Physicochemical Principles of Pharmacy

Fourth edition

Alexander T Florence and David Attwood





Physicochemical Principles of Pharmacy

Physicochemical Principles of Pharmacy

FOURTH EDITION

Alexander T Florence

CBE, DSc, FRSC, FRSE, FRPharmS School of Pharmacy, University of London, UK

David Attwood

PhD, DSc, CChem FRSC School of Pharmacy and Pharmaceutical Sciences University of Manchester, UK



Published by the Pharmaceutical Press

An imprint of RPS Publishing

1 Lambeth High Street, London SE1 7JN, UK 100 South Atkinson Road, Suite 200, Grayslake, IL 60030-7820, USA

© Pharmaceutical Press 2006

(PP) is a trade mark of RPS Publishing

RPS Publishing is the publishing organisation of the Royal Pharmaceutical Society of Great Britain

First, second and third editions published by Palgrave (formerly Macmillan Press Ltd) 1981, 1988, 1998 Third edition reprinted 2004, 2005 Fourth edition printed in 2006 Fourth edition reprinted 2007, 2009

Typeset by MCS Publishing Services Ltd, Salisbury, Wiltshire Printed in Great Britain by Butler, Tanner & Dennis, Frome Somerset

ISBN 978 0 85369 608 7

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, without the prior written permission of the copyright holder.

The publisher makes no representation, express or implied, with regard to the accuracy of the information contained in this book and cannot accept any legal responsibility or liability for any errors or omissions that may be made.

A catalogue record for this book is available from the British Library.

Cover image: Polarised light micrograph of liquid crystals. Magnification x100 at 35 mm size. Reproduced with permission from James Bell/Science Photo Library.

Contents

Preface xv Acknowledgements xvii About the authors xix

Introduction

1

7

1 Solids

1.1 Crystal structure 8 1.2 Crystal form 10 1.2.1 Crystallisation and factors affecting crystal form 11 1.3 Polymorphism 13 1.3.1 Pharmaceutical implications of polymorphism 16 1.4 Crystal hydrates 19 1.4.1 Pharmaceutical consequences of solvate formation 20 1.5 Dissolution of solid drugs 22 1.6 Biopharmaceutical importance of particle size 23 1.7 Wetting of powders 26 1.7.1 Contact angle and wettability of solid surfaces 27 1.7.2 Wettability of powders 27 1.8 Solid dispersions 28 1.8.1 Eutectics and drug identification 30 Summary 31 References 32

2 Gases and volatile agents

2.1 Pressure units 36

2.2 Ideal and nonideal gases 36

vi Contents

- 2.3 Vapour pressure 37
 - 2.3.1 Vapour pressure and solution composition: Raoult's law 37
 - 2.3.2 Variation of vapour pressure with temperature: Clausius–Clapeyron equation 40
 - 2.3.3 Vapour pressure lowering 43
- 2.4 Solubility of gases in liquids 46
 - 2.4.1 Effect of temperature on solubility 46
 - 2.4.2 Effect of pressure on solubility 46
 - 2.4.3 The solubility of volatile anaesthetics in oil 48
- 2.5 The solubility of gases in blood and tissues 49
 - 2.5.1 The solubility of oxygen in the blood 49
 - 2.5.2 The solubility of anaesthetic gases in blood and tissues 50
- Summary 53

References 54

3 Physicochemical properties of drugs in solution

- 3.1 Concentration units 56
 - 3.1.1 Weight concentration 56
 - 3.1.2 Molarity and molality 56
 - 3.1.3 Milliequivalents 56
 - 3.1.4 Mole fraction 57
- 3.2 Thermodynamics a brief introduction 57
 - 3.2.1 Energy 57
 - 3.2.2 Enthalpy 58
 - 3.2.3 Entropy 58
 - 3.2.4 Free energy 60
- 3.3 Activity and chemical potential 62
 - 3.3.1 Activity and standard states 62
 - 3.3.2 Activity of ionised drugs 63
 - 3.3.3 Solvent activity 65
 - 3.3.4 Chemical potential 66
- 3.4 Osmotic properties of drug solutions 69
 - 3.4.1 Osmotic pressure 69
 - 3.4.2 Osmolality and osmolarity 69
 - 3.4.3 Clinical relevance of osmotic effects 70
 - 3.4.4 Preparation of isotonic solution 73
- 3.5 Ionisation of drugs in solution 75
 - 3.5.1 Dissociation of weakly acidic and basic drugs and their salts 75

Contents vii

- 3.5.2 The effect of pH on the ionisation of weakly acidic or basic drugs and their salts 77
- 3.5.3 Ionisation of amphoteric drugs 82
- 3.5.4 Ionisation of polyprotic drugs 83
- 3.5.5 Microdissociation constants 84
- 3.5.6 pK_a values of proteins 85
- 3.5.7 Calculation of the pH of drug solutions 85
- 3.5.8 Preparation of buffer solutions 87
- 3.6 Diffusion of drugs in solution 89
- Summary 90

References 91

4 Drug stability

- 4.1 The chemical decomposition of drugs 94
 - 4.1.1 Hydrolysis 94
 - 4.1.2 Oxidation 95
 - 4.1.3 Isomerisation 98
 - 4.1.4 Photochemical decomposition 99
 - 4.1.5 Polymerisation 102
- 4.2 Kinetics of chemical decomposition in solution 102
 - 4.2.1 Classifying reactions: the order of reaction 103
 - 4.2.2 Zero-order reactions 104
 - 4.2.3 First-order reactions 104
 - 4.2.4 Second-order reactions 106
 - 4.2.5 Third-order reactions 106
 - 4.2.6 Determination of the order of reaction 106
 - 4.2.7 Complex reactions 107
- 4.3 Solid dosage forms: kinetics of chemical decomposition 110
- 4.4 Factors influencing drug stability 113
 - 4.4.1 Liquid dosage forms 113
 - 4.4.2 Semisolid dosage forms 123
 - 4.4.3 Solid dosage forms 123
- 4.5 Stability testing and prediction of shelf-life 127
 - 4.5.1 Effect of temperature on stability 128
 - 4.5.2 Other environmental factors affecting stability 133
 - 4.5.3 Protocol for stability testing 134
- Summary 136
- References 137

viii Contents

5 The solubility of drugs

- 5.1 Definitions 140
 - 5.1.1 Expressions of solubility 140
- 5.2 Factors influencing solubility 141
 - 5.2.1 Structural features and aqueous solubility 142
 - 5.2.2 Hydration and solvation 146
 - 5.2.3 The effect of simple additives on solubility 149
 - 5.2.4 The effect of pH on the solubility of ionisable drugs 150
- 5.3 Measurement of solubility 155
- 5.4 The solubility parameter 156
 - 5.4.1 Solubility parameters and biological processes 157
- 5.5 Solubility in mixed solvents 157
- 5.6 Cyclodextrins as solubilising agents 158
- 5.7 Solubility problems in formulation 160
 - 5.7.1 Mixtures of acidic and basic compounds 160
 - 5.7.2 Choice of drug salt to optimise solubility 161
 - 5.7.3 Drug solubility and biological activity 162
- 5.8 Partitioning 164
 - 5.8.1 Theoretical background 164
 - 5.8.2 Free energies of transfer 166
 - 5.8.3 Octanol as a nonaqueous phase 166
- 5.9 Biological activity and partition coefficients: thermodynamic activity and Ferguson's principle 166
- 5.10 Using log P 168
 - 5.10.1 The relationship between lipophilicity and behaviour of tetracyclines 168
 - 5.10.2 Sorption 171
 - 5.10.3 A chromatographic model for the biophase 174
 - 5.10.4 Calculating log P from molecular structures 174
 - 5.10.5 Drug distribution into human milk 174

