Index

A

Acoustic emission (AE)
application, 304
particle-particle and particle-wall collisions, 303
PAT tool, 304
ultrasound frequency range, 304

Active pharmaceutical ingredient (API)
coated MPs, 163
FDCs, 156–158
HME, 225, 248
inert core, defined, 6
modified release products, 66
multiparticulate system, 3
nanocrystals, 160
physical and chemical properties, 149
solvent evaporation process, 126
water-soluble drugs, 130

Age-appropriate drug formulations, 97

Aqueous coating systems
bottom-spray Wurster system, 286, 287
chlorpheniramine maleate release profiles, 286, 287
environmental concerns and operator safety, 286
extended release oral solid dosage forms, 286
surelease, 286

Aqueous ethyl cellulose ER system, 114
Artequin™ Paediatric, 232

Attention deficit hyperactivity disorder (ADHD), 172, 200, 232

B

Banded capsule, 347–348
Barrier membrane coatings
aqueous and solvent coating, 285
mechanisms, 272
tablet dosage forms, 268

Beads
anti-tacking agents, 250
EC systems, 285
floating and non-floating, 374
gamma scintigraphy, 375, 376
gross examination, 375
inert cores, 6
and nonpareil seeds, 244
oral multiparticulate systems, 1
particle size distribution, 22
production technology advancement, 223

Bioavailability-enhancing drug forms, 160–161
Bio-predictive dissolution testing, 189–190
Biorelevant dissolution system, 188, 190, 193, 195, 204
Biorelevant pH gradient method, 198, 203–205
Black box device, 196
Bottom spray process, 68–71, 244, 245
Brunauer-Emmett-Teller (BET) mathematical model, 30

C

Capsule filling
coating, 348
Capsule filling (cont.)
  direct weight checking systems, 354
  indirect dosage control systems, 351–353
  principles, 335–336
  and product combinations, 346
  quality control
    CPP, 349
    CQA, 349
  in-line controls, 349
  weight and content uniformity tests, 349
  weight control approaches, 350
  solid forms, 345–347
Capsules. See Dosing principles; Capsule shells; Capsule filling
Capsule shells
  automatic unclogging, 336
  bulk density, 25
  damage/deformation, 353
  layer-by-layer adsorption, 125
  types, 336–337
Captopril release profile, 136
CAT. See Colon arrival time (CAT)
Centrifugal extrusion, 127
Chord length distribution (CLD), 307, 308
Coating process
  aqueous EC dispersions, 285
  continuous water-filled channels, 285
  curing process, 285–286
  equipment, 284
  fluid bed drying, 285
  formulation factors, 285
  processing parameters, 284–285
  solubility and diffusivity, 286
Coating zone, 66, 68, 72, 77, 78, 88
Colon, 364–365, 382
Colon delivery and gastrointestinal targeting, 253–254
Colonic transit time (CTT), 187
Combined multi-particulate products, 172
Continuous drug pelleting system (CDP), 52
Cosmetic coatings, 254
Critical process parameters (CPP), 84, 86, 88, 89, 302, 349, 350
Critical quality attributes (CQA), 6, 85, 302, 315, 349, 350
Crospovidone, 44

D
Degree of substitution (DS), 269, 270
Delayed release (DR), 66, 97, 109, 170, 171, 254, 288, 346
Delayed release mini-tabs, 97, 109
Design of experiments (DoE), 85, 88
Differential scanning calorimetry (DSC), 240
Dimethyl sulfoxide (DMSO), 42, 43
Direct weight checking system, 354, 355
Discrete element modeling (DEM), 58
Diskjet, distribution plate, 72, 73
Dissolution methods
  database, 174
  ER pellet formulation, 204
  multiparticulates
    ER, 202, 204–206
    DR, 197, 198, 200, 202
    taste-masked, 195–197
  non-official dissolution methods, 176
  official dissolution methods, 174–177
  QC methods, 177
Dissolution test media
  blank media, 195
  colonic fluids, 194
  fasting and fed conditions, 193–194
  gastric fluids, 193
  saliva fluids, 190–195
  small intestinal fluids, 194
Dosage checking systems, 351, 352
Dosators system, 340
Dose-weight proportional formulation, 3
Dosing principles
  filling pellet multiparticulates, 339, 341, 342
  filling phase, 345
  mini-tabs, 342, 344
  powder dosing, 337–338
  soft gel, 345
Dosing wheel approach, 102
DR. See Delayed release (DR)
Drug layering/film coating
  droplet size, 79, 81
  heat and mass transfer, 76–78
  liquid properties, 82–84
  substrate flow, 78
Drug loading control, 159
Drug release mechanism
  channels/pores, 272
  EC barrier membrane films, 272
  flaws, cracks and imperfections, 272
  osmotic pressure, influence of, 273 (see also EC-coated multiparticulates)
Dry powder layering technology, 291
DS. See Degree of substitution (DS)

