INDEX

absorption, distribution, metabolism, and elimination (ADME), 1, 16
absorption rate constant elimination rate, 12
feathering, 11–12
first-order kinetics, 11
linear regression, 12, 13
moment method, 12, 13
residual vs. time, 12, 13
active transport
eflux transporters, 46–49
influx transporters, 49–51
ADMET™ Predictor and GastroPlus®, 349–351
Advanced Compartmental Absorption and Transit (ACAT) model, 351
aldehyde oxidase (AO), 54, 59, 61, 191–192, 416
aminobenzotriazole (ABT), 360–361
area under the curve (AUC), 5
drug linearity, 17
atomoxetine, 24, 62–63
bacterial microflora, 42–43
Bateman equation, 12
BBB see blood brain barrier (BBB)
BCRP see breast cancer-resistant protein (BCRP)

BCS see biopharmaceutics classification system (BCS)
BDDCS see biopharmaceutics drug disposition classification system (BDDCS)
bile duct hyperplasia (BDH), 23
bile fluid, 41–42
biliary efflux transporters
BSEP, 113
MRP2, 113, 114–117
bioavailability
absolute, 14–15
animal species vs. humans, 36
low-oral
1-aminobenzotriazole, 360–361
CP-100, 356, 362
curcumin, 364
elacridar, 362–364
famotidine and pentagastrin, 366
grape fruit juice, 362
renal recovery in measuring oral absorption, 366–367
Zosuquidar and Ko143, 364–366
oral, 15–16
relative, 15
biopharmaceutics classification system (BCS), 160, 270, 334
biopharmaceutics drug disposition classification system (BDDCS)
high extent of metabolism, 313
P-gp vs., 224–227
principles, 193
solubility classes, 391
blood brain barrier (BBB), 343, 350
breast cancer-resistant protein (BCRP)
absorption of drug molecules, 331–332
efflux transporters, expression of, 49, 50, 91, 248, 336
genetic polymorphisms, 230–232, 233–235
inhibitors, 228–230, 237, 238–247, 365
structure and distribution, 228
Caco-2 and MDCK implementation
\( \text{CYP3A, 54–56} \)
\( \text{CYP2C, 56–57} \)
\( \text{CYP2D, 57–58} \)
\( \text{enzymes, 174, 175–176} \)
cytotoxic drugs and antibiotics, 35
2D descriptors, 348
3D descriptors, 348
DDI see drug-drug interactions (DDI)
deleted in malignant brain tumor (DMBT1), 23
DMPK see drug metabolism and pharmacokinetics (DMPK)
drug discovery and development phases, 4
repeat-dose toxicity studies, 4
toxicity assessment, 3–5
drug disposition, species differences, 23–25
drug dissolution, 150–151, 153
drug–drug interactions (DDI), 91, 95–96, 224, 269, 309, 311, 318, 416
drug metabolism, physiological factors
aldehyde oxidase (AO), 59–61
cytochrome P450 (CYP), 54–58
glucuronosyltransferases (UGT) superfamily, 58–59
species differences in first-pass metabolism, 61–63
drug nonlinear kinetics, 16, 18
drug toxicity, 23, 25, 27
drug transporters, intestinal
monocarboxylate transporters, 289–293
oral drug absorption, 51–53
organic anion transporting polypeptide, 270–284
PepT1 transporter, 284–289
ECCS see extended clearance classification system (ECCS)
efflux transporters
BCRP (ABCG2), 47–48
intestinal
BCRP, 228–232
P-glycoprotein (ABCB1), 204–228
P-gp or BCRP inhibitor, 238–247
P-gp or BCRP substrate, 237
sensitivity analysis, 232–237
MRP2 (ABCC2), 48–49
P-gp (ABCB1), 46–47
elacridar
chemical structure, 362–363
oral AUC ratio of human, 363
topotecan, 364
European Medicines Evaluation Agency (EMEA), 14
excretion, drug routes of
classification system, 77–78
hepatobiliary elimination, 95–117
physicochemical factors, 91, 95
renal elimination, 78–95
extended clearance classification system (ECCS), 77, 118, 177, 377