Summary 175

References 176

6 Surfactants

- 6.1 Amphipathic compounds 178
- 6.2 Surface and interfacial properties of surfactants 179
 - 6.2.1 Effects of amphiphiles on surface and interfacial tension 179
 - 6.2.2 Change of surface tension with surfactant concentration the critical micelle concentration 180

Contents ix

- 6.2.3 Gibbs adsorption equation 180
- 6.2.4 The influence of the surfactant structure on surface activity 182
- 6.2.5 Surface activity of drugs 183
- 6.2.6 Insoluble monolayers 185
- 6.2.7 Pharmaceutical applications of surface film studies 190
- 6.2.8 Adsorption at the solid/liquid interface 194
- 6.3 Micellisation 201
 - 6.3.1 Water structure and hydrophobic bonding 202
 - 6.3.2 Theories of micelle formation 203
 - 6.3.3 Micellar structure 204
 - 6.3.4 Factors affecting the critical micelle concentration and micellar size 207
- 6.4 Liquid crystals and surfactant vesicles 210
 - 6.4.1 Liquid crystals 210
 - 6.4.2 Liposomes, niosomes and surfactant vesicles 215
- 6.5 Properties of some commonly used surfactants 216
 - 6.5.1 Anionic surfactants 216
 - 6.5.2 Cationic surfactants 216
 - 6.5.3 Nonionic surfactants 217
- 6.6 Solubilisation 220
 - 6.6.1 Determination of maximum additive concentration 220
 - 6.6.2 Location of the solubilisate 221
 - 6.6.3 Factors affecting solubilisation 222
 - 6.6.4 Pharmaceutical applications of solubilisation 225
- Summary 227

References 228

7 Emulsions, suspensions and other disperse systems

7.1 Classification of colloids 230

- 7.2 Colloid stability 231
 - 7.2.1 Forces of interaction between colloidal particles 231
 - 7.2.2 Repulsion between hydrated surfaces 235
- 7.3 Emulsions 237
 - 7.3.1 Stability of o/w and w/o emulsions 237
 - 7.3.2 HLB system 239
 - 7.3.3 Multiple emulsions 242
 - 7.3.4 Microemulsions 245
 - 7.3.5 Structured (semisolid) emulsions 247
 - 7.3.6 Biopharmaceutical aspects of emulsions 249

- 7.3.7 Preservative availability in emulsified systems 249
- 7.3.8 Mass transport in oil-in-water emulsions 250
- 7.3.9 Intravenous fat emulsions 251
- 7.3.10 The rheology of emulsions 253
- 7.4 Suspensions 254
 - 7.4.1 Stability of suspensions 255
 - 7.4.2 Aspects of suspension stability 255
 - 7.4.3 Extemporaneous suspensions 259
 - 7.4.4 Suspension rheology 260
 - 7.4.5 Nonaqueous suspensions 261
 - 7.4.6 Adhesion of suspension particles to containers: immersional, spreading and adhesional wetting 262
- 7.5 Applications of colloid stability theory to other systems 265
 - 7.5.1 Cell-cell interactions 265
 - 7.5.2 Adsorption of microbial cells to surfaces 266
 - 7.5.3 Blood as a colloidal system 267
- 7.6 Foams and defoamers 269
 - 7.6.1 Clinical considerations 271

Summary 271

References 272

8 Polymers and macromolecules

- 8.1 Pharmaceutical polymers 274
 - 8.1.1 Definitions 274
 - 8.1.2 Polydispersity 276
 - 8.1.3 Polymer mixtures or blends 278
 - 8.1.4 Solubility 281
- 8.2 Water-soluble polymers 281
- 8.3 General properties of polymer solutions 282
 - 8.3.1 Viscosity of polymer solutions 282
 - 8.3.2 Gelling water-soluble polymers 284
 - 8.3.3 Syneresis 286
 - 8.3.4 Polymer complexes 286
 - 8.3.5 Binding of ions to macromolecules 288
 - 8.3.6 Interaction of polymers with solvents including water 288
 - 8.3.7 Adsorption of macromolecules 291
- 8.4 Some water-soluble polymers used in pharmacy and medicine 293
 - 8.4.1 Carboxypolymethylene (Carbomer, Carbopol) 293
 - 8.4.2 Cellulose derivatives 295

Contents xi

- 8.4.3 Natural gums and mucilages 296
- 8.4.4 Chitosan 298
- 8.4.5 Dextran 298
- 8.4.6 Polyvinylpyrrolidone 300
- 8.4.7 Polyoxyethylene glycols (Macrogols) 300
- 8.4.8 Bioadhesivity of water-soluble polymers 302
- 8.4.9 Polymers as wound dressings 302
- 8.4.10 Polymer crystallinity 303
- 8.5 Water-insoluble polymers and polymer membranes 303
 - 8.5.1 Permeability of polymers 303
 - 8.5.2 Ion-exchange resins 307
 - 8.5.3 Silicone oligomers and polymers 310
- 8.6 Some applications of polymeric systems in drug delivery 311
 - 8.6.1 Film coating 311
 - 8.6.2 Matrices 311
 - 8.6.3 Microcapsules and microspheres 314
 - 8.6.4 Rate-limiting membranes and devices 320
 - 8.6.5 Eroding systems 322
 - 8.6.6 Osmotic pump 322