E
EC. See Ethylcellulose (EC)
EC-coated multiparticulates
  drug characteristics, 282–283
  higher-molecular-weight grades, 274
plasticizers (see Plasticizers)
polymer concentrations, 274
pore formers, 280–282
rate of water ingress, 273
solvent system, 274–275
substrates, 283
viscosity grade, effect of, 273
Effervescent floating multiparticulate system
acidic and alkaline materials, 377
ofloxacin, 377
pellets preparation, 378–379
in vivo characterization, 379–381
Emulsification and solvent evaporation
approach, 133, 142
Encapsulation
CPT, 129
hydrophilic drugs, 130
IFP, 128
polymer encapsulation, 128, 129
in situ polymerization, 128
Encapsulation efficiencies (EE), 136, 142, 149
ER pellet formulation, 204
Esophagus
active and passive mechanisms, 361
adhesion of formulations, 361
advantages, 361
bisphosphonates, 361
during swallowing, 361
Ethylcellulose (EC)
aqueous coating systems, 286–288
aqueous dispersion, 271
chemical structure and, 269
dry powder layering process, 291
DS, 269
film formation (see Film formation)
fluid bed process, 289, 290
nutritional application, 288
Opadry® EC coating system, 283
pharmaceutical formulations, 268
QbD, 290–294
range of viscosity grades, 269 (see also Coating process; Drug release mechanism)
Surelease®, 269
taste masking, bitter drugs, 288
versatile properties, 268
viscosities, 270
water-insoluble cellulose, 269
water-insoluble polymer, 268
EUDRACOL®, 260
EUDRAGIT RS, 109, 132, 138, 205, 206, 260
EUDRAGIT® polymers, 249
EUDRAGIT® RS films, 262
European Paediatric Formulation Initiative (EuPFI), 225
Extended release (ER)
capsules, 346
EUDRACOL®, 260
EUDRAGIT RL and EUDRAGIT RS, 258, 260
formulations, 170
polymeric films, 258
Extrusion
feeding systems, 48
PAT, 49, 50
pellets, 38
process parameters
process control, 49
thermal energy, 48
small-scale, 47, 48
types
melt extrusion, 38
melt solid lipid extrusion, 39
wet extrusion, 38
wet pellets, 38
Extrusion-spheronization
advantages, 39
disadvantages, 40
DMSO, 42
MCC, 41
pelletization aid, 41
pellets, 42
requirements, 40
water, 42
wet mass, 41
F
Fasted-state simulated colonic fluid (FaSSCoF), 195
Fasted-state simulated gastric fluid (FaSSGF), 193
FB. See Fluidized bed (FB) process
FBRM®, See Focused beam reflectance measurement (FBRM®)
Fed pH-gradients, 201
Fed-state simulated colonic fluid (FeSSCoF), 195
Film formation, 242
aqueous dispersion, 272
solvent solution, 271
Fixed-dose combination (FDC)
advantages, 2, 157
coating, MPs, 161, 162
combination therapy, 97
diabetes treatment, 163
Fixed-dose combination (FDC) (cont.)
disadvantages, 157, 158
dosage forms, 162