characteristics of
Class 2, 315, 317
Class 4, 318
Class 1A, 315
Class 3A, 317–318
Class 1B, 315
Class 3B, 318
classification, 407
F and ECCS, 406, 410, 411
f_F and ECCS, 389–391
f_F and ECCS, 391, 406
f_F and ECCS, 406, 408, 409
physiochemical properties, 388–389
hepatic clearance, 310–313
proposition of, 314–315
renal clearance, 313–314
transporters and enzymes, 316–317
F_{in} /F_{out} calculation, 358–359
f_F modulation
f_F, 415
in vitro tools, 414
permeability, 412–414
solubility, 410, 412
famotidine, 205, 318, 366
fasted state simulated intestinal fluid (FaSSIF), 148, 391, 410
FDA guidance, assessment
P-gp or BCRP inhibitor, 238–247
P-gp or BCRP substrate, 237
fed state simulated intestinal fluid (FESSIF), 148
Fick’s First Law, 139
first in human (FIH) clinical trials, 4–5
flip–flop kinetics, 12–14
gastric emptying rate (GER), 14, 39–40, 294
gastrointestinal tract (GIT)
anatomy and physiology, 37–39
barrier, 331
pH, 40–41
transit times, 39–40
glucuronidation, 58, 59, 174, 177, 188, 315, 378
f_m and ECCS, 391, 406
hepatic extraction ratio and f_h calculations, 382
intrinsic clearance, scaling, 380–381
in vitro incubation, 379–380
parallel-tube model, 382
well-stirred model, 381–382
metabolism-mediated, 417
passive diffusion clearance, 310
hepatic clearance, 312–313
of hepatobiliary transport, 312–313
of metabolism, 313
rapid equilibrium, 416
species differences, 186–187
systemic clearance, 416–417
transporter-mediated, 417–418
hepatobiliary elimination
biliary efflux transporters, 113
mathematical principles, 95–96
OATP1B1, OATP1B3, OATP2B1, 97, 98–108
OCT1, 97, 109–112
physicochemical factors, 113
FDA human liver microsomes (HLM)
HTS see high-throughput screening (HTS)
approaches
human liver microsomes (HLM), 173, 309, 387
hydrogen bonding acceptor (HBA) atoms, 149, 174, 206, 214, 229–230, 412, 414
hydrogen-bonding affinity, 141–142
hydrogen bonding donor (HBD), 149, 206, 207–213, 214, 229, 233–234, 348, 412, 414
hydrophobicity, 95, 142–145, 290, 413
indinavir, 24, 62–63, 186–187, 225, 368
influx transporters
index 433
influx transporters (Continued)
  drug absorption and concentration gradient, 294–295
  intestinal drug transporters, 270–293
  OATP2B1 (SLCO2B1), 51
  PEPT1 (SLC15A1), 50–51
in silico predictive permeability models, 348
intestinal permeability and efflux transporters
  Caco-2 and MDCK implementation, 333–338
  drug molecules, passive or active transport, 331–332
  parallel artificial membrane permeability assay, 332–333
  permeability models and technologies, 341–343
  in silico permeability models, 332
  single-pass intestinal perfusion, 338–341
in silico permeability vs. human \( f_{a'} \), 390, 391
leak optimization (LO), 4
  LE-MDCK permeability vs. human \( f_{a'} \), 390, 391
  linearity index (LIN), 227–228
lipophilicity, 9, 63, 95, 113, 140, 142–145, 149, 160, 174, 178, 179–180, 184, 193, 312, 313, 333, 348, 412–413
liquid scintillation counting (LSC), 342
living cell line permeability models
  Lewis Lung Carcinoma Porcine Kidney Cells (LLC-PK1), 341–342
  Rat Fetal Intestinal Epithelial Cells (2/4/A1), 342
  Rat Small Intestine Cells (IEC-18), 342
  L-type amino acid transporters (LAT1), 270
  lymphatic absorption, 43
mass balance principle, 359–360, 365
  MATE1 and MATE2K, 79, 92–94
maximum plasma concentration (Cmax), 11–12
maximum tolerated dose (MTD), 4