Summary 326

References 327

9 Drug absorption and routes of administration

- 9.1 Biological membranes and drug transport 331
 - 9.1.1 Lipophilicity and absorption 334
 - 9.1.2 Permeability and the pH-partition hypothesis 335
 - 9.1.3 Problems in the quantitative application of the pH-partition hypothesis 337
- 9.2 The oral route and oral absorption 341
 - 9.2.1 Drug absorption from the gastrointestinal tract 341
 - 9.2.2 Structure of the gastrointestinal tract 343
 - 9.2.3 Bile salts and fat absorption pathways 344
 - 9.2.4 Gastric emptying, motility and volume of contents 345
- 9.3 Buccal and sublingual absorption 346
 - 9.3.1 Mechanisms of absorption 346
- 9.4 Intramuscular and subcutaneous injection 349
 - 9.4.1 Vehicles 351
 - 9.4.2 Blood flow 351
 - 9.4.3 Formulation effects 352
 - 9.4.4 Insulin 352

xii Contents

- 9.5 Transdermal delivery 335
 - 9.5.1 Routes of skin penetration 356
 - 9.5.2 Influence of drug 357
 - 9.5.3 Influence of vehicle 359
 - 9.5.4 Dilution of topical steroid preparations 362
 - 9.5.5 Transdermal medication: patches and devices 363
 - 9.5.6 Ultrasound and transdermal penetration 365
 - 9.5.7 Jet injectors 365
- 9.6 Medication of the eye and the eye as a route for systemic delivery 366
 - 9.6.1 The eye 366
 - 9.6.2 Absorption of drugs applied to the eye 367
 - 9.6.3 Influence of formulation 369
 - 9.6.4 Systemic effects from eye-drops 374
- 9.7 The ear 374
- 9.8 Absorption from the vagina 375
 - 9.8.1 Delivery systems 376
- 9.9 Inhalation therapy 376
 - 9.9.1 Physical factors affecting deposition of aerosols 377
 - 9.9.2 Experimental observations 379
- 9.10 The nasal route 383
- 9.11 Rectal absorption of drugs 385
- 9.12 Intrathecal drug administration 389
- 9.13 Intracavernosal injection 390
- Summary 390

References 390

10 Physicochemical drug interactions and incompatibilities

- 10.1 pH effects in vitro and in vivo 395
 - 10.1.1 In vitro pH effects 395
 - 10.1.2 In vivo pH effects 395
- 10.2 Dilution of mixed solvent systems 401
- 10.3 Cation-anion interactions 402
- 10.4 Polyions and drug solutions 405
- 10.5 Chelation and other forms of complexation 405
- 10.6 Other complexes 410
 - 10.6.1 Interaction of drugs with cyclodextrins 412
 - 10.6.2 Ion-exchange interactions 413
- 10.7 Adsorption of drugs 414
 - 10.7.1 Protein and peptide adsorption 416
- 10.8 Drug interactions with plastics 417

Contents xiii 10.9 Protein binding 419 10.9.1 Thermodynamics of protein binding 421 10.9.2 Lipophilicity and protein binding 422 10.9.3 Penetration of specialised sites 424 Summary 425 Appendix: Drugs interactions based on physical mechanisms 425 A: Interactions based on absorption of drugs 425 B: Interactions involving protein binding 427 References 429 11 Peptides, proteins and other biopharmaceuticals 431 11.1 Structure and solution properties of peptides and proteins 433 11.1.1 Structure of peptides and proteins 433 11.1.2 Hydrophobicity of peptides and proteins 433 11.1.3 Solubility of peptides and proteins 437 11.2 The stability of proteins and peptides 440 11.2.1 Physical instability 441 11.2.2 Formulation and protein stabilisation 443 11.2.3 Chemical instability 445 11.2.4 Accelerated stability testing of protein formulations 450 11.3 Protein formulation and delivery 451 11.3.1 Protein and peptide transport 451 11.3.2 Lyophilised proteins 452 11.3.3 Water adsorption isotherms 452 11.3.4 Routes of delivery 455 11.4 A therapeutic protein and a peptide 455 11.4.1 Insulin 455 11.4.2 Calcitonin 458 11.5 DNA and oligonucleotides 458 11.5.1 DNA 458 · 11.5.2 Oligonucleotides 459 11.6 Therapeutic monoclonal antibodies 460 Summary 460 References 460 **12** In vitro assessment of dosage forms 463 12.1 Dissolution testing of solid dosage forms 464 12.1.1 Pharmacopoeial and compendial dissolution tests 466 12.1.2 Flow-through systems 466

xiv Contents

- 12.2 In vitro-in vivo correlations 467
- 12.3 In vitro evaluation of nonoral systems 467
 - 12.3.1 Suppository formulations 467
 - 12.3.2 In vitro release from topical products and transdermal systems 467
- 12.4 Rheological characteristics of products 471
- 12.5 Adhesivity of dosage forms 472
- 12.6 Analysis of particle size distribution in aerosols 475

Summary 478

References 478

Index 479

Preface

Physicochemical Principles of Pharmacy emerged first in 1981, partly as a result of the authors' frustration when teaching physical pharmacy to undergraduate pharmacy students that there was no European book which covered the subject using pharmaceutical examples to illustrate the topics. Having been brought up ourselves on a diet of physical chemistry of little implicit pharmaceutical relevance, we decided that a book should be compiled which illustrated pharmaceutical not chemical themes. We argued that if a particular concept had never been used in a published pharmacy or pharmaceutical science paper, then it perhaps could be ignored. For too long pharmacy students have been subjected to shards of material more suited for honours students in pure disciplines. We have felt that the book served as a component of the science of pharmacy, as opposed to science for pharmacy. The first edition was well received and a second and third followed. It was encouraging that the text was used widely throughout the world in spite of it being difficult to purchase in the Americas and elsewhere. Charles Fry in a previous existence encouraged us to publish the book. His career took him away from Macmillan Press, who published the first three editions, but in his senior capacity at the Pharmaceutical Press he negotiated the rights of the book and reapplied the ever so gentle pressure for us to complete the fourth edition.

We thank Charles Fry and Paul Weller for their patience and faith in the text.

The present edition has of course been updated. Some students have found 'Florence and Attwood' difficult and prefer simpler texts, but we have not pandered and have not reduced the rigour of the material, in the firm belief of the vital importance of the physicochemical basis of pharmacy to the future strength of pharmacy. We have tried wherever possible to make links with real situations that occur with medicines or that might be important in the future. Some of the examples we have used are those in the original editions, because they have now become classics. New material has been added, but we have always reminded ourselves that this is not a monograph on the latest advances but a textbook for undergraduates and postgraduates.

We hope that the book will continue to be used in undergraduate and postgraduate pharmacy courses and by students of pharmaceutical science and the increasing number of students of cognate disciplines interested in pharmaceutical formulation and medicines.

> Alexander T Florence London David Attwood Manchester September 2005

Acknowledgements

THE NEW EDITION has taken many hours of patient work by Bridget Perez at the School of Pharmacy in London interpreting scribbled insertions and deletions and carrying out detective work on myriad queries. Useful comments have been received over the years from users of previous editions.

We thank Charles Fry and Paul Weller for gentle encouragement and understanding when deadlines were missed and all those at Pharmaceutical Press who have nursed the book through various stages.

About the authors

ALEXANDER FLORENCE is Dean of The School of DAVID ATTWOOD is Professor of Pharmacy at Pharmacy at the University of London; he was previously James P. Todd Professor of Pharmaceutics at the University of Strathclyde. His research and teaching interests are drug delivery and targeting, dendrimers, nanoparticles, non-aqueous emulsions, novel solvents for use in pharmacy and general physical pharmaceutics. He co-authored the book Surfactant Systems: their Chemistry, Pharmacy and Biology with David Attwood.

the University of Manchester; he previously lectured at the University of Strathclyde. His research interests are in the physicochemical properties of drugs and surfactants, and in polymeric drug delivery systems. He has many years' experience in the teaching of physical pharmacy.