dual-release tablet, 162
Logimax, 161, 164
MP cores
  bioavailability-enhancing drug forms, 160
drug loading control, 159–160
  processes and physical properties, 159–161
release profile control, 160
TB therapy, 163
Fluid bed coating
applications, 66
  bottom spray processing, 68, 70, 71
coating materials, 66
coating zone, 66
  Hüttlin fluid bed, 71, 72
  intrinsic properties, 66
  rotor/centrifugal processing, 73, 75
top spray (see Top spray process)
Fluidized bed (FB) process
agglomeration, 289
batch to batch variability, 290
device characteristics, 315
in-line particle measurement factors, 313, 314
process characteristics, 314
product characteristics, 313, 314
scale-up considerations
  CPP, 84, 86, 88, 89
  CQA, 85, 87, 89
dissolution testing, 86
DoE, 87
  filters, 87
  fluidization, 91
  mass flow, 89, 90, 92
peak spray rate, 85
  Pilot-scale Wursters, 88
  scaling factors, 88
tracings, 90
small-scale and research
development batches, 289
  spray drying, 289
  static charge, 289
technology, 127
Focused beam reflectance measurement (FBRM®), 307
Friability
mini-tabs coating, 102
of pellets, 31–33
properties, 44
  substrate hardness and, 345
G
Gamma scintigraphy
gamma emitters, 366
  orally administered dosage forms, 366
  pharmaceutical, 369, 370
  radioactive materials, 367
  radiolabeling techniques, 367–369
Gas anti-solvent (GAS), 129
Gastric emptying time (GET), 182, 183
Gastrointestinal (GI) tract, 170
  anatomy, 178–179
  emptying, 182, 183
  function, morphology
  and physiology, 360, 361
GI motility patterns, 182
  immediate-release formulations, 181
  large intestinal (colonic) motility
    and passage times, 186, 187
  large intestinal (colonic) physiology, 186
  and microenvironmental conditions, 360
  monolithic enteric-coated dosage forms, 183, 184
  oral dosage forms, 181
  physiology, 180, 184, 185
  small intestinal motility and passage times, 185, 186
Gastro-resistant formulations
  anti-tacking agents, 250
  EUDRAGIT FS 30 D, 251
  EUDRAGIT L 100-55, 249
  EUDRAGIT L 30 D-55, 249, 252, 253
Gastro retentive multiparticulate system
  buoyancy, 374
  clinical protocol, 375–377
  floating and non-floating beads, 374
  formulator, 374
  gastric emptying, 374
  manufacturing and radiolabeling, 374–375
Generally regarded as safe (GRAS), 230, 268, 288
GI. See Gastrointestinal (GI) tract
Glatt CPS rotor processor, 74, 75
GraphPad Prism Software, 136
Gravimetric pellet dosing, 340
H
Hard shell capsules
dosing (see Dosing principles)
  filling principles, 335–336
  shell types, 336
solid forms, 345
Hot melt extrusion (HME) process, 225, 247–249
Index