MDCK (Madin–Darby Canine Kidney), 177, 215, 237, 315, 332, 334–337
mean absorption residence time (MAT), 14
mean residence time (MRT), 5–6, 9–12, 14, 16
metabolic clearance, \( \text{in vitro} \) tools
  hepatocytes, 379
  liver microsomes, 378
liver S9 fractions, 378
  supersomes, 378–379
metabolic stability
  aldehyde oxidase, strategies, 191–192
  blood hepatic clearance, 184–186
  of enantiomers, 190–191
  \( f_g \), metabolizing enzyme, 189–190
  fluorine or chlorine, 182–184
  and intestinal permeability on \( f_g \), 188–189
  ionized group, 180
  labile functional group and soft spots, 180–182
  lipophilicity, 178, 179–180
  polarity, 178
  prodrugs, use of, 188
  species differences in hepatic clearance, 186–187
  steric hindrance, 184
Michaelis–Menten kinetics, 16, 17
minipumps, 369–370
MIST (metabolites in safety testing), 25–26
  multiple nonlinear regression (MNLR)
  molecular descriptors, 348–349, 350
  moment method, 12, 13
  monocarboxylate transporters (MCT1)
  genetic polymorphism, 293
  mechanism of drug uptake, 290–291
  structure and distribution, 289–290
  substrates and inhibitors, 291–293
MRP2 see multidrug resistance-associated protein 2 (MRP2)
multidrug resistance-associated protein 2 (MRP2), 48–49, 113, 114–117, 228, 312, 336, 342, 362, 389, 410
  multiple linear regressions (MLR), 348
  multiple nonlinear regression (MNLR), 348–349
  multivariate analysis (MVA), 348–349
new chemical entity (NCE), 3, 5, 35–36, 40, 49, 54, 61
new drug application (NDA), 3
new molecular entities (NMEs), 77, 173–174, 193, 347, 367–371
noncell line permeability models
  blood brain barrier, 343
  chromatographic methods, 342–343
  noncompartmental pharmacokinetics, 19
  no observed adverse effect level (NOAEL), 4, 18
oral drug absorption
  active transport, 46–51
  intestinal transporters, 51–54
  passive diffusion, 43–46, 140
  paracellular diffusion, 140
  transcellular pathway, 140
physiological factors, 36–43
organic anion transporting polypeptide (OATP2B1), 97, 98–108
drug uptake, mechanism of, 273–276
estrone sulfate (ES), 274–275
fexofenadine and pravastatin, 275–276
genetic polymorphism, 281–284
in human, 270, 272
intestinal transporter, 270, 271
PEPT1 and MCT1, 270, 271
physicochemical properties, 277, 280
protein expression, 272, 273
structural activity relationship, 279–281
structure and distribution, 270–273
substrates and inhibitors, 277–279
organic cation/zwitterion transporters (OCTN1), 270

parallel artificial membrane permeability assay (PAMPA)
donor/acceptor compartments, 332
metrics, 333
strengths and shortcomings, 333
system design, 332–333
parallel-tube model, 382
passive diffusion
hydrophilic drug absorption, 43, 45
intestinal enterocytes, drug absorption, 43, 44
transcellular pathway, 46
passive membrane permeability, 391, 392–405
pentagastrin, 366
peptide transporter (PepT1) transporter
drug uptake, mechanism of, 285
genetic polymorphism, 289
structural activity relationship, 287–289
structure and distribution, 284–285
substrates and inhibitors, 285–287
permeability
and efflux transporters, 412–413, 414 (see also intestinal permeability and efflux transporters)
and influx transporters, 412, 413–414
and paracellular pathway, 413
passive diffusion or active transport, 412
and transcellular pathway, 413
P-glycoprotein (P-gp), 91
drug efflux, mechanism of, 205
genetic polymorphism, 223–224, 226