3

Physicochemical properties of drugs in solution

- 3.1 Concentration units 56
- 3.2 Thermodynamics a brief introduction 57
- 3.3 Activity and chemical potential 62
- 3.4 Osmotic properties of drug solutions 69
- 3.5 Ionisation of drugs in solution 75
 3.6 Diffusion of drugs in solution 89
 Summary 90
 References 91

In this chapter we examine some of the important physicochemical properties of drugs in aqueous solution which are of relevance to such liquid dosage forms as injections, solutions, and eye drops. Some basic thermodynamic concepts will be introduced, particularly that of thermodynamic activity, an important parameter in determining drug potency. It is important that parenteral solutions are formulated with osmotic pressure similar to that of blood serum; in this chapter we will see how to adjust the tonicity of the formulation to achieve this aim. Most drugs are at least partially ionised at physiological pH and many studies have suggested that the charged group is essential for biological activity. We look at the influence of pH on the ionisation of several types of drug in solution and consider equations that allow the calculation of the pH of solutions of these drugs.

First, however, we recount the various ways to express the strength of a solution, since it is of fundamental importance that we are able to interpret the various units used to denote solution concentration and to understand their interrelationships, not least in practice situations.

3.1 Concentration units

A wide range of units is commonly used to express solution concentration, and confusion often arises in the interconversion of one set of units to another. Wherever possible throughout this book we have used the SI system of units. Although this is the currently recommended system of units in Great Britain, other more traditional systems are still widely used and these will be also described in this section.

3.1.1 Weight concentration

Concentration is often expressed as a weight of solute in a unit volume of solution; for example, $g dm^{-3}$, or % w/v, which is the number of grams of solute in 100 cm³ of solution. This is not an exact method when working at a range of temperatures, since the volume of the solution is temperaturedependent and hence the weight concentration also changes with temperature.

Whenever a hydrated compound is used, it is important to use the correct state of hydration in the calculation of weight concentration. Thus $10\% \text{ w/v} \text{ CaCl}_2$ (anhydrous) is approximately equivalent to 20% w/vCaCl₂·6H₂O and consequently the use of the vague statement '10% calcium chloride' could result in **gross** error. The SI unit of weight concentration is kg m⁻³ which is numerically equal to g dm⁻³.

3.1.2 Molarity and molality

These two similar-sounding terms must not be confused. The *molarity* of a solution is the number of moles (gram molecular weights) of solute in 1 litre (1 dm^3) of *solution*. The *molal-ity* is the number of moles of solute in 1 kg of *solvent*. Molality has the unit, mol kg⁻¹, which

is an accepted SI unit. Molarity may be converted to SI units using the relationship 1 mol litre⁻¹ = 1 mol dm⁻³ = 10³ mol m⁻³. Interconversion between molarity and molality requires a knowledge of the density of the solution.

Of the two units, molality is preferable for a precise expression of concentration because it does not depend on the solution temperature as does molarity; also, the molality of a component in a solution remains unaltered by the addition of a second solute, whereas the molarity of this component decreases because the total volume of solution increases following the addition of the second solute.

3.1.3 Milliequivalents

The unit milliequivalent (mEq) is commonly used clinically in expressing the concentration of an ion in solution. The term 'equivalent', or gram equivalent weight, is analogous to the mole or gram molecular weight. When monovalent ions are considered, these two terms are identical. A 1 molar solution of sodium bicarbonate, NaHCO₃, contains 1 mol or 1 Eq of Na⁺ and 1 mol or 1 Eq of HCO₃ per litre (dm⁻³) of solution. With multivalent ions, attention must be paid to the valency of each ion; for example, 10% w/v CaCl₂·2H₂O contains 6.8 mmol or 13.6 mEq of Ca²⁺ in 10 cm³.

The Pharmaceutical $Codex^1$ gives a table of milliequivalents for various ions and also a simple formula for the calculation of milliequivalents per litre (see Box 3.1).

In analytical chemistry a solution which contains 1 Eq dm⁻³ is referred to as a *normal* solution. Unfortunately the term 'normal' is also used to mean physiologically normal with reference to saline solution. In this usage, a physiologically normal saline solution contains 0.9 g NaCl in 100 cm³ aqueous solution and *not* 1 equivalent (58.44 g) per litre.

Box 3.1 Calculation of milliequivalents

The number of milliequivalents in 1 g of substance is given by

For example, $CaCl_2 \cdot 2H_2O$ (mol. wt. = 147.0)

mEq Ca²⁺ in 1 g CaCl₂ · 2H₂O =
$$\frac{2 \times 1000 \times 147.0}{147.0}$$

= 13.6 mEq

and

mEq Cl⁻ in 1 g CaCl₂ · 2H₂O =
$$\frac{1 \times 1000 \times 2}{147.0}$$

= 13.6 mEq

that is, each gram of CaCl₂·2H₂O represents 13.6 mEq of calcium and 13.6 mEq of chloride

3.1.4 Mole fraction

The mole fraction of a component of a solution is the number of moles of that component divided by the total number of moles present in solution. In a two-component (binary) solution, the mole fraction of solvent, x_1 , is given by $x_1 = n_1/(n_1 + n_2)$, where n_1 and n_2 are respectively the numbers of moles of solvent and of solute present in solution. Similarly, the mole fraction of solute, x_2 , is given by $x_2 = n_2/(n_1 + n_2)$. The sum of the mole fractions of all components is, of course, unity, i.e. for a binary solution, $x_1 + x_2 = 1$.

EXAMPLE 3.1 Units of concentration

Isotonic saline contains 0.9% w/v of sodium chloride (mol. wt. = 58.5). Express the concentration of this solution as: (a) molarity; (b) molality; (c) mole fraction and (d) milliequivalents of Na⁺ per litre. Assume that the density of isotonic saline is 1 g cm⁻³.

Answer

(a) 0.9% w/v solution of sodium chloride contains 9 g dm⁻³ = 0.154 mol dm⁻³.

(b) 9 g of sodium chloride are dissolved in 991 g of water (assuming density = 1 g dm^{-3}).

Therefore 1000 g of water contains 9.08 g of sodium chloride = 0.155 moles, i.e. molality = $0.155 \text{ mol kg}^{-1}$.

(c) Mole fraction of sodium chloride, x₁, is given by

$$x_1 = \frac{n_1}{n_1 + n_2} = \frac{0.154}{0.154 + 55.06} = 2.79 \times 10^{-3}$$

(Note 991 g of water contains 991/18 moles, i.e. $n_2 = 55.06$.)

(d) Since Na⁺ is monovalent, the number of milliequivalents of Na⁺ = number of millimoles.

Therefore the solution contains 154 mEq dm⁻³ of Na⁺.