Hot melt microencapsulation, 124, 125
Humidity control systems, 83
Hüttlin bottom spray processor, 72
Hüttlin fluid bed, 71, 72
Hydroxypropyl methylcellulose acetate succinate (HPMCAS), 260

Eudragit RS-coated diclofenac sodium pellets, 206
mesalazine formulations, 199
Ritalin LA, 201
Theophyllin AL, 203
IPP 70 probe system, 312

K
Kopcha model, 145

L
Large intestinal (colonic) physiology, 186
Linear variable displacement transducer (LDVT), 352
Liquid manufacturing vehicle (LMV), 125
Logimax, 161, 164

M
Magnetic marker monitoring (MMM) bar magnets/electromagnets, 370
electrical currents and elevators, 370
iron oxide magnetite (Fe₃O₄), 370
SQUIDs, 370
tracking of magnetic material, 370
in vivo behavior, multiparticulates, 370
Magnetic resonance imaging (MRI), 371
Makoid–Banakar model, 145
MCC. See Microcrystalline cellulose (MCC)
MDR. See Multidrug resistant (MDR) bacterial strains
Mechanical Mini Tablet System (mMTS), 104
Melt extrusion, 38
Melt-spray-congealing (MSC) process, 159
Mesh-type bonnet, 87
Methacrylates, 238
Meth-acrylic acid copolymers drug delivery bottom spray process, 244–245
gastro-resistant (see Gastro-resistant formulations)
pan coating processes, 246
pellet manufacturing, 247, 248	
tablet formulations, 246, 247
top spray process, 245
MFFT. See Minimum film formation temperature (MFFT)
Microcapsules
agglomeration, 141
angle of repose (AOR), 142
Microcapsules (cont.)
- Büchner funnel, 135
- burst release, 145
- carbonless copy paper, 120
- characterization, 135, 136
- CPT, 132, 139, 142, 144–146
- CQAs, 132
- data analysis, 137
- EE, 142
- emulsification and solvent evaporation approach, 133
- liquid paraffin, 130
- packability and flowability parameters, 143
- properties, 130, 131
- RSM, 132
- SEM micrographs, 143, 144
- types, 122
Microclimates, 72
Microcrystalline cellulose (MCC), 7, 8, 41, 134
Microencapsulation
- benefits, 122
- classification, 121
- features, 122
- oil-in-water solvent evaporation process, 129
- physico-chemical processes
  - coacervation phase separation, 124
  - hot melt, 124, 125
  - layer-by-layer polyelectrolyte deposition, 125
  - phase inversion, 125
  - solvent evaporation, 125, 126
- physico-mechanical process
  - centrifugal extrusion, 127
  - fluidized-bed technology, 127
  - pan coating, 127
  - spray drying and congealing, 126
  - processes and particle size ranges, 124
  - spray drying, 123
  - sprinkles, 123
  - solvents selection, 131
  - vitamin C, 123
Microsphere, 120, 121, 125, 126, 128, 130, 135, 145
Minimum film formation temperature (MFFT), 272
Mini-tablets, 4, 342–344, 347, 360
- applications, 114–115
- aqueous ethyl cellulose ER system, 114
- benefits, 97
- commercial products, 97
- disintegration testing, 104
- dissolution testing
  - enteric-coated, 105, 106
  - ER film coating, 114
  - hydrophilic ER mini-matrices, 106, 108
  - hydrophilic mini-matrices, 107
- paddle method, 104
- DR (see Modified drug release applications)
  - hard-shell capsules, 102
  - IR and ER, 97
- manufacture
  - coating, 101, 102
  - hot-melt extrusion, 101
  - particle size, 99
  - shear stress, 100
  - tooling, 98
- mMTS, 104
- MP, 96
  - pediatric application, 98
  - preschool-aged children, 98
- release control, 97
- solid and liquid formulation, 96
MMM. See Magnetic marker monitoring (MMM)
mMTS. See Mechanical Mini Tablet System (mMTS)
Modified drug release applications
- delayed release, 109
- extended release, 109–113
MRI. See Magnetic resonance imaging (MRI)
MSC. See Melt-spray-congealing (MSC) process
Multidrug resistant (MDR) bacterial strains, 163
Multiparticulates (MPs)
- APIs, 156, 163
- children, 232
- coating, 161
- cores
  - bioavailability-enhancing drug forms, 160, 161
  - drug loading control, 160
  - processes and physical properties, 159
  - drug release mechanisms, 224 (see also Ethylcellulose (EC))
- dosage forms, 162, 163
- dual-release formulation, 164
- modified release (MR) profiles, 156
Multiunit particulate systems (MUPS), 268
Near-infrared spectroscopy (NIR), 50, 304

ODF. See Orally disintegrating/dissolving formulation (ODF)

ODT. See Orally disintegrating tablets (ODT)

