a different ($D : S$) ratio for some drugs in some countries.

2.2. Solubility

Data for the solubility (in mg/ml) over the entire range pH value 1–7.5 at 37 °C were located whenever possible. In some cases, where only limited solubility data were available (e.g. solubility at just one pH value in this range), it was nonetheless clear that the solubility was too low at at least one relevant pH condition for the drug to fall into the 'highly soluble' category. In some cases, the pH-dependency of the solubility was determined by Prof. Dressman's group at the University of Frankfurt and collaborators at Hoffmann-La Roche and Merck KGaA. The solubility experiments at the University of Frankfurt were carried out for aciclovir, allopurinol, aspirin, carbamazepine, chloroquine phosphate, doxycycline, diazepam, erythromycin, ibuprofen, mebendazole, metronidazole, potassium phenoxymethylpenicillin and rifampicin using the saturation shake-flask method. The solubility of saquinavir was determined with a similar method at Hoffmann-La Roche. The values for albendazole, glibenclamide, griseofulvin, levothyroxine T4, niclosamide and phenytoin were determined at Merck KGaA. These solubility experiments were typically conducted over 24 h at 37 °C in buffers at pH values of 1.2, 4.5 and 6.8 and in deionised water. In all cases, the samples were analysed by UV-spectroscopy or HPLC and values were determined in triplicate.

Dividing the dose (mg) by the solubility (mg/ml) yields a ratio with volumetric units (ml). This $D : S$ ratio is then compared with the FDA criterion of 250 ml to establish whether the drug is highly soluble or not.

2.3. Permeability

For permeability determinations the FDA prefers pharmacokinetic data in humans, human perfusion data, data from in vivo or in situ animal models or results in validated cell-culture monolayers [1]. To date, computational methods (e.g. based on polar surface area or log P of the molecule) have not been accepted by the FDA as sufficiently reliable for this purpose.

In this work, fraction absorbed data in human studies was the primary source for permeability data. In some cases where data from Caco-2 cells experiments as well as in humans were available (cimetidine, ciprofloxacin, furosemide, phenoxymethylpenicillin, phenytoin and propranolol), these were also taken into consideration as additional evidence. In a few exceptional cases, animal data was also utilised (acetazolamide, benznidazole, furosemide, sulfadiazine).

Data in humans was taken from papers using the following experimental designs:

- Oral vs. i.v. application,
- urinary recovery,
- radioactive-labelled drugs, or
- human perfusion studies.

The fraction absorbed was located if possible, otherwise the absolute bioavailability was recorded. In some cases, it was apparent that the bioavailability of the drug was compromised by degradation in the GI-tract or due to a first-pass effect. These drugs are marked with an asterisk in the tables.

For poorly soluble drugs, it was not always possible to determine whether bioavailabilities of $<90\%$ were due exclusively to solubility problems or whether poor permeability characteristics also played a role. In some cases, the higher bioavailability of the drug when administered with food was taken as an indication that the reason for $<90\%$ absorption in the fasted state was primarily a solubility problem rather than a permeability problem [2].

On the basis of these data, the drugs were then classified according to the guidelines given in the FDA biowaiver guidance [1].

3. Results

For better comprehension, the list has been divided in three parts.

3.1. Drugs with reliable solubility and permeability data

Table 1 includes all drugs with sufficient data for both solubility and permeability to predict the BCS classification with certainty. Sixty-four of the 130 drugs (49%) of the WHO 'Essential drug list' could be assigned to a specific BCS class with certainty.

3.2. Drugs for which complete solubility and/or permeability data are lacking

Table 2 contains drugs for which either the solubility or permeability data (or both) were not completely satisfactory. For example, if specific solubility data in the required pH range could not be found or if bioavailability data were only available from a secondary source. Also, in some cases, the type of data generated was not appropriate for a definitive classification (e.g. urinary excretion data from oral administration without i.v. comparison). In all cases, however, it was possible to provisionally assign the drug to a specific BCS class. Twenty-five of the drugs (20%) could be provisionally assigned to one of the BCS classes.

3.3. Drugs with inconclusive data

Table 3 includes drugs which could not be assigned to a specific BCS class based on the data available, e.g. class II/IV drugs where bioavailability was $<90\%$, but the low bioavailability could be the result of either low solubility or poor permeability or both. Another case would be contradictory data from different sources (e.g. for the solubility of verapamil).

For drugs shown in Table 3, we found conflicting or insufficient data for either solubility or permeability or both. Assignment to a specific BCS class was not possible, but the decision could be narrowed to one of two classes. This was the case for 41 (32%) of the orally administered drugs on the WHO list.

4. Discussion

As stated in Section 1, assignment of a drug to a particular BCS class is an important parameter for biopharmaceutical questions. The availability of high quality data for solubility and permeability is very important to avoid wrong classifications and wasting resources on performing unnecessary human studies to establish bioequivalence. Finding suitable information about solubility and permeability data proved to be a lot more cumbersome than expected. The authors of most articles reviewed here did not, of course, have the suitability of their articles for BCS classification in mind at the time of writing, so a good deal of the data is only partially helpful.

4.1. Dose

According to the FDA biowaiver guidance, the highest dose administered must be used to determine the $(D : S)$ ratio in the BCS. For the classifications in our tables, we used the highest doses recommended in the WHO list. This recommendation may differ from the one given by the manufacturers. For example, in the case of aspirin, the WHO list indicates a range of 100–500 mg as a single dose, but in German prescribing information values of up to 1000 mg are found. Obviously, the choice of the maximum recommended dose has an impact on the calculation of the $D : S$ ratio and, for some drugs, may shift the classification from 'highly' soluble to 'not highly' soluble.

4.2. Solubility

To our knowledge no database available in the public domain with solubility data suitably reported for BCS purposes exist. The data found in articles usually consists of data measured at 25 °C and often at only one pH-value. As the FDA guidance demands that the solubility of a drug has to be determined at 37 °C over the pH range 1–7.5, the information found is therefore often not sufficient for a conclusive classification. This applies particularly to ionisable drugs whose solubility can change dramatically depending on pH. Further, it was not always clear whether

Table 1
Classification of orally administered drugs on the WHO model list of Essential Medicines according to the BCS: *Drugs with reliable solubility and permeability data*

Drug	Solubility	Permeability	Dose (mg)	BCS class[a]	References
Abacavir antiretroviral	**High**	**Low**	**300 (sulfate)**	**III**	**[4–7]**
Acetylsalicylic acid pain relief	**High**	**Low**	**100–500**	**III*/****	**[8–18]**
Aciclovir antiviral	**High**	**Low**	**200**	**III**	**[12,19–25]**
Allopurinol gout	**High**	**Low**	**100**	**III**	**[12,16,25–31]**
Aluminium hydroxide gastro-intestinal agent	Low	Low	500	IV	[30,32–34]
Amiloride diuretic	*High*	*High*	*5 (hydrochloride)*	*I*	[12,16,30,35,36]
Ascorbic acid vitamin	**High**	**Low**	**50 (−1000)**	**III#**	**[12,16,37]**
Atenolol ß-blocker	High	Low	50; 100	III	[1,12,16,38–42]
Captopril antihypertensive	High	Low	25	III	[12,16,43,44]
Carbamazepin antiepileptic	Low	High	100; 200	II	[1,25,45,46]
Chloramphenicol antibiotic	**High**	**Low**	**250**	**III**	**[12,16,47,48]**
Chloroquine antimalarial agent	*High*	*High*	*100 (Phosphate) 150 (Sulfate)*	*I*	[12,23,25,49]
Cimetidine H2-receptor antagonist	High	Low	200	III	[12,16,38,50–56]
Sodium Cloxacillin antibiotic	High	Low	500; 1000 (Na-salz)	III	[12,16,57,58]
Codeine phosphate antitussive/analgetic	**High**	**Low**	**30**	**III**	**[12,16,59,60]**
Colchicine antigout agent	High	Low	0.5	III	[12,61–63]
Cyclophosphamide antineoplastic	*High*	*High*	*25*	*I*	[12,64–66]
Dapsone antirheumatic/leprosy	Low	High	25; 50; 100	II	[12,16,23,30,67,68]
Diazepam Benzodiazepine	*High*	*High*	*2; 5*	*I*	[12,16,25,69–72]
Digoxine cardiac glycoside	*High*	*High*	*0.625; 0.25*	*I#*	[69,73–81]
Doxycycline antibiotic	*High*	*High*	*100 (Hydrochlorid)*	*I*	[12,23,25,82]
Ergotamine Tartrate migraine	High	Low	1 (tartrate)	III*	[12,16,83–86]
Fluconazole antifungal	*High*	*High*	*50*	*I*	[16,91–95]
Furosemide diuretic	Low	Low	40	IV*	[12,38,42,56,70,96–102]
Griseofulvin antifungal	Low	High	125; 250	II	[25,79,103–105]
Hydralazine antihypertensive	High	Low	25; 50 (hydrochloride)	III*	[4,12,16,106,107]
Hydrochlorothiazide diuretic	High	Low	25	III	[1,12,16,23,30,102]
Ibuprofen pain relief	Low	High	200; 400	II	[12,25,108–110]
Indinavir antiviral	Low	Low	200; 300; 400 (Sulfat)	IV*	[4,16,30,111–113,284]
Levodopa + (Carbidopa) Parkinson's disease	*High*	*High*	*100 + 10; 250 + 25*	*I**	[12,16,30,42,114,115]
Levonorgestrel hormone	*High*	*High*	*0.15 (+0.03 Ethinylestradiol) 0.25 (+0.05 Ethinylestradiol) 0.75 (pack of two) + D43*	*I*	[12,16,116,117]
Levothyroxine thyroid	High	Low	0.05; 0.1 (Sodium salt)	III	[12,25,118–120]
Metformine antidiabetic	High	Low	500 (hydrochloride)	III#	[12,16,38,121–123]
Methyldopa antihypertensive	High	Low	250	III*/#	[1,12,30,124,125]
Metronidazole antibiotic	*High*	*High*	*200–500*	*I*	[12,25,126–128]
Nelfinavir antiviral	Low	Low	250 (mesilate)	IV*	[30,33,112,129,284]
Nifedipine Ca-channel blocker	Low	High	10	II*	[12,16,38,130–132]
Nitrofurantoin antibacterial	Low	High	100	II	[12,16,30,133]
Paracetamol (Acetaminophen) pain relief	**High**	**Low**	**100–500**	**III***	**[12,16,38,69,134–137]**
Penicillamine Chron. Polyarthritis	High	Low	250	III	[12,16,138–140]
Phenobarbital barbiturate	*High*	*High*	*15–100*	*I*	[12,16,23,30,141]
Phenoxy-methylpenicillin anitbiotic	*High*	*High*	*250 (Potassium salt)*	*I*	[12,25,142,143]
Phenytoin antiepileptic	Low	High	25; 50; 100	II	[12,23,25,56,144–146]
Prednisolone glucocorticoid	*High*	*High*	*5*	*I*	[16,69,147–149]
Primaquine antimalarial	*High*	*High*	*7.5; 15 (diphosphate)*	*I*	[12,150]
Promethazine antihistamine	**High**	**Low**	**10; 25 (hydrochloride)**	**III***	**[12,16,151,152]**
Propranolol ß-blocker	*High*	*High*	*20; 40 (hydrochloride)*	*I**	[1,12,38,153–155]
Propylthiouracil cystostatic	**High**	**Low**	**50**	**III**	**[12,16,30,156,157]**
Pyrazinamide tuberculotsis	*High*	*High*	*400*	*I*	[12,16,158]
Pyridostigmine Myasthenia gravis	High	Low	60 (bromide)	III	[12,159–161]
Riboflavin vitamin	*High*	*High*	*5*	*I#*	[12,16,162]
Ritonavir antiviral	Low	Low	100	IV*	[4,165,284]
Salbutamol ß-sympathomimetic	*High*	*High*	*4 (sulfate)*	*I**	[12,166–168]
Saquinavir antiviral	Low	Low	200, available as mesylate (hard gelatine capsule) or as free base (soft gelatine capsule)	IV (mesylate)/IV (free base)*	[25,30,33,112,169,284]
Stavudine antiviral	*High*	*High*	*15; 20; 30; 40*	*I*	[170–172]
Sulfamethoxazole antibiotic	Low	High	100; 400	II	[12,16,173–175]