3.2 Thermodynamics – a brief introduction

The importance of thermodynamics in the pharmaceutical sciences is apparent when it is realised that such processes as the partitioning of solutes between immiscible solvents, the solubility of drugs, micellisation and drug-receptor interaction can all be treated in thermodynamic terms. This brief section merely introduces some of the concepts of thermodynamics which are referred to throughout the book. Readers requiring a greater depth of treatment should consult standard texts on this subject.^{2, 3}

3.2.1 Energy

Energy is a fundamental property of a system. Some idea of its importance may be gained by considering its role in chemical reactions, where it determines what reactions may occur, how fast the reaction may proceed and in which direction the reaction will occur. Energy takes several forms: kinetic energy is that which a body possesses as a result of its motion; potential energy is the energy which a body has due to its position, whether gravitational potential energy or coulombic potential energy which is associated with charged particles at a given distance apart. All forms of energy are related, but in converting between the various types it is not possible to create or destroy energy. This forms the basis of the *law of conservation of energy*.

The *internal energy U* of a system is the sum of all the kinetic and potential energy contributions to the energy of all the atoms, ions and molecules in that system. In thermodynamics we are concerned with *change* in internal energy, ΔU , rather than the internal energy itself. (Notice the use of Δ to denote a finite change). We may change the internal energy of a closed system (one that cannot exchange matter with its surroundings) in only two ways: by transferring energy as *work* (*w*) or as *heat* (*q*). An expression for the change in internal energy is

$$\Delta U = w + q \tag{3.1}$$

If the system releases its energy to the surroundings ΔU is negative, i.e. the total internal energy has been reduced. Where heat is absorbed (as in an endothermic process) the internal energy will increase and consequently q is positive. Conversely, in a process which releases heat (an exothermic process) the internal energy is decreased and q is negative. Similarly, when energy is supplied to the system as work, w is positive; and when the system loses energy by doing work, w is negative.

It is frequently necessary to consider infinitesimally small changes in a property; we denote these by the use of d rather than Δ . Thus for an infinitesimal change in internal energy we write equation (3.1) as

$$\mathrm{d}U = \mathrm{d}w + \mathrm{d}q \tag{3.2}$$

We can see from this equation that it does not really matter whether energy is supplied as heat or work or as a mixture of the two: the change in internal energy is the same. Equation (3.2) thus expresses the principle of the law of conservation of energy but is much wider in its application since it involves changes in heat energy, which were not encompassed in the conservation law.

It follows from equation (3.2) that a system which is completely isolated from its surroundings, such that it cannot exchange heat or interact mechanically to do work, cannot experience any change in its internal energy. In other words *the internal energy of an isolated system is constant* – this is the *first law of thermodynamics*.

3.2.2 Enthalpy

Where a change occurs in a system at *constant pressure* as, for example, in a chemical reaction in an open vessel, then the increase in internal energy is not equal to the energy supplied as heat because some energy will have been lost by the work done (against the atmosphere) during the expansion of the system. It is convenient, therefore, to consider the heat change in isolation from the accompanying changes in work. For this reason we consider a property that is equal to the heat supplied at constant pressure: this property is called the *enthalpy* (*H*). We can define enthalpy by

$$\Delta H = q \text{ at constant pressure}$$
(3.3)

 ΔH is positive when heat is supplied to a system which is free to change its volume and negative when the system releases heat (as in an exothermic reaction). Enthalpy is related to the internal energy of a system by the relationship

$$H = U + pV \tag{3.4}$$

where p and V are respectively the pressure and volume of the system.

Enthalpy changes accompany such processes as the dissolution of a solute, the formation of micelles, chemical reaction, adsorption onto solids, vaporisation of a solvent, hydration of a solute, neutralisation of acids and bases, and the melting or freezing of solutes.

3.2.3 Entropy

The first law, as we have seen, deals with the conservation of energy as the system changes

from one state to another, but it does not specify which particular changes will occur spontaneously. The reason why some changes have a natural tendency to occur is not that the system is moving to a lower-energy state but that there are changes in the randomness of the system. This can be seen by considering a specific example: the diffusion of one gas into another occurs without any external intervention - i.e. it is spontaneous - and yet there are no differences in either the potential or kinetic energies of the system in its equilibrium state and in its initial state where the two gases are segregated. The driving force for such spontaneous processes is the tendency for an increase in the chaos of the system - the mixed system is more disordered than the original.

A convenient measure of the randomness or disorder of a system is the *entropy* (S). When a system becomes more chaotic, its entropy increases in line with the degree of increase in disorder caused. This concept is encapsulated in the *second law of thermodynamics* which states that *the entropy of an isolated system increases in a spontaneous change*.

The second law, then, involves entropy change, ΔS , and this is defined as the heat absorbed in a *reversible* process, q_{rev} , divided by the temperature (in kelvins) at which the change occurred.

For a finite change

$$\Delta S = \frac{q_{\text{rev}}}{T} \tag{3.5}$$

and for an infinitesimal change

$$dS = \frac{dq_{rev}}{T}$$
(3.6)

By a 'reversible process' we mean one in which the changes are carried out infinitesimally slowly, so that the system is always in equilibrium with its surroundings. In this case we infer that the temperature of the surroundings is infinitesimally higher than that of the system, so that the heat changes are occurring at an infinitely slow rate, so that the heat transfer is smooth and uniform.

We can see the link between entropy and disorder by considering some specific examples.

For instance, the entropy of a perfect gas changes with its volume V according to the relationship

$$\Delta S = nR \ln \frac{V_{\rm f}}{V_{\rm i}} \tag{3.7}$$

59

where the subscripts f and i denote the final and initial states. Note that if $V_f > V_i$ (i.e. if the gas expands into a larger volume) the logarithmic (ln) term will be positive and the equation predicts an increase of entropy. This is expected since expansion of a gas is a spontaneous process and will be accompanied by an increase in the disorder because the molecules are now moving in a greater volume.

Similarly, increasing the temperature of a system should increase the entropy because at higher temperature the molecular motion is more vigorous and hence the system more chaotic. The equation which relates entropy change to temperature change is

$$\Delta S = C_{\rm V} \ln \frac{T_{\rm f}}{T_{\rm i}} \tag{3.8}$$

where C_v is the molar heat capacity at constant volume. Inspection of equation (3.8) shows that ΔS will be positive when $T_f > T_i$, as predicted.

The entropy of a substance will also change when it undergoes a phase transition, since this too leads to a change in the order. For example, when a crystalline solid melts, it changes from an ordered lattice to a more chaotic liquid (see Fig. 3.1) and consequently an increase in entropy is expected. The entropy change accompanying the melting of a solid is given by

$$\Delta S = \frac{\Delta H_{\rm fus}}{T} \tag{3.9}$$

where ΔH_{fus} is the enthalpy of fusion (melting) and *T* is the melting temperature. Similarly, we may determine the entropy change when a liquid vaporises from

$$\Delta S = \frac{\Delta H_{\text{vap}}}{T} \tag{3.10}$$

where ΔH_{vap} is the enthalpy of vaporisation and *T* now refers to the boiling point. Entropy



Figure 3.1 Melting of a solid involves a change from an ordered arrangement of molecules, represented by (a), to a more chaotic liquid, represented by (b). As a result, the melting process is accompanied by an increase in entropy.

changes accompanying other phase changes, such as change of the polymorphic form of crystals (see section 1.2), may be calculated in a similar manner.