Oil-in-water solvent evaporation process, 129

On-line NIR, 304

Opadry® EC coating system, 283

Oral cavity and swallowing process, 180

Oral dosage forms, 120

Oral drug delivery, 1, 2

Oral multiparticulate systems

colon, 364, 365, 382
combined products, 172
dissolution test (see Dissolution test method)
DR multiparticulates, 171
drug development process, 365
ER formulations, 170
esophagus, 361
food, effect of, 374
formulation performance, 365
gamma scintigraphy (see Gamma scintigraphy)
genral differences between animal and rats, 365
GI tract (see Gastrointestinal (GI) tract)
ICH quality standards, 373
institutional review boards, 373
IntelliCap System, 372
IR formulations, 170
MMM, 370
MRI, 371
mucoadhesion, 365
nasogastric pH probes, 372
pharmaceutical technology, 360
pharmacokinetic (PK) sampling, 372
(see also Effervescent floating multiparticulate system;
Gastroretentive multiparticulates)
small intestine, 363–364
SR multiparticulates, 171
stomach, 362–363
taste-masked formulations, 173
terminologies, clinical investigation, 373
X-ray, 371

Orally disintegrating tablets (ODT), 256

Orally disintegrating/dissolving formulation (ODF), 180

Packability and flowability parameters, 143

Paediatric dosage forms, 218, 219, 221

Paediatric drug delivery characteristics

absorption, 215, 216
distribution, 217
elimination, 217
metabolism, 217
definition, 214, 215
population, 215
use
adolescence, 219
duration of illness, 218
preterm infants, 215

Paediatric formulation excipients, safe use, 230, 231
extemporaneous preparation, 230
palatability, 225
duration of illness, 218

Paediatric therapy. See also Paediatric formulations

advantages and constraints, 222, 223
classification, 215
regulatory guidelines/recommendations, 219–220
taste masking, 227, 228

Pan coating process, 127, 246

Particle image velocimetry (PIV), 57

Particles from gas-saturated solution (PGSS), 129

PAT. See Process analytical technologies (PAT)

PBPK. See Physiologically based pharmacokinetic (PBPK) model

PD. See Pharmacodynamics (PD)

Pellet coating process

bimodal distributions, 325, 326
calculation, 326, 327
characteristic values, 321–324
FLEX STREAM™ module, 327
flow with increasing/decreasing of spray rate, 326, 327
in-line Particle Probe IPP 70-S installation, 321
Pellet coating process (cont.)
number-based density distributions, 323, 324
processes and process optimization, 323
size growth, 325
top, bottom and side/tangential spray, 320
twins and triplets, 323
volume-based density distributions, 321, 322
Wurster configuration, 320
Pelletization aid
crospovidone, 44
disintegrating pellets, 44
DMSO, 42
MCC, 41, 42, 45
requirements, 44
wet mass, 41
Pellets, 38
density
bulk, 25
envelope, 24
true density, 24
dosators and pistons, 339
dosing accuracy, 342
double slide system, 339
dynamic image analysis, 16
gravimetric dosing, 339
materials and manufacturing, 8, 9
particle size distributions, 11, 13, 15, 19, 20
product quality, 7
QbD principles, 18
robustness and processability, 31, 32
shape, 26, 27
static image analysis, 16
sugar spheres, 17
surface area, 10, 11
surface morphology, 28, 30
vacuum-assisted dosing, 341
volumetric dosing, 342
volume vs. number distribution, 21–23
PGSS. See Particles from gas-saturated solution (PGSS)
Pharmaceutical gamma scintigraphy imaging
GI transit, ambulatory subjects, 369
image analysis, 369
procedures, 369
Pharmacodynamics (PD), 156
Pharmacokinetics (PK), 3, 156
Phase inversion microencapsulation, 125
Physiologically based pharmacokinetic (PBPK) model, 206
Pilot-scale Wursters, 88
PIV. See Particle image velocimetry (PIV)
Plasticizers
chlorpheniramine maleate release profiles, 278, 279
drug release from EC films, 277, 278
film pliability, 276
free film modulus and stress values, 277
glass transition (Tg), 277
optimum plasticization, 277
PEG efficiency, 276
permeability coefficient, 277
solubility parameters, 276
types, 276
water-soluble and water-insoluble, 277
Polymer encapsulation, 128, 129
Poly(meth)acrylates
EUDRAGIT®, 238
film formation, 242–243
methacrylates, 238
physicochemical properties, 240, 241
structure and functionality, 238, 239
Powder dosing, 339
Predictive dissolution methods
biorelevant dissolution system, 188
drug dissolution and release, 187
GI tract, 188
physiological (see Gastrointestinal (GI) tract)
requirements, 177
Process analytical technologies (PAT), 49–50, 302, 303
Process interface
defined, 317
in-line Disperser D11, 319
in-line SFT Probe IPP 70 with disperser D23, 318
long service life between cleaning intervals, 317
purge cells and dispersers, 318
Pulsatile delivery systems, 200, 201
Q
Quality by design (QbD), 132, 158, 302, 316
acetaminophen release profiles, 290
ETHOCEL variation, 290, 291
ETHOCEL-coated multiparticulates, 291, 294
metoprolol tartrate release, 290, 293
R
Radiolabeling technique
dual-isotope imaging, 369
erosion kinetics, 368
GI transit, multiparticulates, 368
neutron activation method, 367
pellet transit behavior, 368
radiolabeled enteric-coated delayed release dosage form, 368
sorption method, 367
in vitro evaluation, 368
Rapid expansion of supercritical solution (RESS), 129
Release profile, 170, 172, 174, 177, 198, 202, 204, 205
Release profile control, 160
Response surface methodology (RSM), 132
Rotor/centrifugal processing, 73–76