inhibitors, 206, 216–222, 223
nonlinear PK of CYP3A4 and P-gp substrates, 227–228
P-gp vs. BDDCS, 224–227, 231
structure and distribution, 204–205
substrates, 206, 207–213, 214–215
pharmacodynamics (PD), 1, 367–3671
intraperitoneal dosing, 368–369
minipumps, 369–370
reboxetine plasma exposure, 370–371
subcutaneous dosing, 369
pharmacokinetics (PK), 1
attrition, NCEs, 1, 2, 3–4
linear and nonlinear, 16–18
AUC, 16, 17
drug nonlinear kinetics, 16, 18
Michaelis–Menten kinetics, 16, 17
noncompartmental, 19
plasma concentration–time curve, 3, 10
pharmacologically active metabolites, 26
physicochemical and biopharmaceutical properties
hepatic/intestinal first-pass effect increased metabolic stability, 177–192
known SAR of CYP and UGTs enzymes, 174–177
influencing dissolution
amorphous form, 153, 155–156
cocrystal drug, 156–157
use of nanosuspension, 156
passive permeability
hydrogen-bonding affinity, 141–142, 143
hydrophobicity, 142–145
pH partition theory and pK\textsubscript{a}, 145, 146–147
rule of five (RO5), 145–147, 148
transcellular pathway, 141
physiologically based pharmacokinetic (PBPK) models, 350, 388
advantages, 22
drug parameters, 21–22
drug’s distribution, 21
perfusion- and permeability-limited distribution, 22
PK/TK modeling, 18–19
plasma, 4
pooling methods, 26
vs. blood clearance, 7
polarity, 178, 230, 269, 289, 312–313, 412
preclinical approaches, \textit{in vivo}
in in drug discovery and development, 357
first-pass effect contribution, 360–367
fraction of dose, portal blood, 358–360
oral absorption of NMEs, 357
of oral bioavailability and components, 358
pharmacodynamics activity of NME, 367–371
prodrugs
ester, 285, 286
solubility and permeability, 157–159
reactive metabolites, 26
renal clearance
of drug molecules, 313–314
renal clearance (Continued)
  mathematical principles, 78–79
  physicochemical determinants, 314
  renal secretion, 314
  uptake renal transporters, 79
renal efflux transporters
  BCRP, 91
  MATE1 and MATE2K, 79, 92–94
  P-glycoprotein (P-gp), 91
renal transporters
  OAT1 and OAT3, 79, 80–87
  OCT2, 79, 88–90
rule of five (RO5), 145–147

sandwich culture human hepatocytes (SCHH), 309, 315
SAR see structural activity relationship (SAR)
saturable intestinal uptake, 294–295
screening, 4, 23
sensitivity analysis, 232, 236–237
SimCYP® and ADAM Model, 351
single and multiple dose pharmacokinetic profile, 23
single-pass intestinal perfusion (SPIP)
  P-gp and efflux transporters, 339–340
  strengths and shortcomings, 340–341
  system design, 338–339
sodium-multivitamin transport (SMVT), 270
solubility
  BDDCS, 391
  fₐ modulation, 410, 412
  and permeability, 157–159
physicochemical and biopharmaceutical properties
  complexation, 151–153, 154
  counterion/salt selection, 150–151
  crystal lattice energy and solubility, 149–150
  pH and salt interplay, 150
  polymorphism and amorphous form, 148–149
structure–activity relationships (SARs), 173, 279–281, 287–289, 388
subcutaneous (SC) dosing, 186, 351, 369, 370–371
supersomes, 378–379, 383
talinolol, 203, 225, 226, 228, 232, 236
time of maximum concentration (tₘₓ), 11
toxicogenomics and biomarkers, 23, 27
toxicokinetics (TK), 1, 23
UGT see glucuronosyltransferases (UGT)
superfamily
unstirred water layer (UWL), 39, 152–153
volume of distribution
  at steady state, 9
  tissue and blood binding, 8–9
well-stirred model, 381–382
Zosuquidar and Ko143, 364–366