At absolute zero all the thermal motions of the atoms of the lattice of a crystal will have ceased and the solid will have no disorder and hence a zero entropy. This conclusion forms the basis of the *third law of thermodynamics*, which states that *the entropy of a perfectly crystalline material is zero when* T = 0.

3.2.4 Free energy

The free energy is derived from the entropy and is, in many ways, a more useful function to use. The free energy which is referred to when we are discussing processes at constant pressure is the *Gibbs free energy* (*G*). This is defined by

$$G = H - TS \tag{3.11}$$

The change in the free energy at constant temperature arises from changes in enthalpy and entropy and is

$$\Delta G = \Delta H - T \,\Delta S \tag{3.12}$$

Thus, at constant temperature and pressure,

$$\Delta G = -T \Delta S \tag{3.13}$$

from which we can see that the change in free energy is another way of expressing the change in overall entropy of a process occurring at constant temperature and pressure.

In view of this relationship we can now consider changes in free energy which occur during a spontaneous process. From equation (3.13) we can see that ΔG will decrease during a spontaneous process at constant temperature and pressure. This decrease will occur until the system reaches an equilibrium state when ΔG becomes zero. This process can be thought of as a gradual using up of the system's ability to perform work as equilibrium is approached. Free energy can therefore be looked at in another way in that it represents the maximum amount of work, $w_{\rm max}$ (other than the work of expansion), which can be extracted from a system undergoing a change at constant temperature and pressure; i.e.

 $\Delta G = w_{\max} \tag{3.14}$

at constant temperature and pressure

This nonexpansion work can be extracted from the system as electrical work, as in the case of a chemical reaction taking place in an electrochemical cell, or the energy can be stored in biological molecules such as adenosine triphosphate (ATP).

When the system has attained an equilibrium state it no longer has the ability to reverse itself. Consequently *all spontaneous processes are irreversible*. The fact that all spontaneous processes taking place at constant temperature and pressure are accompanied by a negative free energy change provides a useful criterion of the spontaneity of any given process.

By applying these concepts to chemical equilibria we can derive (see Box 3.2) the following simple relationship between free energy change and the equilibrium constant of a reversible reaction, K:

$$\Delta G^{\circ} = -RT \ln K$$

where the standard free energy G° is the free energy of 1 mole of gas at a pressure of 1 bar.

A similar expression may be derived for reactions in solutions using the *activities* (see

Eyenovia Exhibit 1053, Page 23 of 55

Box 3.2 Relationship between free energy change and the equilibrium constant

Consider the following reversible reaction taking place in the gaseous phase

 $aA + bB \rightleftharpoons cC + dD$

According to the law of mass action, the equilibrium constant, K, can be expressed as

$$K = \frac{(p'_{c})^{c} (p'_{b})^{d}}{(p'_{b})^{a} (p'_{b})^{b}}$$
(3.15)

where p' terms represent the partial pressures of the components of the reaction at equilibrium.

The relationship between the free energy of a perfect gas and its partial pressure is given by

$$\Delta G = G - G^{\circ} = RT \ln p \tag{3.16}$$

where G^e is the free energy of 1 mole of gas at a pressure of 1 bar.

Applying equation (3.16) to each component of the reaction gives

$$aG_{A} = a(G_{B}^{e} + RT \ln p_{A})$$

$$bG_{B} = b(G_{B}^{e} + RT \ln p_{B})$$

etc. As

$$\Delta G = \sum G_{\text{prod}} - \sum G_{\text{read}}$$

so

$$\Delta G = \Delta G^{\ominus} + RT \ln \frac{(p_{\rm C})^{\rm e} (p_{\rm D})^{\rm e}}{(p_{\rm A})^{\rm e} (p_{\rm B})^{\rm b}}$$

 $\Delta G^{\rm e}$ is the standard free energy change of the reaction, given by

$$\Delta G^{\circ} = cG_{C}^{\circ} + dG_{D}^{\circ} - aG_{A}^{\circ} - bG_{B}^{\circ}$$

As we have noted previously, the free energy change for systems at equilibrium is zero, and hence equation (3.17) becomes

$$\Delta G^{\circ} = -RT \ln \frac{(\mathbf{p}'_{c})^{c} (\mathbf{p}'_{b})^{d}}{(\mathbf{p}'_{A})^{\alpha} (\mathbf{p}'_{B})^{b}}$$
(3.18)

Substituting from equation (3.15) gives

$$\Delta G^{\circ} = -RT \ln K \tag{3.19}$$

Substituting equation (3.19) into equation (3.17) gives

$$\Delta G = -RT \ln K + RT \ln \frac{(\boldsymbol{p}_{c})^{c} (\boldsymbol{p}_{b})^{d}}{(\boldsymbol{p}_{A})^{o} (\boldsymbol{p}_{B})^{b}}$$
(3.20)

Equation (3.20) gives the change in free energy when a moles of A at a partial pressure p_A and b moles of B at a partial pressure p_B react together to yield c moles of C at a partial pressure p_C and d moles of D at a partial pressure p_D . For such a reaction to occur spontaneously, the free energy change must be negative, and hence equation (3.20) provides a means of predicting the ease of reaction for selected partial pressures (or concentrations) of the reactants,

section 3.3.1) of the components rather than the partial pressures. ΔG° values can readily be calculated from the tabulated data and hence equation (3.19) is important because it provides a method of calculating the equilibrium constants without resort to experimentation.

(3.17)

A useful expression for the temperature dependence of the equilibrium constant is the *van't Hoff equation* (equation 3.23), which may be derived as outlined in Box 3.3. A more general form of this equation is

$$\log K = \frac{-\Delta H^{\odot}}{2.303RT} + \text{constant}$$
(3.24)

Plots of log *K* against 1/T should be linear with a slope of $-\Delta H^{\Theta}/2.303R$, from which ΔH^{Θ} may be calculated.

Equations (3.19) and (3.24) are fundamental equations which find many applications in the broad area of the pharmaceutical sciences: for example, in the determination of equilibrium constants in chemical reactions and for micelle formation; in the treatment of stability data for some solid dosage forms (see section 4.4.3); and for investigations of drug–receptor binding.

Box 3.3 Derivation of the van't Hoff equation

From equation (3.19),

 $\frac{-\Delta G^{\odot}}{RT} = \ln K$

Since

 $\Delta G^{\oplus} = \Delta H^{\oplus} - T \Delta S^{\oplus}$

then at a temperature T_1

$$\ln K_1 = \frac{-\Delta G^{\odot}}{RT_1} = \frac{-\Delta H^{\odot}}{RT_1} + \frac{\Delta S^{\odot}}{R}$$
(3.21)

and at temperature T_2

$$\ln K_2 = \frac{-\Delta G^{\ominus}}{RT_2} = \frac{-\Delta H^{\ominus}}{RT_2} + \frac{\Delta S^{\ominus}}{R}$$
(3.22)

If we assume that the standard enthalpy change ΔH° and the standard entropy change ΔS^{e} are independent of temperature, then subtracting equation (3.21) from equation (3.22) gives

$$\ln K_2 - \ln K_1 = -\frac{\Delta H^{\oplus}}{R} \left(\frac{1}{T_2} - \frac{1}{T_1} \right)$$
or
$$K_2 = \Delta H^{\oplus} \quad (T_2 - T_1)$$

$$\log \frac{K_2}{K_1} = \frac{\Delta H^{\circ}}{2.303R} \frac{(T_2 - T_1)}{T_1 T_2}$$
(3.23)

Equation (3.23), which is often referred to as the van't Hoff equation, is useful for the prediction of the equilibrium constant K_2 at a temperature T_2 from its value K_1 at another temperature T_1 .