S
SFT. See Spatial filtering technique (SFT)
Simulated colonic fluid (SCoF), 195
Simulated saliva fluids (SSFs), 192
Single-unit dosage forms, 120
Site-specific delivery systems, 171, 198
Small intestinal physiology, 184–185
Small intestinal transit time (SITT), 369
Small intestine
formulation scientist, 364
gastric emptying rate, 363
intestinal transit conditions, 363
segmentation and peristalsis, 363
Softgel, 345
Solid lipid extrusion, 39
Solvent evaporation approach, 126, 149
Solvent system
binary mixtures, 275
description, 274
organic solvent residues, 275
phase separation principle, 275
polymer coils, 274
solubility parameters, 274
variety of, 274
Spatial filtering technique (SFT)
fluid particles population, 308
impulse generation, spot scanning, 309, 310
laser Doppler anemometry, 309
optical fibres, 310, 311
parameters, 312
principle, 308, 309
types of, 309
Spherization
applications, 58, 59
equipment, 50–51
mechanism, 52–54
process variables
DEM, 58
friction plate speed, 56
material load, 56
pelletization aid, 55
PIV, 57
powder formulation, 54
residence time, 56
water, 55
Spray-drying approach, 123, 126
Spray granulation, 75
Sprinkles, 123, 222, 224
SQUIDs. See Superconducting quantum interference devices (SQUIDs)
SSFs. See Simulated saliva fluids (SSFs)
Stomach
array of biopharmaceutical interactions, 362
floating multiparticulates, 362
magenstrasse influence, 363
median pH values, 362
MMC phases, 363
rate of gastric emptying, 362
Sugar sphere, 7
friability values, 33
monograph specification, 8
particle size, 11, 14
tensile strength, 32
Superconducting quantum interference devices (SQUIDs), 370
Sustained-release (SR) multiparticulate formulations, 171–172

T
Tablet formulations, 246, 247
Target product profile (TPP), 132
Taste masking
antimalarial quinine sulfate, 256
EUDRAGIT E PO, 257
film coating polymers, 226, 227, 229
formulations, 173
HME, 225
human taste panels, 226
moisture-protective coating, 257
ODT, 256
physico-chemical modification, 228
Theoretical capsule fill weights, 25
Top spray process, 67, 68, 245
U
USP dissolution methods, 175

V
Vacuum-assisted pellet dosing, 341
Versatile dosage forms, 222

Viscosities
Dow Chemical Company, 270
pharmacopeia specification, 270
polymer molecular weight, 271
product nomenclature, 270
and substitution ranges, pharmaceutical applications, 270

W
Weight control approaches, 350
Wet extrusion, 38
Wet pellets, 38
Wurster bottom spray, 69, 84
Wurster system, 68, 70, 71

X
X-ray-based system, 353
X-ray technology, 353

Z
Zanasi Lab 16, 103