(*continued on next page*)

Table 1 (*continued*)

Drug	Solubility	Permeability	Dose (mg)	BCS class[a]	References
Theophylline antiasthmatic	*High*	*High*	*100; 200; 300*	*I*	[1,12,16,176–178]
Thiamine vitamin	High	Low	50 (hydrochloride)	III[#]	[12,16,33,179]
Trimethoprim antibiotic	Low	High	100; 200	II	[12,16,173–175]
Valproic acid antiepileptic	Low	High	200; 500 (sodium salt)	II	[12,16,23,180]
Zidovudine antiviral	*High*	*High*	*300 (tablet); 100; 250 (capsule)*	*I**	[7,12,16,21,181,182]

[a] Italics denotes class I drugs according to the FDA criteria; bold text denotes class III drugs with permeabilities corresponding to at least 80% absorption.
[*] First pass effect; [**] Degradation in the GI-Tract; [#] active transport.

the experiment was done in a buffer solution or if the pH was only adjusted with acid or base, and if the pH was checked before *and* after the experiment was conducted. Moreover, the comparison of different experiments is often difficult because of a lack of standard deviation values and statistical calculations. Some articles, however, did provide appropriate data for the BCS classification, e.g. where the intrinsic solubility of drugs (where the solubility is the lowest) was provided. If this intrinsic solubility lies between pH 1 and 7.5, the classification of the solubility of the drug can be made with the help of its pK_a and the Hendersson–Hasselbalch equation.

4.3. Permeability

Permeability data from humans is also not easy to find. As with solubility data, a database with freely available, reliable permeability data useful for BCS purposes was not found. The most common type of studies found were bioavailability studies. Since first-pass effects, degradation in the intestine and solubility-limited absorption can all influence the bioavailability, these studies can usually give at most a general indication of the permeability of the drug. The best and safest way to classify a drug as highly permeable is an absolute bioavailability study with a

Table 2
Classification of orally administered drugs on the WHO model list of Essential Medicines according to the BCS: *Drugs for which complete solubility and/or permeability data are lacking*

Drug	Solubility	Permeability	Dose (mg)	BCS class[a]	References
Acetazolamide diuretic	Low	Low	250	IV	[16,183]
Amoxicillin antibiotic	*High*	*High*	*250; 500 (anhydrous)*	*I*[#]	[1,12,16,23,30,36]
Azathioprine immunosuppressive	Low	Low	50	IV	[12,16,23,184]
Benznidazole antiprotozoal agent	*High*	*High*	*100*	*I*	[30,185]
Biperiden antimuscarinic agent	High	Low	2 (hydrochloride)	III*	[12,186]
Didanosine antiviral	High	Low	25; 50; 100; 150; 200 (buff. chew., disp tablet)	III**	[16,21,187–189]
Diethylcarbamazine anthelmentic	*High*	*High*	*50; 100 (Citrat)*	*I*	[12,165]
DL-Methionine chelating agent antidote	*High*	*High*	*250*	*I*[#]	[12,30,33]
Ergocalciferol vitamin	**High**	**Low**	**1.25**	**III**	**[12,33]**
Ergometrine postpartum haemorrhage	High	Low	0.2 (hydrogen maleate)	III	[12,190,191]
Erythromycin antibiotic	High	Low	250 (Stearat od. Ethylsuccinat)	III*/**	[12,25,33,87–90]
Ethambutol hydrochloride tuberculosis	**High**	**Low**	**100–400 (Hydrochlorid)**	**III**	**[12,16,23,33]**
Ethosuximide antiepileptic	*High*	*High*	*250*	*I*	[12,23,192,193]
Iopanoic acid contrast medium	Low	High	500	II	[12,16,30]
Isoniazid tuberculosis	*High*	*High*	*100–300*	*I**	[12,16,23,194]
Lithium carbonate antidepressant	*High*	*High*	*300*	*I*	[12,16,23,30]
Methotrexate antirheumatic/antineoplastic	High	Low	2.5 (sodium salt)	III[#]	[12,195–198]
Nalidixic acid antibacterial agent	Low	High	250; 500	II	[12,30]
Neostigmine Myasthenia gravis	High	Low	15 (bromide)	III	[12,23,160]
Nevirapine antiviral	Low	High	200	II	[30,199]
Nicotinamide vitamin	*High*	*High*	*50*	*I*	[12,16,33]
Nifurtimox antiprotozoal agent	**High**	**Low**	**30; 120; 250**	**III***	**[12,200]**
Norethisterone hormone	*High*	*High*	*1 (+0.035 Ethinylestradiol)*	*I**	[12,165]
	High	*High*	*5*	*I**	
Praziquantel antihelmentic	Low	High	150; 600	II*	[12,16,30]
Proguanil antimalarial	*High*	*High*	*100 (hydrochloride)*	*I**	[12,165]
Pyridoxine vitamin	*High*	*High*	*25 (hydrochloride)*	*I*	[12,16,201]
Reserpine antihypertensive	High	Low	0.1; 0.25	III	[12,16]
Rifampicin antituberculotic	Low	High	150; 300	II*	[12,25,68,163,164]

[a] Italics denotes class I drugs according to the FDA criteria; bold text denotes class III drugs with permeabilities corresponding to at least 80% absorption.
[*] First pass effect; [**] Degradation in the GI-Tract; [#] active transport.

Table 3
Classification of orally administered drugs on the WHO model list of Essential Medicines according to the BCS: drugs with inconclusive data

Drug	Solubility	Permeability	Dose (mg)	BCS class[a]	References
Albendazole antiparasitic	Low	Low/High	400	II/IV*	[25,202–206]
Amitriptyline antidepressive	Low/High	High	25 (hydrochloride)	I/II*	[12,16,24,207–209]
Artemether + Lumefantrine antimalarial agents	Low	Low/High	20 + 120	II/IV*	[12,30,33,210–213]
Atropine Sulphate parasympatholytic	High	Low/High	1	I/III*	[12,16,23,32,70,214]
Chlorpheniramine antihistamine	High	Low/High	4 (Hydrogenmaleat)	I/III*	[12,16,41,151,215]
Chlorpromazine antidepressive	Low	Low/High	100 (hydrochloride)	II/IV*	[12,16,24,216,217]
Ciprofloxacin antibiotic	Low	Low/High	250 (Hydrochlorid)	II/IV*	[12,17,24,218–222]
Clofazimine antibacterial agent	Low	Low/High	50; 100	II/IV	[69,223,224]
Clomiphene hormone	High	?	50 (citrate)	I/III	[12,16]
Clomipramine antidepressive	High	Low/High	10; 25 (hydrochloride)	I/III*	[12,225,226]
Dexamethasone glucocorticoide	High	Low/High	0.5; 4	I/III*	[12,16,69,227–230]
Diloxanide antiprotozoal agent	Low	Low/High	500 (furoate)	II/IV**	[12,16,231]
Efavirenz antiviral	Low	Low/High	50; 100; 200	II/IV	[31,33,232]
Ethinylestradiol hormone	High	Low/High	0.03 (+0.15 Levonorgestrel) 0.05 (+0.25 Levonorgestrel) 0.01; 0.05;	I/III*	[12,116,233]
Folic acid	Low	Low/High	1; 5	II/IV	[12,30,234,235]
Glibenclamide antidiabetic	Low	Low/High	2.5; 5	II/IV	[12,25,38,236]
Glyceryl Trinitrate Angina pectoris	High	Low/High	0.5	I/III*	[12,237,238]
Haloperidol neuroleptic	Low	Low/High	2; 5	II/IV*	[12,16,30,70,239–243]
Isosorbid dinitrate Angina pectoris	High	Low/High	5	I/III	[16,30,244,245]
Ivermectin anthelmentic	Low	Low/High	3; 6	II/IV	[12,16,30]
Lamivudin antiviral	High	Low/High	150	I/III	[7,246–248]
Levamisole anthelmentic	High	Low/High	50; 150 (Hydrochlorid)	I/III	[202,249–251]
Lopinavir antiviral	Low	Low/High	133.3 (+33.3 Ritonavir)	II/IV*	[30,252]
Mebendazole antihelmentic	Low	Low/High	100; 500	II/IV	[25,253,254]
Mefloquine antimalarial	Low	Low/High	250 (hydrochloride)	II/IV	[16,255]
Metoclopramide prokinetic agent	High	Low/High	10 (hydrochloride)	I/III*	[12,256–260]
Morphine sulfate pain relief	High	Low/High	10	I/III*	[12,16,261–264]
Niclosamide anthelmentic	Low	Low/High	500	II/IV	[12,265]
Nystatin antifungal	Low/High	Low	100 000 IU; 500 000 IU (~5000 IU = 1 mg) - > ~20-100 mg	III/IV	[12,30,33]
Pyrantel anthelmentic	Low	Low/High	250 (embonate)	II/V	[12,165]
Pyrimethamine Toxoplasmose	Low	Low/High	25	II/IV	[12,266,267]
Quinine antimalarial	High	Low/High	300 (bisulfate or sulfate)	I/III	[12,176,268,269]
Retinol vitamin	Low	Low/High	10 000 IU (palmitate) (5.5 mg) 200 000 IU (palmitate) (110 mg)	II/IV[#]	[12,270,271]
Senna laxative	?	?	7.5 (sennosides)		[12]
Sodium iodide iodine deficiency	High	???	60	I/III	[12]
Spironolactone diuretic	Low	Low/High	25	II/IV*	[12,16,35,272,273]
Sulfadiazine antibacterial agent	Low	Low/High	500	II/IV	[12,23,274,275]
Sulfasalazine Colitis Ulcerosa/Morbus Crohn	Low	Low/High	500	II/IV	[12,16,276,277]
Triclabendazole anthelmentic	Low	Low/High	250	II/IV	[32,278]
Verapamil hydrochloride Ca-channel blocker	Low/High	High	40; 80 (hydrochloride)	I/II*	[1,12,16,38,70,131,221,279–282]
Warfarin Sodium anticoagulant	Low/High	High	1; 2; 5 (sodium salt)	I/II	[12,16,41,46,221,283]

[*] First pass effect; [**] Degradation in the GI-Tract; [#] active transport.

bioavailability greater than 90%. In cases where the bioavailability was lower than 90%, the influence of the above-mentioned factors has to be taken into account. Where low bioavailability (<90%) could be attributed with certainty to degradation in the GI-tract or because of a first-pass effect, these findings have been marked in the tables with asterisks. Data based on experiments where the amount of drug was measured by urinary excretion sometimes lacked i.v. comparison or determination of metabolites, both of which are necessary for a sure classification of the permeability characteristics.