3.3 Activity and chemical potential

3.3.1 Activity and standard states

The term *activity* is used in the description of the departure of the behaviour of a solution from ideality. In any real solution, interactions occur between the components which reduce the effective concentration of the solution. The activity is a way of describing this effective concentration. In an ideal solution or in a real solution at infinite dilution, there are no interactions between components and the activity equals the concentration. Nonideality in real solutions at higher concentrations causes a divergence between the values of

activity and concentration. The ratio of the activity to the concentration is called the activity coefficient, γ ; that is,

$$\gamma = \frac{\text{activity}}{\text{concentration}}$$
(3.25)

Depending on the units used to express concentration we can have either a molal activity coefficient, γ_m , a molar activity coefficient, γ_c , or, if mole fractions are used, a *rational* activity coefficient, γ_x .

In order to be able to express the activity of a particular component numerically, it is necessary to define a reference state in which the activity is arbitrarily unity. The activity of a particular component is then the ratio of its value in a given solution to that in the reference state. For the solvent, the reference state is invariably taken to be the pure liquid and, if this is at a pressure of 1 atmosphere and at a definite temperature, it is also the standard state. Since the mole fraction as well as the activity is unity: $\gamma_{\rm r} = 1$.

Several choices are available in defining the standard state of the solute. If the solute is a liquid which is miscible with the solvent (as, for example, in a benzene-toluene mixture), then the standard state is again the pure liquid. Several different standard states have been used for solutions of solutes of limited solubility. In developing a relationship between drug activity and thermodynamic activity, the pure substance has been used as the standard state. The activity of the drug in solution was then taken to be the ratio of its concentration to its saturation solubility. The use of a pure substance as the standard state is of course of limited value since a different state is used for each compound. A more feasible approach is to use the infinitely dilute solution of the compound as the reference state. Since the activity equals the concentration in such solutions, however, it is not equal to unity as it should be for a standard state. This difficulty is overcome by defining the standard state as a hypothetical solution of unit concentration possessing, at the same time, the properties of an infinitely dilute solution. Some workers⁴ have chosen to

define the standard state in terms of an alkane solvent rather than water; one advantage of this solvent is the absence of specific solute– solvent interactions in the reference state which would be highly sensitive to molecular structure.

3.3.2 Activity of ionised drugs

A large proportion of the drugs that are administered in aqueous solution are salts which, on dissociation, behave as electrolytes. Simple salts such as ephedrine hydrochloride $(C_6H_5CH(OH)CH(NHCH_3)CH_3HCl)$ are 1:1 (or uni-univalent) electrolytes; that is, on dissociation each mole yields one cation, $C_6H_5CH(OH)CH(N^+H_2CH_3)CH_3$, and one anion, Cl⁻. Other salts are more complex in their ionisation behaviour; for example, ephedrine sulfate is a 1:2 electrolyte, each mole giving two moles of the cation and one mole of SO_4^{2-} ions.

The activity of each ion is the product of its activity coefficient and its concentration, that is

$$a_+ = \gamma_+ m_+$$
 and $a_- = \gamma_- m_-$

The anion and cation may each have a different ionic activity in solution and it is not possible to determine individual ionic activities experimentally. It is therefore necessary to use combined terms, for example the combined activity term is the *mean ionic activity*, a_{\pm} . Similarly, we have the *mean ion activity coefficient*, γ_{\pm} , and the *mean ionic molality*, m_{\pm} . The relationship between the mean ionic parameters is then

$$\gamma_{\pm} = \frac{a_{\pm}}{m_{\pm}}$$

More details of these combined terms are given in Box 3.4.

Values of the mean ion activity coefficient may be determined experimentally using several methods, including electromotive force measurement, solubility determinations and colligative properties. It is possible, however, to calculate γ_{\pm} in very dilute solution using a theoretical method based on the Debye–Hückel theory. In this theory each ion is considered to be surrounded by an 'atmosphere' in which there is a slight excess of ions of opposite charge. The electrostatic energy due to this effect is related to the chemical potential of the ion to give a limiting expression for dilute solutions

$$-\log \gamma_{\pm} = z_{+} z_{-} A \sqrt{I} \tag{3.36}$$

where z_+ and z_- are the valencies of the ions, A is a constant whose value is determined by the dielectric constant of the solvent and the temperature (A = 0.509 in water at 298 K), and I is the total ionic strength defined by

$$I = \frac{1}{2}\sum(mz^2) = \frac{1}{2}(m_1z_1^2 + m_2z_2^2 + \dots)$$
(3.37)

where the summation is continued over all the different species in solution. It can readily be shown from equation (3.37) that for a 1:1 electrolyte the ionic strength is equal to its molality; for a 1:2 electrolyte I = 3m; and for a 2:2 electrolyte, I = 4m.

The Debye–Hückel expression as given by equation (3.36) is valid only in dilute solution ($I < 0.02 \text{ mol kg}^{-1}$). At higher concentrations a modified expression has been proposed:

$$\log \gamma_{\pm} = \frac{-A Z_{\pm} Z_{\pm} \sqrt{I}}{1 + a_{i} \beta \sqrt{I}}$$
(3.38)

where a_i is the mean distance of approach of the ions or the mean effective ionic diameter, and β is a constant whose value depends on the solvent and temperature. As an approximation, the product $a_i\beta$ may be taken to be unity, thus simplifying the equation. Equation (3.38) is valid for *I* less than 0.1 mol kg⁻¹

EXAMPLE 3.2 Calculation of mean ionic activity coefficient

Calculate: (a) the mean ionic activity coefficient and the mean ionic activity of a $0.002 \text{ mol kg}^{-1}$ aqueous solution of ephedrine sulfate; (b) the mean ionic activity coefficient of an aqueous solution containing $0.002 \text{ mol kg}^{-1}$ ephedrine sulfate and 0.01 mol kg^{-1} sodium chloride. Both solutions are at 25°C.

Answer

(a) Ephedrine sulfate is a 1:2 electrolyte and hence the ionic strength is given by equation (3.37) as

$$I = \frac{1}{2} [(0.002 \times 2 \times 1^2) + (0.002 \times 2^2)]$$

= 0.006 mol kg⁻¹

From the Debye–Hückel equation (equation 3.36),

$$-\log \gamma_{\pm} = 0.509 \times 1 \times 2 \times \sqrt{0.006}$$

 $\log \gamma_{\pm} = -0.0789$
 $\gamma_{\pm} = 0.834$

The mean ionic activity may be calculated from equation (3.35):

$$a_{\pm} = 0.834 \times 0.002 \times (2^2 \times 1)^{1/3}$$
$$= 0.00265$$

(b) Ionic strength of 0.01 mol kg⁻¹ NaCl = $\frac{1}{2}(0.01 \times 1^2) + (0.01 \times 1^2) = 0.01$ mol kg⁻¹.