Good data was found in papers using the intestinal perfusion technique in humans, as these provided direct permeability data. Data from experiments with cell culture monolayers (mostly Caco-2 cells) were often available. However, absolute values reported can vary by orders of magnitude among laboratories [3] and unless the methodology is validated according to the FDA biowaiver

guidance, it is difficult to assign the drug to 'high' or 'low' permeability with certainty. Therefore, Caco-2 cell data was considered in most cases as supplementary rather than primary information.

Of the 130 orally administered drugs found in the WHO list, 61 could be classified reliably (49%). Twenty-one of these 61 (34%) were classified as class I drugs, 10 as class II drugs (17%), 24 as class III drugs (39%) and 6 as class IV drugs (10%). Taking into account drugs with provisional classification (Table 2) as well as certain (Table 1) classification, a total of 89 drugs could be classified. Thirty-two of these are class I drugs (36%), 15 class II drugs (17%), 34 class III drugs (38%) and 8 are class IV drugs (9%).

A considerable number of the orally administered drugs were classified as class I drugs, namely 32 These are highlighted in italics in the tables. These are potential candidates for consideration of a biowaiver for solid, orally administered dosage forms. Of the 34 drugs assigned to class III in Tables 1 and 2, 13 had a permeability consistent with $>80\%$ oral absorption and therefore might be additionally considered as potential candidates for biowaivers. These are highlighted in bold in the tables.

The information provided here should help pharmaceutical manufacturers of generic drug products to lower the cost of bringing a product onto the market. This is of particular interest in countries with highly restricted health care budgets. Of course, to be considered for a biowaiver other drug product characteristics, such as the therapeutic index of the drug and the potential influence of the excipients on the rate or extent of absorption, have to be considered as well.

Further research on the provisionally or indecisively classified drugs should be encouraged to increase the quality and certainty of the data. In fact, an ongoing and thorough analysis of the literature for every drug should be conducted and the findings carefully evaluated by specialists in the pertinent field. This will enable a detailed risk analysis and lead to recommendations as to whether a specific drug/drug product can be considered for a biowaiver or not. Coordination of WHO activities with those of the special interest group 'Bioavailability/Bioequivalence' of the International Pharmaceutical Federation on the field application of the BCS, as well as general issues of bioequivalence, has been initiated.

Acknowledgements

This work was partially funded by the World Health Organization and forms the basis of a Working Document on the BCS Classification of the Essential Medicines List.

The opinions expressed in this article are those of the authors and do not necessarily represent the decisions or stated policy of the World Health Organization.

Note added in proof

A review of the data and additional information revealed that, for three compounds, the certainty of the classification did not justify inclusion in Table 1. These compounds have been moved to Table 2. Further, for two additional compounds, the classification of either the permeability or solubility was reevaluated. These changes are reflected in the current tables.

References

[1] FDA, Waiver of in vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms based on a Biopharmaceutics Classification System, 2000.
[2] D. Horter, J.B. Dressman, Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract, Adv. Drug Deliv. Rev. 46 (2001) 75–87.
[3] P. Artursson, K. Palm, K. Luthman, Caco-2 monolayers in experimental and theoretical predictions of drug transport, Adv. Drug Deliv. Rev. 46 (2001) 27–43.
[4] Various Authors, USP 26: Board of Trustees, Rockville, MD, 2003.
[5] G.E. Chittick, C. Gillotin, J.A. McDowell, Y. Lou, K.D. Edwards, W.T. Prince, D.S. Stein, Abacavir: absolute bioavailability, bioequivalence of three oral formulations, and effect of food, Pharmacotherapy 19 (1999) 932–942.
[6] J.A. McDowell, G.E. Chittick, J.R. Ravitch, R.E. Polk, T.M. Kerkering, D.S. Stein, Pharmacokinetics of [(14)C]abacavir, a human immunodeficiency virus type 1 (HIV-1) reverse transcriptase inhibitor, administered in a single oral dose to HIV-1-infected adults: a mass balance study, Antimicrob. Agents Chemother. 43 (1999) 2855–2861.
[7] Trizivir™ prescribing information, Glaxo Smith Kline.
[8] Safety data sheet: http://www.chemicalland21.com/arokorhi/lifescience/phar/acetylsalicylic%20acid.htm.
[9] S. Ito, R. Oka, A. Tsuchida, H. Yoshioka, Disposition of single-dose intravenous and oral aspirin in children, Dev. Pharmacol. Ther. 17 (1991) 180–186.
[10] C.J. Needs, P.M. Brooks, Clinical pharmacokinetics of the salicylates, Clin. Pharmacokinet. 10 (1985) 164–177.
[11] H. Schroder, K. Schror, Clinical pharmacology of acetylsalicylic acid, Z. Kardiol. 81 (Suppl. 4) (1992) 171–175.
[12] S.C. Sweetman, Martindale 33, Martindale The Extra Pharmacopoeia, Council of the Royal Pharmaceutical Society of Great Britain, London, 2002.
[13] A.K. Pedersen, G.A. FitzGerald, Dose-related kinetics of aspirin. Presystemic acetylation of platelet cyclooxygenase, N. Engl. J. Med. 311 (1984) 1206–1211.
[14] R.O. Day, P.D. Paull, G.D. Champion, G.G. Graham, Evaluation of an enteric coated aspirin preparation, Aust. N. Z. J. Med. 6 (1976) 45–50.
[15] P. Paull, R. Day, G. Graham, D. Champion, Single-dose evaluation of a new enteric-coated aspirin preparation, Med. J. Aust. 1 (1976) 617–619.
[16] Various Authors, Analytical Profiles of Drug Substances: K. Florey, Academic Press, Inc., New York, 1972.
[17] C.A. Bergstrom, U. Norinder, K. Luthman, P. Artursson, Experimental and computational screening models for prediction of aqueous drug solubility, Pharm. Res. 19 (2002) 182–188.
[18] P.E. McKinney, R. Gillilan, W.A. Watson, The preadministration of activated charcoal and aspirin absorption, J. Toxicol. Clin. Toxicol. 30 (1992) 549–556.
[19] A.P. Bras, D.S. Sitar, F.Y. Aoki, Comparative bioavailability of acyclovir from oral valacyclovir and acyclovir in patients treated for

recurrent genital herpes simplex virus infection, Can. J. Clin. Pharmacol. 8 (2001) 207–211.
[20] P. de Miranda, M.R. Blum, Pharmacokinetics of acyclovir after intravenous and oral administration, J. Antimicrob. Chemother. 12 (Suppl. B) (1983) 29–37.
[21] G.D. Morse, M.J. Shelton, A.M. O'Donnell, Comparative pharmacokinetics of antiviral nucleoside analogues, Clin. Pharmacokinet. 24 (1993) 101–123.
[22] O.L. Laskin, Clinical pharmacokinetics of acyclovir, Clin. Pharmacokinet. 8 (1983) 187–201.
[23] Joel G. Hardman, Goodman and Gilman The Pharmacological Basis of Therapeutics, McGraw-Hill Professional, 2001.
[24] A. Avdeef, Determination of drug solubility using a potentiometric acid–base titration method compared to the saturation shake-flask method: http://www.pion-inc.com/images/aaps00_solubility1.pdf.
[25] Data on file.
[26] S.J. Appelbaum, M. Mayersohn, R.T. Dorr, D. Perrier, Allopurinol kinetics and bioavailability. Intravenous, oral and rectal administration, Cancer Chemother. Pharmacol. 8 (1982) 93–98.
[27] B. Breithaupt, M. Tittel, Kinetics of allopurinol after single intravenous and oral doses. Noninteraction with benzbromarone and hydrochlorothiazide, Eur. J. Clin. Pharmacol. 22 (1982) 77–84.
[28] G.A. Murrell, W.G. Rapeport, Clinical pharmacokinetics of allopurinol, Clin. Pharmacokinet. 11 (1986) 343–353.
[29] K. Turnheim, P. Krivanek, R. Oberbauer, Pharmacokinetics and pharmacodynamics of allopurinol in elderly and young subjects, Br. J. Clin. Pharmacol. 48 (1999) 501–509.
[30] S. Budavari, The Merck Index 12, The Merck Index, Merck Research Laboratories, Whitehouse Station, NJ, 1996.
[31] D.T. Klopp, Pharmazeutische Stoffliste, ABDA, Eschborn/Germany, 2002.
[32] H.W. Artur Burger, Hunnius, Walter de Gruyter&Co, Berlin, 1998.
[33] German Fachinfo: Eryhexal®, Hexal AG; Myambutol Filmtabletten®, Riemser; Sustiva®, Bristol-Myers Squibb; Methionin-ratiopharm®, Ratiopharm AG; Vitamin B1-ratiopharm®, Ratiopharm AG; Biofanal Dragees®, Pfleger; Nicobion®, Merck KGaA; Inivirase®, Hoffmann-La Roche; Frubiase calcium forte 500®, Boehringer Ingelheim; Riamet®, Novartis Pharma, Teplite®, ICN.
[34] N.D. Priest, R.J. Talbot, J.G. Austin, J.P. Day, S.J. King, K. Fifield, R.G. Cresswell, The bioavailability of 26Al-labelled aluminium citrate and aluminium hydroxide in volunteers, Biometals 9 (1996) 221–228.
[35] B. Beermann, Aspects on pharmacokinetics of some diuretics, Acta Pharmacol. Toxicol. (Copenh) 54 (Suppl. 1) (1984) 17–29.
[36] H. Lennernas, L. Knutson, T. Knutson, A. Hussain, L. Lesko, T. Salmonson, G.L. Amidon, The effect of amiloride on the in vivo effective permeability of amoxicillin in human jejunum: experience from a regional perfusion technique, Eur. J. Pharm. Sci. 15 (2002) 271–277.
[37] A. Kallner, D. Hartmann, D. Hornig, On the absorption of ascorbic acid in man, Int. J. Vitam. Nutr. Res. 47 (1977) 383–388.
[38] DPHG. GSP, Gute Substitutions Praxis: http://www.dphg.de/lib/dphg_leitlinie01_gsp_02-1.pdf.
[39] W. Kirch, K.G. Gorg, Clinical pharmacokinetics of atenolol—a review, Eur. J. Drug Metab. Pharmacokinet. 7 (1982) 81–91.
[40] H. Lennernas, O. Ahrenstedt, A.L. Ungell, Intestinal drug absorption during induced net water absorption in man; a mechanistic study using antipyrine, atenolol and enalaprilat, Br. J. Clin. Pharmacol. 37 (1994) 589–596.
[41] Y. Ishihama, M. Nakamura, T. Miwa, T. Kajima, N. Asakawa, A rapid method for pK_a determination of drugs using pressure-assisted capillary electrophoresis with photodiode array detection in drug discovery, J. Pharm. Sci. 91 (2002) 933–942.
[42] U. Fagerholm, M. Johansson, H. Lennernas, Comparison between permeability coefficients in rat and human jejunum, Pharm. Res. 13 (1996) 1336–1342.
[43] K.L. Duchin, S.M. Singhvi, D.A. Willard, B.H. Migdalof, D.N. McKinstry, Captopril kinetics, Clin. Pharmacol. Ther. 31 (1982) 452–458.
[44] K.L. Duchin, D.N. McKinstry, A.I. Cohen, B.H. Migdalof, Pharmacokinetics of captopril in healthy subjects and in patients with cardiovascular diseases, Clin. Pharmacokinet. 14 (1988) 241–259.
[45] A. Gerardin, J.P. Dubois, J. Moppert, L. Geller, Absolute bioavailability of carbamazepine after oral administration of a 2% syrup, Epilepsia 31 (1990) 334–338.
[46] A.K. Mandagere, T.N. Thompson, K.K. Hwang, Graphical model for estimating oral bioavailability of drugs in humans and other species from their Caco-2 permeability and in vitro liver enzyme metabolic stability rates, J. Med. Chem. 45 (2002) 304–311.
[47] P.J. Ambrose, Clinical pharmacokinetics of chloramphenicol and chloramphenicol succinate, Clin. Pharmacokinet. 9 (1984) 222–238.
[48] W.G. Kramer, E.R. Rensimer, C.D. Ericsson, L.K. Pickering, Comparative bioavailability of intravenous and oral chloramphenicol in adults, J. Clin. Pharmacol. 24 (1984) 181–186.
[49] L.L. Gustafsson, O. Walker, G. Alvan, B. Beermann, F. Estevez, L. Gleisner, B. Lindstrom, F. Sjoqvist, Disposition of chloroquine in man after single intravenous and oral doses, Br. J. Clin. Pharmacol. 15 (1983) 471–479.
[50] S.P. Katrukha, E.V. Karpenko, S.M. Davydov, I.L. Blinkov, V.G. Kukes, Cimetidine pharmacokinetics, Farmakol. Toksikol. 49 (1986) 36–40.
[51] K. Kawai, Does H2 receptor antagonist-resistant ulcer exist? A review based on bioavailability in man, Gastroenterol. Jpn 27 (1992) 418–423.
[52] P.V. Pedersen, R. Miller, Pharmacokinetics and bioavailability of cimetidine in humans, J. Pharm. Sci. 69 (1980) 394–398.
[53] W.J. Sandborn, S.C. Forland, R.E. Cutler, R.M. Strong, Pharmacokinetics and pharmacodynamics of oral and intravenous cimetidine in seriously ill patients, J. Clin. Pharmacol. 30 (1990) 568–571.
[54] A. Somogyi, R. Gugler, Clinical pharmacokinetics of cimetidine, Clin. Pharmacokinet. 8 (1983) 463–495.
[55] N. Takamatsu, O.N. Kim, L.S. Welage, N.M. Idkaidek, Y. Hayashi, J. Barnett, R. Yamamoto, E. Lipka, H. Lennernas, A. Hussain, L. Lesko, G.L. Amidon, Human jejunal permeability of two polar drugs: cimetidine and ranitidine, Pharm. Res. 18 (2001) 742–744.
[56] V. Pade, S. Stavchansky, Link between drug absorption solubility and permeability measurements in Caco-2 cells, J. Pharm. Sci. 87 (1998) 1604–1607.
[57] E.H. Nauta, H. Mattie, Dicloxacillin and cloxacillin: pharmacokinetics in healthy and hemodialysis subjects, Clin. Pharmacol. Ther. 20 (1976) 98–108.
[58] M. Spino, R.P. Chai, A.F. Isles, J.J. Thiessen, A. Tesoro, R. Gold, S.M. MacLeod, Cloxacillin absorption and disposition in cystic fibrosis, J. Pediatr. 105 (1984) 829–835.
[59] K. Persson, M. Hammarlund-Udenaes, O. Mortimer, A. Rane, The postoperative pharmacokinetics of codeine, Eur. J. Clin. Pharmacol. 42 (1992) 663–666.
[60] Q.Y. Yue, J.O. Svensson, F. Sjoqvist, J. Sawe, A comparison of the pharmacokinetics of codeine and its metabolites in healthy Chinese and Caucasian extensive hydroxylators of debrisoquine, Br. J. Clin. Pharmacol. 31 (1991) 643–647.
[61] B. Bittner, A. Guenzi, P. Fullhardt, G. Zuercher, R.C. Gonzalez, R.J. Mountfield, Improvement of the bioavailability of colchicine in rats by co-administration of D-alpha-tocopherol polyethylene glycol 1000 succinate and a polyethoxylated derivative of 12-hydroxystearic acid, Arzneimittelforschung 52 (2002) 684–688.
[62] G.M. Ferron, M. Rochdi, W.J. Jusko, J.M. Scherrmann, Oral absorption characteristics and pharmacokinetics of colchicine in healthy volunteers after single and multiple doses, J. Clin. Pharmacol. 36 (1996) 874–883.
[63] M. Rochdi, A. Sabouraud, C. Girre, R. Venet, J.M. Scherrmann, Pharmacokinetics and absolute bioavailability of colchicine after i.v.

and oral administration in healthy human volunteers and elderly subjects, Eur. J. Clin. Pharmacol. 46 (1994) 351–354.
[64] M. Matthias, R. Sohr, R. Preiss, B. Brockmann, Bioavailability of cyclophosphamide following oral administration in high doses, Onkologie 7 (1984) 48–49.
[65] R.F. Struck, D.S. Alberts, K. Horne, J.G. Phillips, Y.M. Peng, D.J. Roe, Plasma pharmacokinetics of cyclophosphamide and its cytotoxic metabolites after intravenous versus oral administration in a randomized, crossover trial, Cancer Res. 47 (1987) 2723–2726.
[66] T. Wagner, K. Fenneberg, Pharmacokinetics and bioavailability of cyclophosphamide from oral formulations, Arzneimittelforschung 34 (1984) 313–316.
[67] F.A. Pieters, J. Zuidema, The absolute oral bioavailability of dapsone in dogs and humans, Int. J. Clin. Pharmacol. Ther. Toxicol. 25 (1987) 396–400.
[68] K. Venkatesan, Clinical pharmacokinetic considerations in the treatment of patients with leprosy, Clin. Pharmacokinet. 16 (1989) 365–386.
[69] T.S. Wiedmann, L. Kamel, Examination of the solubilization of drugs by bile salt micelles, J. Pharm. Sci. 91 (2002) 1743–1764.
[70] ACD/pKa Database, http://www.scienceserve.com/software/acd/acd_pka_db.htm.
[71] M. Divoll, D.J. Greenblatt, H.R. Ochs, R.I. Shader, Absolute bioavailability of oral and intramuscular diazepam: effects of age and sex, Anesth. Analg. 62 (1983) 1–8.
[72] H.R. Ochs, H. Otten, D.J. Greenblatt, H.J. Dengler, Diazepam absorption: effects of age, sex, and Billroth gastrectomy, Dig. Dis. Sci. 27 (1982) 225–230.
[73] T. Beveridge, E. Nuesch, E.E. Ohnhaus, Absolute bioavailability of digoxin tablets, Arzneimittelforschung 28 (1978) 701–703.
[74] D.J. Greenblatt, T.W. Smith, J. Koch-Weser, Bioavailability of drugs: the digoxin dilemma, Clin. Pharmacokinet. 1 (1976) 36–51.
[75] P.H. Hinderling, D. Hartmann, Pharmacokinetics of digoxin and main metabolites/derivatives in healthy humans, Ther. Drug Monit. 13 (1991) 381–401.
[76] E. Iisalo, Clinical pharmacokinetics of digoxin, Clin. Pharmacokinet. 2 (1977) 1–16.
[77] A.D. Mooradian, Digitalis. An update of clinical pharmacokinetics, therapeutic monitoring techniques and treatment recommendations, Clin. Pharmacokinet. 15 (1988) 165–179.
[78] B.F. Johnson, J. O'Grady, G.A. Sabey, C. Bye, Effect of a standard breakfast on digoxin absorption in normal subjects, Clin. Pharmacol. Ther. 23 (1978) 315–319.
[79] L.X. Yu, An integrated model for determining causes of poor oral drug absorption, Pharm. Res. 16 (1999) 1883–1887.
[80] D.H. Huffman, C.V. Manion, D.L. Azarnoff, Absorption of digoxin from different oral preparations in normal subjects during steady state, Clin. Pharmacol. Ther. 16 (1974) 310–317.
[81] M.F. Fromm, P-glycoprotein: a defense mechanism limiting oral bioavailability and CNS accumulation of drugs, Int. J. Clin. Pharmacol. Ther. 38 (2000) 69–74.
[82] J.L. Riond, J.E. Riviere, Pharmacology and toxicology of doxycycline, Vet. Hum. Toxicol. 30 (1988) 431–443.
[83] W.H. Aellig, E. Nuesch, Comparative pharmacokinetic investigations with tritium-labeled ergot alkaloids after oral and intravenous administration man, Int. J. Clin. Pharmacol. Biopharm. 15 (1977) 106–112.
[84] K. Ekbom, A.E. Krabbe, G. Paalzow, L. Paalzow, P. Tfelt-Hansen, E. Waldenlind, Optimal routes of administration of ergotamine tartrate in cluster headache patients. A pharmacokinetic study, Cephalalgia 3 (1983) 15–20.
[85] J.J. Ibraheem, L. Paalzow, P. Tfelt-Hansen, Low bioavailability of ergotamine tartrate after oral and rectal administration in migraine sufferers, Br. J. Clin. Pharmacol. 16 (1983) 695–699.
[86] V.L. Perrin, Clinical pharmacokinetics of ergotamine in migraine and cluster headache, Clin. Pharmacokinet. 10 (1985) 334–352.
[87] J.P. Butzler, R. Vanhoof, N. Clumeck, P. de Mol, M.P. Vanderlinden, E. Yourassowsky, Clinical and pharmacological evaluation of different preparations of oral erythromycin, Chemotherapy 25 (1979) 367–372.
[88] E.D. Ehrenpreis, D. Zaitman, H. Nellans, Which form of erythromycin should be used to treat gastroparesis? A pharmacokinetic analysis, Aliment Pharmacol. Ther. 12 (1998) 373–376.
[89] L.E. Mather, K.L. Austin, C.R. Philpot, P.J. McDonald, Absorption and bioavailability of oral erythromycin, Br. J. Clin. Pharmacol. 12 (1981) 131–140.
[90] A.A. Somogyi, F. Bochner, D. Hetzel, D.B. Williams, Evaluation of the intestinal absorption of erythromycin in man: absolute bioavailability and comparison with enteric coated erythromycin, Pharm. Res. 12 (1995) 149–154.
[91] K.W. Brammer, P.R. Farrow, J.K. Faulkner, Pharmacokinetics and tissue penetration of fluconazole in humans, Rev. Infect. Dis. 12 (Suppl. 3) (1990) S318–S326.
[92] D. Debruyne, J.P. Ryckelynck, Clinical pharmacokinetics of fluconazole, Clin. Pharmacokinet. 24 (1993) 10–27.
[93] K. Shiba, A. Saito, T. Miyahara, Safety and pharmacokinetics of single oral and intravenous doses of fluconazole in healthy subjects, Clin. Ther. 12 (1990) 206–215.
[94] S. Tett, S. Moore, J. Ray, Pharmacokinetics and bioavailability of fluconazole in two groups of males with human immunodeficiency virus (HIV) infection compared with those in a group of males without HIV infection, Antimicrob. Agents Chemother. 39 (1995) 1835–1841.
[95] A.S. Uch, Intestinal Uptake of Azole Antifungals in Rats, Department of Biochemistry, Pharmaceutics and Food Chemistry, Johann Wolfgang Goethe University, Frankfurt, 1999.
[96] A. Grahnen, M. Hammarlund, T. Lundqvist, Implications of intraindividual variability in bioavailability studies of furosemide, Eur. J. Clin. Pharmacol. 27 (1984) 595–602.
[97] M.M. Hammarlund, L.K. Paalzow, B. Odlind, Pharmacokinetics of furosemide in man after intravenous and oral administration. Application of moment analysis, Eur. J. Clin. Pharmacol. 26 (1984) 197–207.
[98] M.G. Lee, W.L. Chiou, Evaluation of potential causes for the incomplete bioavailability of furosemide: gastric first-pass metabolism, J. Pharmacokinet. Biopharm. 11 (1983) 623–640.
[99] J.L. McCrindle, T.C. Li Kam Wa, W. Barron, L.F. Prescott, Effect of food on the absorption of frusemide and bumetanide in man, Br. J. Clin. Pharmacol. 42 (1996) 743–746.
[100] M.D. Murray, K.M. Haag, P.K. Black, S.D. Hall, D.C. Brater, Variable furosemide absorption and poor predictability of response in elderly patients, Pharmacotherapy 17 (1997) 98–106.
[101] M. Lesne, Comparison of the pharmacokinetics and pharmacodynamics of torasemide and furosemide in healthy volunteers, Arzneimittelforschung 38 (1988) 160–163.
[102] A. Avdeef, C.M. Berger, C. Brownell, pH-metric solubility. 2 Correlation between the acid–base titration and the saturation shake-flask solubility-pH methods, Pharm. Res. 17 (2000) 85–89.
[103] T.R. Bates, H.J. Pieniaszek Jr., J.A. Sequeira, J.E. Rasmussen, Gastrointestinal absorption of griseofulvin from corn oil-in-water emulsions: effect of amount of corn oil ingested in man, Arch. Dermatol. 113 (1977) 302–306.
[104] W.L. Chiou, S. Riegelman, Absorption characteristics of solid dispersed and micronized griseofulvin in man, J. Pharm. Sci. 60 (1971) 1376–1380.
[105] F.A. Ogunbona, I.F. Smith, O.S. Olawoye, Fat contents of meals and bioavailability of griseofulvin in man, J. Pharm. Pharmacol. 37 (1985) 283–284.
[106] A.M. Shepherd, T.M. Ludden, J.L. McNay, M.S. Lin, Hydralazine kinetics after single and repeated oral doses, Clin. Pharmacol. Ther. 28 (1980) 804–811.
[107] T. Talseth, Studies on hydralazine. III. Bioavailability of hydralazine in man, Eur. J. Clin. Pharmacol. 10 (1976) 395–401.

[108] H. Cheng, J.D. Rogers, J.L. Demetriades, S.D. Holland, J.R. Seibold, E. Depuy, Pharmacokinetics and bioinversion of ibuprofen enantiomers in humans, Pharm. Res. 11 (1994) 824–830.
[109] W. Martin, G. Koselowske, H. Toberich, T. Kerkmann, B. Mangold, J. Augustin, Pharmacokinetics and absolute bioavailability of ibuprofen after oral administration of ibuprofen lysine in man, Biopharm. Drug Dispos. 11 (1990) 265–278.
[110] S.C. Tan, B.K. Patel, S.H. Jackson, C.G. Swift, A.J. Hutt, Stereoselectivity of ibuprofen metabolism and pharmacokinetics following the administration of the racemate to healthy volunteers, Xenobiotica 32 (2002) 683–697.
[111] P.L. Carver, D. Fleisher, S.Y. Zhou, D. Kaul, P. Kazanjian, C. Li, Meal composition effects on the oral bioavailability of indinavir in HIV-infected patients, Pharm. Res. 16 (1999) 718–724.
[112] R.B. Kim, M.F. Fromm, C. Wandel, B. Leake, A.J. Wood, D.M. Roden, G.R. Wilkinson, The drug transporter P-glycoprotein limits oral absorption and brain entry of HIV-1 protease inhibitors, J. Clin. Invest. 101 (1998) 289–294.
[113] K.C. Yeh, J.A. Stone, A.D. Carides, P. Rolan, E. Woolf, W.D. Ju, Simultaneous investigation of indinavir nonlinear pharmacokinetics and bioavailability in healthy volunteers using stable isotope labeling technique: study design and model-independent data analysis, J. Pharm. Sci. 88 (1999) 568–573.
[114] D.R. Robertson, N.D. Wood, H. Everest, K. Monks, D.G. Waller, A.G. Renwick, C.F. George, The effect of age on the pharmacokinetics of levodopa administered alone and in the presence of carbidopa, Br. J. Clin. Pharmacol. 28 (1989) 61–69.
[115] K. Sasahara, T. Nitanai, T. Habara, T. Morioka, E. Nakajima, Dosage form design for improvement of bioavailability of levodopa II: bioavailability of marketed levodopa preparations in dogs and Parkinsonian patients, J. Pharm. Sci. 69 (1980) 261–265.
[116] D.J. Back, S.F. Grimmer, S. Rogers, P.J. Stevenson, M.L. Orme, Comparative pharmacokinetics of levonorgestrel and ethinyloestradiol following intravenous, oral and vaginal administration, Contraception 36 (1987) 471–479.
[117] S.F. Grimmer, D.J. Back, M.L. Orme, A. Cowie, I. Gilmore, J. Tjia, The bioavailability of ethinyloestradiol and levonorgestrel in patients with an ileostomy, Contraception 33 (1986) 51–59.
[118] H.R. Maxon, W.A. Ritschel, C.P. Volle, M.A. Eldon, I.W. Chen, M.F. Fernandez, J. Cline, G. Mayfield, Pilot study on the absolute and relative bioavailability of Synthroid and Levothroid, two brands of sodium levothyroxine, Int. J. Clin. Pharmacol. Ther. Toxicol. 21 (1983) 379–382.
[119] K. Hasselstrom, K. Siersbaek-Nielsen, I.B. Lumholtz, J. Faber, C. Kirkegaard, T. Friis, The bioavailability of thyroxine and 3,5,3′-triiodothyronine in normal subjects and in hyper- and hypothyroid patients, Acta Endocrinol. (Copenh) 110 (1985) 483–486.
[120] M.T. Hays, K.R. Nielsen, Human thyroxine absorption: age effects and methodological analyses, Thyroid 4 (1994) 55–64.
[121] P.H. Marathe, Y. Wen, J. Norton, D.S. Greene, R.H. Barbhaiya, I.R. Wilding, Effect of altered gastric emptying and gastrointestinal motility on metformin absorption, Br. J. Clin. Pharmacol. 50 (2000) 325–332.
[122] P.J. Pentikainen, P.J. Neuvonen, A. Penttila, Pharmacokinetics of metformin after intravenous and oral administration to man, Eur. J. Clin. Pharmacol. 16 (1979) 195–202.
[123] A.J. Scheen, Clinical pharmacokinetics of metformin, Clin. Pharmacokinet. 30 (1996) 359–371.
[124] E. Myhre, H.E. Rugstad, T. Hansen, Clinical pharmacokinetics of methyldopa, Clin. Pharmacokinet. 7 (1982) 221–233.
[125] A. Skerjanec, N.R. Campbell, S. Robertson, Y.K. Tam, Pharmacokinetics and presystemic gut metabolism of methyldopa in healthy human subjects, J. Clin. Pharmacol. 35 (1995) 275–280.
[126] N.M. Idkaidek, N.M. Najib, Enhancement of oral absorption of metronidazole suspension in humans, Eur. J. Pharm. Biopharm. 50 (2000) 213–216.
[127] K.C. Lamp, C.D. Freeman, N.E. Klutman, M.K. Lacy, Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials, Clin. Pharmacokinet. 36 (1999) 353–373.
[128] R.C. Urtasun, H.R. Rabin, J. Partington, Human pharmacokinetics and toxicity of high-dose metronidazole administered orally and intravenously, Surgery 93 (1983) 145–148.
[129] Viracept® prescribing information, Agouron Pharmaceuticals, Inc.
[130] H. Bode, E. Brendel, G. Ahr, U. Fuhr, S. Harder, A.H. Staib, Investigation of nifedipine absorption in different regions of the human gastrointestinal (GI) tract after simultaneous administration of 13C- and 12C-nifedipine, Eur. J. Clin. Pharmacol. 50 (1996) 195–201.
[131] H. Echizen, M. Eichelbaum, Clinical pharmacokinetics of verapamil, nifedipine and diltiazem, Clin. Pharmacokinet. 11 (1986) 425–449.
[132] T.J. Rashid, U. Martin, H. Clarke, D.G. Waller, A.G. Renwick, C.F. George, Factors affecting the absolute bioavailability of nifedipine, Br. J. Clin. Pharmacol. 40 (1995) 51–58.
[133] B. Hoener, S.E. Patterson, Nitrofurantoin disposition, Clin. Pharmacol. Ther. 29 (1981) 808–816.
[134] M. Eandi, I. Viano, S. Ricci Gamalero, Absolute bioavailability of paracetamol after oral or rectal administration in healthy volunteers, Arzneimittelforschung 34 (1984) 903–907.
[135] M.D. Rawlins, D.B. Henderson, A.R. Hijab, Pharmacokinetics of paracetamol (acetaminophen) after intravenous and oral administration, Eur. J. Clin. Pharmacol. 11 (1977) 283–286.
[136] J.J. Tukker, J.M. Sitsen, C.F. Gusdorf, Bioavailability of paracetamol after oral administration to healthy volunteers. Influence of caffeine on rate and extent of absorption, Pharm. Weekl. Sci. 8 (1986) 239–243.
[137] B. Ameer, M. Divoll, D.R. Abernethy, D.J. Greenblatt, L. Shargel, Absolute and relative bioavailability of oral acetaminophen preparations, J. Pharm. Sci. 72 (1983) 955–958.
[138] W.R. Kukovetz, E. Beubler, F. Kreuzig, A.J. Moritz, G. Nirnberger, L. Werner-Breitenecker, Bioavailability and pharmacokinetics of D-penicillamine, J. Rheumatol. 10 (1983) 90–94.
[139] P. Netter, B. Bannwarth, P. Pere, A. Nicolas, Clinical pharmacokinetics of D-penicillamine, Clin. Pharmacokinet. 13 (1987) 317–333.
[140] R.H. Wiesner, E.R. Dickson, G.L. Carlson, L.W. McPhaul, V.L. Go, The pharmacokinetics of D-penicillamine in man, J. Rheumatol. Suppl. 7 (1981) 51–55.
[141] E. Nelson, J.R. Powell, K. Conrad, K. Likes, J. Byers, S. Baker, D. Perrier, Phenobarbital pharmacokinetics and bioavailability in adults, J. Clin. Pharmacol. 22 (1982) 141–148.
[142] A. Frick, H. Moller, E. Wirbitzki, Biopharmaceutical characterization of oral immediate-release drug products. In vitro/in vivo comparison of phenoxymethylpenicillin potassium, glimepiride and levofloxacin, Eur. J. Pharm. Biopharm. 46 (1998) 305–311.
[143] K. Josefsson, T. Bergan, Pharmacokinetics of phenoxymethylpenicillin in volunteers, Chemotherapy 28 (1982) 241–246.
[144] J. Estruch, D. Galdames, A. Martinetti, I. Saavedra, Phenytoin pharmacokinetics in young and older adults, Rev. Med. Chil. 120 (1992) 1106–1109.
[145] R. Gugler, C.V. Manion, D.L. Azarnoff, Phenytoin: pharmacokinetics and bioavailability, Clin. Pharmacol. Ther. 19 (1976) 135–142.
[146] M.R. Hirji, H. Measuria, S. Kuhn, J.C. Mucklow, A comparative study of the bioavailability of five different phenytoin preparations, J. Pharm. Pharmacol. 37 (1985) 570–572.
[147] H. Bergrem, P. Grottum, H.E. Rugstad, Pharmacokinetics and protein binding of prednisolone after oral and intravenous administration, Eur. J. Clin. Pharmacol. 24 (1983) 415–419.
[148] J.J. Ferry, A.M. Horvath, I. Bekersky, E.C. Heath, C.F. Ryan, W.A. Colburn, Relative and absolute bioavailability of prednisone and prednisolone after separate oral and intravenous doses, J. Clin. Pharmacol. 28 (1988) 81–87.
[149] U. Tauber, D. Haack, B. Nieuweboer, G. Kloss, P. Vecsei, H. Wendt, The pharmacokinetics of fluocortolone and prednisolone after

intravenous and oral administration, Int. J. Clin. Pharmacol. Ther. Toxicol. 22 (1984) 48–55.
[150] G.W. Mihaly, S.A. Ward, G. Edwards, D.D. Nicholl, M.L. Orme, A.M. Breckenridge, Pharmacokinetics of primaquine in man. I. Studies of the absolute bioavailability and effects of dose size, Br. J. Clin. Pharmacol. 19 (1985) 745–750.
[151] D.M. Paton, D.R. Webster, Clinical pharmacokinetics of H1-receptor antagonists (the antihistamines), Clin. Pharmacokinet. 10 (1985) 477–497.
[152] G. Taylor, J.B. Houston, J. Shaffer, G. Mawer, Pharmacokinetics of promethazine and its sulphoxide metabolite after intravenous and oral administration to man, Br. J. Clin. Pharmacol. 15 (1983) 287–293.
[153] F. Keller, U. Kunzendorf, G. Walz, H. Haller, G. Offermann, Saturable first-pass kinetics of propranolol, J. Clin. Pharmacol. 29 (1989) 240–245.
[154] N. Takamatsu, L.S. Welage, N.M. Idkaidek, D.Y. Liu, P.I. Lee, Y. Hayashi, J.K. Rhie, H. Lennernas, J.L. Barnett, V.P. Shah, L. Lesko, G.L. Amidon, Human intestinal permeability of piroxicam, propranolol, phenylalanine, and PEG 400 determined by jejunal perfusion, Pharm. Res. 14 (1997) 1127–1132.
[155] H. Potthast, ZL-Untersuchung von Propranolol Präparaten, Pharmazeutische Zeitung 146 (2001).
[156] J. Kampmann, L. Skovsted, The pharmacokinetics of propylthiouracil, Acta Pharmacol. Toxicol. (Copenh) 35 (1974) 361–369.
[157] J.P. Kampmann, J.M. Hansen, Clinical pharmacokinetics of antithyroid drugs, Clin. Pharmacokinet. 6 (1981) 401–428.
[158] G.A. Ellard, Absorption, metabolism and excretion of pyrazinamide in man, Tubercle 50 (1969) 144–158.
[159] S.M. Aquilonius, S.A. Eckernas, P. Hartvig, B. Lindstrom, P.O. Osterman, Pharmacokinetics and oral bioavailability of pyridostigmine in man, Eur. J. Clin. Pharmacol. 18 (1980) 423–428.
[160] S.M. Aquilonius, P. Hartvig, Clinical pharmacokinetics of cholinesterase inhibitors, Clin. Pharmacokinet. 11 (1986) 236–249.
[161] U. Breyer-Pfaff, U. Maier, A.M. Brinkmann, F. Schumm, Pyridostigmine kinetics in healthy subjects and patients with myasthenia gravis, Clin. Pharmacol. Ther. 37 (1985) 495–501.
[162] J. Zempleni, J.R. Galloway, D.B. McCormick, Pharmacokinetics of orally and intravenously administered riboflavin in healthy humans, Am. J. Clin. Nutr. 63 (1996) 54–66.
[163] J.R. Koup, J. Williams-Warren, C.T. Viswanathan, A. Weber, A.L. Smith, Pharmacokinetics of rifampin in children. II. Oral bioavailability, Ther. Drug Monit. 8 (1986) 17–22.
[164] U. Loos, E. Musch, J.C. Jensen, G. Mikus, H.K. Schwabe, M. Eichelbaum, Pharmacokinetics of oral and intravenous rifampicin during chronic administration, Klin. Wochenschr. 63 (1985) 1205–1211.
[165] Data-base Merck KGaA.
[166] D.W. Boulton, J.P. Fawcett, Enantioselective disposition of salbutamol in man following oral and intravenous administration, Br. J. Clin. Pharmacol. 41 (1996) 35–40.
[167] D.A. Goldstein, Y.K. Tan, S.J. Soldin, Pharmacokinetics and absolute bioavailability of salbutamol in healthy adult volunteers, Eur. J. Clin. Pharmacol. 32 (1987) 631–634.
[168] D.J. Morgan, J.D. Paull, B.H. Richmond, E. Wilson-Evered, S.P. Ziccone, Pharmacokinetics of intravenous and oral salbutamol and its sulphate conjugate, Br. J. Clin. Pharmacol. 22 (1986) 587–593.
[169] H.H. Kupferschmidt, K.E. Fattinger, H.R. Ha, F. Follath, S. Krahenbuhl, Grapefruit juice enhances the bioavailability of the HIV protease inhibitor saquinavir in man, Br. J. Clin. Pharmacol. 45 (1998) 355–359.
[170] M.N. Dudley, K.K. Graham, S. Kaul, S. Geletko, L. Dunkle, M. Browne, K. Mayer, Pharmacokinetics of stavudine in patients with AIDS or AIDS-related complex, J. Infect. Dis. 166 (1992) 480–485.
[171] K.Z. Rana, M.N. Dudley, Clinical pharmacokinetics of stavudine, Clin. Pharmacokinet. 33 (1997) 276–284.
[172] Zerit prescribing information, Bristol-Meyers Squibb.
[173] T.W. Chin, A. Vandenbroucke, I.W. Fong, Pharmacokinetics of trimethoprim–sulfamethoxazole in critically ill and non-critically ill AIDS patients, Antimicrob. Agents Chemother. 39 (1995) 28–33.
[174] R. Dahlan, C. McDonald, V.B. Sunderland, Solubilities and intrinsic dissolution rates of sulphamethoxazole and trimethoprim, J. Pharm. Pharmacol. 39 (1987) 246–251.
[175] M.E. Klepser, Z. Zhu, D.P. Nicolau, M.A. Banevicius, P.P. Belliveau, J.W. Ross, L. Broisman, R. Quintiliani, C.H. Nightingale, Oral absorption of trimethoprim–sulfamethoxazole in patients with AIDS, Pharmacotherapy 16 (1996) 656–662.
[176] H. Fuder, R. Herzog, W. Vaupel, N. Wetzelsberger, P.W. Lucker, Study on the absolute bioavailability of quinine and theophylline from tablets after single dose oral administration as compared to intravenous infusion in healthy male non-smoking volunteers, Methods Find Exp. Clin. Pharmacol. 16 (1994) 651–660.
[177] H.S. Kaumeier, O.H. Kehrhahn, G. Neugebauer, D. Schuppan, J.A. Schwarz, A.H. Staib, A cross-over study of oral and intravenous administration of theophylline in male volunteers. Absolute bioavailability of theophylline tablets, Arzneimittelforschung 34 (1984) 92–95.
[178] V.W. Steinijans, H.U. Schulz, A. Bohm, W. Beier, Absolute bioavailability of theophylline from a sustained-release formulation using different intravenous reference infusions, Eur. J. Clin. Pharmacol. 33 (1987) 523–526.
[179] C.M. Tallaksen, A. Sande, T. Bohmer, H. Bell, J. Karlsen, Kinetics of thiamin and thiamin phosphate esters in human blood, plasma and urine after 50 mg intravenously or orally, Eur. J. Clin. Pharmacol. 44 (1993) 73–78.
[180] G. Zaccara, A. Messori, F. Moroni, Clinical pharmacokinetics of valproic acid, 1988, Clin. Pharmacokinet. 15 (1988) 367–389.
[181] M.R. Blum, S.H. Liao, S.S. Good, P. de Miranda, Pharmacokinetics and bioavailability of zidovudine in humans, Am. J. Med. 85 (1988) 189–194.
[182] K.A. Macnab, M.J. Gill, L.R. Sutherland, N. De Boer Visser, D. Church, Erratic zidovudine bioavailability in HIV seropositive patients, J. Antimicrob. Chemother. 31 (1993) 421–428.
[183] M.K. Alberts, C.R. Clarke, C.G. MacAllister, L.M. Homer, Pharmacokinetics of acetazolimide after intravenous and oral administration in horses, Am. J. Vet. Res. 61 (2000) 965–968.
[184] E.C. Van Os, B.J. Zins, W.J. Sandborn, D.C. Mays, W.J. Tremaine, D.W. Mahoney, A.R. Zinsmeister, J.J. Lipsky, Azathioprine pharmacokinetics after intravenous, oral, delayed release oral and rectal foam administration, Gut 39 (1996) 63–68.
[185] P. Workman, R.A. White, M.I. Walton, L.N. Owen, P.R. Twentyman, Preclinical pharmacokinetics of benznidazole, Br. J. Cancer 50 (1984) 291–303.
[186] R. Grimaldi, E. Perucca, G. Ruberto, C. Gelmi, F. Trimarchi, M. Hollmann, A. Crema, Pharmacokinetic and pharmacodynamic studies following the intravenous and oral administration of the antiparkinsonian drug biperiden to normal subjects, Eur. J. Clin. Pharmacol. 29 (1986) 735–737.
[187] C.A. Knupp, W.C. Shyu, E.A. Morgenthien, J.S. Lee, R.H. Barbhaiya, Biopharmaceutics of didanosine in humans and in a model for acid-labile drugs, the pentagastrin-pretreated dog, Pharm. Res. 10 (1993) 1157–1164.
[188] M.J. Shelton, A.M. O'Donnell, G.D. Morse, Didanosine, Ann. Pharmacother. 26 (1992) 660–670.
[189] http://aidsinfo.nih.gov/document/data/drug_lib/technical/drug_tech_0016.html
[190] A.N. de Groot, T.B. Vree, Y.A. Hekster, M. van den Biggelaar-Martea, P.W. van Dongen, J. van Roosmalen, Pharmacokinetics and bioavailability of oral ergometrine in male volunteers, Biopharm. Drug Dispos. 15 (1994) 65–73.
[191] R. Mantyla, T. Kleimola, J. Kanto, Methylergometrine (methylergonovine) concentrations in the human plasma and urine, Int. J. Clin. Pharmacol. Biopharm. 16 (1978) 254–257.

[192] M.A. el Sayed, W. Loscher, H.H. Frey, Pharmacokinetics of ethosuximide in the dog, Arch. Int. Pharmacodyn. Ther. 234 (1978) 180–192.
[193] I.H. Patel, R.H. Levy, T.G. Bauer, Pharmacokinetic properties of ethosuximide in monkeys. I. Single-dose intravenous and oral administration, Epilepsia 16 (1975) 705–716.
[194] C. Zent, P. Smith, Study of the effect of concomitant food on the bioavailability of rifampicin, isoniazid and pyrazinamide, Tuber Lung Dis. 76 (1995) 109–113.
[195] B. Bannwarth, F. Pehourcq, L. Lequen, Pharmacokinetics of methotrexate in rheumatoid arthritis: therapeutic implications, Therapie 52 (1997) 129–132.
[196] M.A. Campbell, D.G. Perrier, R.T. Dorr, D.S. Alberts, P.R. Finley, Methotrexate: bioavailability and pharmacokinetics, Cancer Treat Rep. 69 (1985) 833–838.
[197] R.A. Herman, P. Veng-Pedersen, J. Hoffman, R. Koehnke, D.E. Furst, Pharmacokinetics of low-dose methotrexate in rheumatoid arthritis patients, J. Pharm. Sci. 78 (1989) 165–171.
[198] G.D. Kozloski, J.M. De Vito, J.C. Kisicki, J.B. Johnson, The effect of food on the absorption of methotrexate sodium tablets in healthy volunteers, Arthritis Rheum. 35 (1992) 761–764.
[199] M.J. Lamson, J.P. Sabo, T.R. MacGregor, J.W. Pav, L. Rowland, A. Hawi, M. Cappola, P. Robinson, Single dose pharmacokinetics and bioavailability of nevirapine in healthy volunteers, Biopharm. Drug Dispos. 20 (1999) 285–291.
[200] C. Paulos, J. Paredes, I. Vasquez, S. Thambo, A. Arancibia, G. Gonzalez-Martin, Pharmacokinetics of a nitrofuran compound, nifurtimox, in healthy volunteers, Int. J. Clin. Pharmacol. Ther. Toxicol. 27 (1989) 454–457.
[201] H.M. Middleton 3rd, In vivo absorption and phosphorylation of pyridoxine. HCl in rat jejunum, Gastroenterology 76 (1979) 43–49.
[202] G. Edwards, A.M. Breckenridge, Clinical pharmacokinetics of anthelmintic drugs, Clin. Pharmacokinet. 15 (1988) 67–93.
[203] H. Jung, L. Medina, L. Garcia, I. Fuentes, R. Moreno-Esparza, Absorption studies of albendazole and some physicochemical properties of the drug and its metabolite albendazole sulphoxide, J. Pharm. Pharmacol. 50 (1998) 43–48.
[204] H. Lange, R. Eggers, J. Bircher, Increased systemic availability of albendazole when taken with a fatty meal, Eur. J. Clin. Pharmacol. 34 (1988) 315–317.
[205] G. Merino, A.I. Alvarez, J.G. Prieto, R.B. Kim, The anthelminthic agent albendazole does not interact with p-glycoprotein, Drug Metab. Dispos. 30 (2002) 365–369.
[206] J. Nagy, H.G. Schipper, R.P. Koopmans, J.J. Butter, C.J. Van Boxtel, P.A. Kager, Effect of grapefruit juice or cimetidine coadministration on albendazole bioavailability, Am. J. Trop. Med. Hyg. 66 (2002) 260–263.
[207] J.E. Burch, D.G. Herries, The demethylation of amitriptyline administered by oral and intramuscular routes, Psychopharmacology (Berlin) 80 (1983) 249–253.
[208] B. Vandel, M. Sandoz, S. Vandel, G. Allers, R. Volmat, Biotransformation of amitriptyline in depressive patients: urinary excretion of seven metabolites, Eur. J. Clin. Pharmacol. 22 (1982) 239–245.
[209] German Standardinformationen für Klinikapotheker, Amineurin®, Hexal AG.
[210] F. Ezzet, M. van Vugt, F. Nosten, S. Looareesuwan, N.J. White, Pharmacokinetics and pharmacodynamics of lumefantrine (benflumetol) in acute falciparum malaria, Antimicrob. Agents Chemother. 44 (2000) 697–704.
[211] J. Karbwang, K. Na-Bangchang, K. Congpuong, P. Molunto, A. Thanavibul, Pharmacokinetics and bioavailability of oral and intramuscular artemether, Eur. J. Clin. Pharmacol. 52 (1997) 307–310.
[212] V. Navaratnam, S.M. Mansor, N.W. Sit, J. Grace, Q. Li, P. Olliaro, Pharmacokinetics of artemisinin-type compounds, Clin. Pharmacokinet. 39 (2000) 255–270.
[213] N.J. White, M. van Vugt, F. Ezzet, Clinical pharmacokinetics and pharmacodynamics and pharmacodynamics of artemether–lumefantrine, Clin. Pharmacokinet. 37 (1999) 105–125.
[214] C. Volz-Zang, T. Waldhauser, B. Schulte, D. Palm, Comparison of the effects of atropine in vivo and ex vivo (radioreceptor assay) after oral and intramuscular administration to man, Eur. J. Clin. Pharmacol. 49 (1995) 45–49.
[215] S.M. Huang, N.K. Athanikar, K. Sridhar, Y.C. Huang, W.L. Chiou, Pharmacokinetics of chlorpheniramine after intravenous and oral administration in normal adults, Eur. J. Clin. Pharmacol. 22 (1982) 359–365.
[216] R. Koytchev, R.G. Alken, V. Kirkov, G. Neshev, M. Vagaday, U. Kunter, Absolute bioavailability of chlorpromazine, promazine and promethazine, Arzneimittelforschung 44 (1994) 121–125.
[217] P.K. Yeung, J.W. Hubbard, E.D. Korchinski, K.K. Midha, Pharmacokinetics of chlorpromazine and key metabolites, Eur. J. Clin. Pharmacol. 45 (1993) 563–569.
[218] J.T. Lettieri, M.C. Rogge, L. Kaiser, R.M. Echols, A.H. Heller, Pharmacokinetic profiles of ciprofloxacin after single intravenous and oral doses, Antimicrob. Agents Chemother. 36 (1992) 993–996.
[219] R.C. Owens Jr., K.B. Patel, M.A. Banevicius, R. Quintiliani, C.H. Nightingale, D.P. Nicolau, Oral bioavailability and pharmacokinetics of ciprofloxacin in patients with AIDS, Antimicrob. Agents Chemother. 41 (1997) 1508–1511.
[220] K. Vance-Bryan, D.R. Guay, J.C. Rotschafer, Clinical pharmacokinetics of ciprofloxacin, Clin. Pharmacokinet. 19 (1990) 434–461.
[221] C.A. Bergstrom, M. Strafford, L. Lazorova, A. Avdeef, K. Luthman, P. Artursson, Absorption classification of oral drugs based on molecular surface properties, J. Med. Chem. 46 (2003) 558–570.
[222] www.pion-inc.com
[223] M.R. Holdiness, Clinical pharmacokinetics of clofazimine. A review, Clin. Pharmacokinet. 16 (1989) 74–85.
[224] Z. Schaad-Lanyi, W. Dieterle, J.P. Dubois, W. Theobald, W. Vischer, Pharmacokinetics of clofazimine in healthy volunteers, Int. J. Lepr. Other Mycobact. Dis. 55 (1987) 9–15.
[225] A.E. Balant-Gorgia, M. Gex-Fabry, L.P. Balant, Clinical pharmacokinetics of clomipramine, Clin. Pharmacokinet. 20 (1991) 447–462.
[226] M.D. Peters 2nd, S.K. Davis, L.S. Austin, Clomipramine: an antiobsessional tricyclic antidepressant, Clin. Pharm. 9 (1990) 165–178.
[227] T.R. Brophy, J. McCafferty, J.H. Tyrer, M.J. Eadie, Bioavailability of oral dexamethasone during high dose steroid therapy in neurological patients, Eur. J. Clin. Pharmacol. 24 (1983) 103–108.
[228] D.E. Duggan, K.C. Yeh, N. Matalia, C.A. Ditzler, F.G. McMahon, Bioavailability of oral dexamethasone, Clin. Pharmacol. Ther. 18 (1975) 205–209.
[229] B.T. O'Sullivan, D.J. Cutler, G.E. Hunt, C. Walters, G.F. Johnson, I.D. Caterson, Pharmacokinetics of dexamethasone and its relationship to dexamethasone suppression test outcome in depressed patients and healthy control subjects, Biol. Psychiatry 41 (1997) 574–584.
[230] G.G. Toth, C. Kloosterman, D.R. Uges, M.F. Jonkman, Pharmacokinetics of high-dose oral and intravenous dexamethasone, Ther. Drug Monit. 21 (1999) 532–535.
[231] www.medicaltribune.de
[232] S. Mouly, K.S. Lown, D. Kornhauser, J.L. Joseph, W.D. Fiske, I.H. Benedek, P.B. Watkins, Hepatic but not intestinal CYP3A4 displays dose-dependent induction by efavirenz in humans, Clin. Pharmacol. Ther. 72 (2002) 1–9.
[233] D.J. Back, S. Madden, M.L. Orme, Gastrointestinal metabolism of contraceptive steroids, Am. J. Obstet. Gynecol. 163 (1990) 2138–2145.
[234] P.M. Finglas, C.M. Witthoft, L. Vahteristo, A.J. Wright, S. Southon, F.A. Mellon, B. Ridge, P. Maunder, Use of an oral/intravenous dual-label stable-isotope protocol to determine folic acid bioavailability

from fortified cereal grain foods in women, J. Nutr. 132 (2002) 936–939.
[235] A. Menke, H.J. Weimann, G. Achtert, O. Schuster, G. Menke, Absolute bioavailability of folic acid after oral administration of a folic acid tablet formulation in healthy volunteers, Arzneimittelforschung 44 (1994) 1063–1067.
[236] G. Neugebauer, G. Betzien, V. Hrstka, B. Kaufmann, E. von Mollendorff, U. Abshagen, Absolute bioavailability and bioequivalence of glibenclamide (Semi-Euglucon N), Int. J. Clin. Pharmacol. Ther. Toxicol. 23 (1985) 453–460.
[237] M.G. Bogaert, Clinical pharmacokinetics of nitrates, Cardiovasc. Drugs Ther. 8 (1994) 693–699.
[238] P.K. Noonan, L.Z. Benet, The bioavailability of oral nitroglycerin, J. Pharm. Sci. 75 (1986) 241–243.
[239] Y.F. Cheng, L.K. Paalzow, U. Bondesson, B. Ekblom, K. Eriksson, S.O. Eriksson, A. Lindberg, L. Lindstrom, Pharmacokinetics of haloperidol in psychotic patients, Psychopharmacology (Berlin) 91 (1987) 410–414.
[240] J.S. Froemming, Y.W. Lam, M.W. Jann, C.M. Davis, Pharmacokinetics of haloperidol, Clin. Pharmacokinet. 17 (1989) 396–423.
[241] F.O. Holley, J.R. Magliozzi, D.R. Stanski, L. Lombrozo, L.E. Hollister, Haloperidol kinetics after oral and intravenous doses, Clin. Pharmacol. Ther. 33 (1983) 477–484.
[242] W.H. Chang, Y.W. Lam, M.W. Jann, H. Chen, Pharmacokinetics of haloperidol and reduced haloperidol in Chinese schizophrenic patients after intravenous and oral administration of haloperidol, Psychopharmacology (Berlin) 106 (1992) 517–522.
[243] J.R. Magliozzi, L.E. Hollister, Elimination half-life and bioavailability of haloperidol in schizophrenic patients, J. Clin. Psychiatry 46 (1985) 20–21.
[244] P. Straehl, R.L. Galeazzi, Isosorbide dinitrate bioavailability, kinetics, and metabolism, Clin. Pharmacol. Ther. 38 (1985) 140–149.
[245] H.L. Fung, Pharmacokinetics and pharmacodynamics of isosorbide dinitrate, Am. Heart J. 110 (1985) 213–216.
[246] J. Jiang, P. Hu, H. Xie, H. Chen, F. Fan, A. Harker, M.A. Johnson, The pharmacokinetics of lamivudine in healthy Chinese subjects, Br. J. Clin. Pharmacol. 48 (1999) 250–253.
[247] M.A. Johnson, K.H. Moore, G.J. Yuen, A. Bye, G.E. Pakes, Clinical pharmacokinetics of lamivudine, Clin. Pharmacokinet. 36 (1999) 41–66.
[248] G.J. Yuen, D.M. Morris, P.K. Mydlow, S. Haidar, S.T. Hall, E.K. Hussey, Pharmacokinetics, absolute bioavailability, and absorption characteristics of lamivudine, J. Clin. Pharmacol. 35 (1995) 1174–1180.
[249] J.G. Adams, Pharmacokinetics of levamisole, J. Rheumatol. Suppl. 4 (1978) 137–142.
[250] A.M. Sahagun, M.T. Teran, J.J. Garcia, N. Fernandez, M. Sierra, M.J. Diez, Oral bioavailability of levamisole in goats, J. Vet. Pharmacol. Ther. 24 (2001) 439–442.
[251] A.D. Watson, N.C. Sangster, D.B. Church, H. Van Gogh, Levamisole pharmacokinetics and bioavailability in dogs, Res. Vet. Sci. 45 (1988) 411–413.
[252] Kaletra® prescribing info, Abbott Laboratories.
[253] M. Dawson, R.J. Allan, T.R. Watson, The pharmacokinetics and bioavailability of mebendazole in man: a pilot study using [3H]-mebendazole, Br. J. Clin. Pharmacol. 14 (1982) 453–455.
[254] M. Dawson, P.A. Braithwaite, M.S. Roberts, T.R. Watson, The pharmacokinetics and bioavailability of a tracer dose of [3H]-mebendazole in man, Br. J. Clin. Pharmacol. 19 (1985) 79–86.
[255] C. Crevoisier, J. Handschin, J. Barre, D. Roumenov, C. Kleinbloesem, Food increases the bioavailability of mefloquine, Eur. J. Clin. Pharmacol. 53 (1997) 135–139.
[256] D.N. Bateman, C. Kahn, D.S. Davies, The pharmacokinetics of metoclopramide in man with observations in the dog, Br. J. Clin. Pharmacol. 9 (1980) 371–377.
[257] M.R. Wright, J.E. Axelson, D.W. Rurak, B. McErlane, G.H. McMorland, R.C. Ongley, Y.K. Tam, J.D. Price, Linearity of metoclopramide kinetics at doses of 5–20 mg, Br. J. Clin. Pharmacol. 26 (1988) 469–473.
[258] W.B. Taylor, D.N. Bateman, Oral bioavailability of high-dose metoclopramide, Eur. J. Clin. Pharmacol. 31 (1986) 41–44.
[259] C. Graffner, P.O. Lagerstrom, P. Lundborg, O. Ronn, Pharmacokinetics of metoclopramide intravenously and orally determined by liquid chromatography, Br. J. Clin. Pharmacol. 8 (1979) 469–474.
[260] D.N. Bateman, Clinical pharmacokinetics of metoclopramide, Clin. Pharmacokinet. 8 (1983) 523–529.
[261] J. Hasselstrom, J. Sawe, Morphine pharmacokinetics and metabolism in humans. Enterohepatic cycling and relative contribution of metabolites to active opioid concentrations, Clin. Pharmacokinet. 24 (1993) 344–354.
[262] P.J. Hoskin, G.W. Hanks, G.W. Aherne, D. Chapman, P. Littleton, J. Filshie, The bioavailability and pharmacokinetics of morphine after intravenous, oral and buccal administration in healthy volunteers, Br. J. Clin. Pharmacol. 27 (1989) 499–505.
[263] S.D. Roy, G.L. Flynn, Solubility behavior of narcotic analgesics in aqueous media: solubilities and dissociation constants of morphine, fentanyl, and sufentanil, Pharm. Res. 6 (1989) 147–151.
[264] D. Westerling, C. Persson, P. Hoglund, Plasma concentrations of morphine, morphine-3-glucuronide, and morphine-6-glucuronide after intravenous and oral administration to healthy volunteers: relationship to nonanalgesic actions, Ther. Drug Monit. 17 (1995) 287–301.
[265] http://www-vetpharm.unizh.ch/
[266] C.R. Clarke, G.E. Burrows, C.G. MacAllister, D.K. Spillers, P. Ewing, A.K. Lauer, Pharmacokinetics of intravenously and orally administered pyrimethamine in horses, Am. J. Vet. Res. 53 (1992) 2292–2295.
[267] A. Le Liboux, H. Duquesne, G. Montay, D. Chassard, E. Pichard, J.J. Thebault, A. Frydman, J. Gaillot, Pharmacokinetics of pyrimethamine in healthy young volunteers using a new solid phase extraction/HPLC method, Eur. J. Drug Metab. Pharmacokinet., Spec. No. 3 (1991) 284–290.
[268] S. Krishna, N.J. White, Pharmacokinetics of quinine, chloroquine and amodiaquine, Clin. Implic., Clin. Pharmacokinet. 30 (1996) 263–299.
[269] G. Paintaud, G. Alvan, O. Ericsson, The reproducibility of quinine bioavailability, Br. J. Clin. Pharmacol. 35 (1993) 305–307.
[270] D. Hollander, K.S. Muralidhara, Vitamin A1 intestinal absorption in vivo: influence of luminal factors on transport, Am. J. Physiol. 232 (1977) E471–E477.
[271] D.V. Reinersdorff, E. Bush, D.J. Liberato, Plasma kinetics of vitamin A in humans after a single oral dose of [8,9,19-13C]retinyl palmitate, J. Lipid Res. 37 (1996) 1875–1885.
[272] A. Karim, J. Zagarella, J. Hribar, M. Dooley, Spironolactone. I. Disposition and metabolism, Clin. Pharmacol. Ther. 19 (1976) 158–169.
[273] H.W. Overdiek, F.W. Merkus, Influence of food on the bioavailability of spironolactone, Clin. Pharmacol. Ther. 40 (1986) 531–536.
[274] T. Bergan, B. Ortengren, D. Westerlund, Clinical pharmacokinetics of co-trimazine, Clin. Pharmacokinet. 11 (1986) 372–386.
[275] R. Kumar, A.P. Singh, M. Kapoor, A.K. Rai, Pharmacokinetics, bioavailability and dosage regimen of sulphadiazine (SDZ) in camels (*Camelus dromedarius*), J. Vet. Pharmacol. Ther. 21 (1998) 393–399.
[276] K.M. Das, R. Dubin, Clinical pharmacokinetics of sulphasalazine, Clin. Pharmacokinet. 1 (1976) 406–425.
[277] U. Klotz, Clinical pharmacokinetics of sulphasalazine, its metabolites and other prodrugs of 5-aminosalicylic acid, Clin. Pharmacokinet. 10 (1985) 285–302.

[278] J.B. Lecaillon, J. Godbillon, J. Campestrini, C. Naquira, L. Miranda, R. Pacheco, R. Mull, A.A. Poltera, Effect of food on the bioavailability of triclabendazole in patients with fascioliasis, Br. J. Clin. Pharmacol. 45 (1998) 601–604.

[279] K. Dilger, K. Eckhardt, U. Hofmann, K. Kucher, G. Mikus, M. Eichelbaum, Chronopharmacology of intravenous and oral modified release verapamil, Br. J. Clin. Pharmacol. 47 (1999) 413–419.

[280] M. Eichelbaum, A. Somogyi, G.E. von Unruh, H.J. Dengler, Simultaneous determination of the intravenous and oral pharmacokinetic parameters of D,L-verapamil using stable isotope-labelled verapamil, Eur. J. Clin. Pharmacol. 19 (1981) 133–137.

[281] M. Schomerus, B. Spiegelhalder, B. Stieren, M. Eichelbaum, Physiological disposition of verapamil in man, Cardiovasc. Res. 10 (1976) 605–612.

[282] R. Sandstrom, A. Karlsson, L. Knutson, H. Lennernas, Jejunal absorption and metabolism of R/S-verapamil in humans, Pharm. Res. 15 (1998) 856–862.

[283] D.R. Mungall, T.M. Ludden, J. Marshall, D.W. Hawkins, R.L. Talbert, M.H. Crawford, Population pharmacokinetics of racemic warfarin in adult patients, J. Pharmacokinet. Biopharm. 13 (1985) 213–227.

[284] G. Williams, P. Sinko, Oral absorption of the HIV proteases inhibitors: a current update, Adv. Drug Deliv. Rev. 39 (1999) 211–238.