Total ionic strength =
$$0.006 + 0.01 = 0.016$$

 $-\log \gamma_{\pm} = 0.509 \times 2 \times \sqrt{0.016}$
 $\log \gamma_{\pm} = -0.1288$
 $\gamma_{\pm} = 0.743$

Box 3.4 Mean ionic parameters

In general, we will consider a strong electrolyte which dissociates according to

$$\mathsf{C}_{\nu+}\mathsf{A}_{\nu-} \longrightarrow \nu_{+}\mathsf{C}^{z+} + \nu_{-}\mathsf{A}^{z-}$$

where v_+ is the number of cations, C^{z_+} , of valence z_+ , and v_- is the number of anions, A^{z_-} , of valence z_- . The activity, a, of the electrolyte is then

$$a = a_{\pm}^{\nu +} a_{-}^{\nu -} = a_{\pm}^{\nu} \tag{3.26}$$

where $v = v_+ + v_-$.

In the simple case of a solution of the 1 : 1 electrolyte sodium chloride, the activity will be

$$a = a_{Na}^+ \times a_{Cl}^- = a_{\pm}^2$$

whereas for morphine sulfate, which is a 1:2 electrolyte,

 $a = a_{\text{morph}^{-}}^2 \times a_{SO_4^{2-}} = a_{\pm}^3$

Similarly, we may also define a mean ion activity coefficient, γ_{\pm} , in terms of the individual ionic activity coefficients γ_{\pm} and γ_{-} :

$$\gamma_{\pm}^{\nu} = \gamma_{\pm}^{\nu+} \gamma_{-}^{\nu-}$$
 (3.27
or

$$\gamma_{\pm} = (\gamma_{+}^{\nu+} \gamma_{-}^{\nu-})^{1/\nu} \tag{3.28}$$

$$\gamma_{\pm} = (\gamma_{+}\gamma_{-})^{1/2}$$
(3.29)

Finally, we define a mean ionic molality,
$$m_{\pm}$$
, as

$$m_{\pm}^{\nu} = m_{+}^{\nu_{+}} m_{-}^{\nu_{-}}$$
(3.30)
or
$$m_{\pm} = (m_{+}^{\nu_{+}} m_{-}^{\nu_{-}})^{1/\nu}$$
(3.31)

For a 1 : 1 electrolyte, equation (3.31) reduces to

$$m_{+} = (m_{+}m_{-})^{1/2} = m$$
 (3.32)

that is, mean ionic molality may be equated with the molality of the solution.

The activity of each ion is the product of its activity coefficient and its concentration

 $a_+ = \gamma_+ m_+$ and $a_- = \gamma_- m_-$

so that

$$\gamma_{+} = \frac{a_{+}}{m_{+}}$$
 and $\gamma_{-} = \frac{a_{-}}{m_{-}}$

Expressed as the mean ionic parameters, we have

$$\gamma_{\pm} = \frac{a_{\pm}}{m_{+}} \tag{3.33}$$

Substituting for m_{\pm} from equation (3.31) gives

$$\gamma_{\pm} = \frac{a_{\pm}}{(m_{\pm}^{\nu+} m_{\pm}^{\nu-})^{1/\nu}}$$
(3.34)

This equation applies in any solution, whether the ions are added together, as a single salt, or separately as a mixture of salts. For a solution of a single salt of molality *m*:

 $m_+ = \nu_+ m$ and $m_- = \nu_- m$

Equation (3.34) reduces to

$$\gamma_{\pm} = \frac{a_{\pm}}{m(\nu_{+}^{\nu} \nu_{-}^{\nu)/\nu}}$$
(3.35)

For example, for morphine sulfate, $\nu_+ = 2$, $\nu_- = 1$, and thus

$$\gamma_{\pm} = \frac{\alpha_{\pm}}{(2^2 \times 1)^{1/3} m} = \frac{\alpha_{\pm}}{4^{1/3} m}$$

Activity and chemical potential 65

3.3.3 Solvent activity

Although the phrase 'activity of a solution' usually refers to the activity of the *solute* in the solution as in the preceding section, we also can refer to the activity of the *solvent*. Experimentally, solvent activity a_1 may be determined as the ratio of the vapour pressure p_1 of the solvent in a solution to that of the pure solvent p_1° , that is

$$a_1 = \frac{p_1}{p_1^{\circ}} = \gamma_1 x_1 \tag{3.39}$$

where γ_1 is the solvent activity coefficient and x_1 is the mole fraction of solvent.

The relationship between the activities of the components of the solution is expressed by the Gibbs–Duhem equation

$$x_1 d(\ln a_1) + x_2 d(\ln a_2) = 0 \tag{3.40}$$

which provides a way of determining the

activity of the solute from measurements of vapour pressure.

Water activity and bacterial growth

When the aqueous solution in the environment of a microorganism is concentrated by the addition of solutes such as sucrose, the consequences for microbial growth result mainly from the change in water activity a_w . Every microorganism has a limiting a_w below which it will not grow. The minimum a_w levels for growth of human bacterial pathogens such as streptococci, Klebsiella, Escherichia coli, Corynebacterium, Clostridium perfringens and other clostridia, and Pseudomonas is 0.91.5 *Staphylococcus aureus* can proliferate at an a_w as low as 0.86. Figure 3.2 shows the influence of a_{w} , adjusted by the addition of sucrose, on the growth rate of this microorganism at 35°C and pH 7.0. The control medium, with a water





Reproduced from J. Chirife, G. Scarmato and C. Herszage, Lancet, 319, 560–561 (1982) with permission.

activity value of $a_w = 0.993$, supported rapid growth of the test organism. Reduction of a_w of the medium by addition of sucrose progressively increased generation times and lag periods and lowered the peak cell counts. Complete growth inhibition was achieved at an a_w of 0.858 (195 g sucrose per 100 g water) with cell numbers declining slowly throughout the incubation period.

The results reported in this study explain why the old remedy of treating infected wounds with sugar, honey or molasses is successful. When the wound is filled with sugar, the sugar dissolves in the tissue water, creating an environment of low a_{w} , which inhibits bacterial growth. However, the difference in water activity between the tissue and the concentrated sugar solution causes migration of water out of the tissue, hence diluting the sugar and raising a_w . Further sugar must then be added to the wound to maintain growth inhibition. Sugar may be applied as a paste with a consistency appropriate to the wound characteristics; thick sugar paste is suitable for cavities with wide openings, a thinner paste with the consistency of thin honey being more suitable for instillation into cavities with small openings.

An in vitro study has been reported⁶ of the efficacy of such pastes, and also of those prepared using xylose as an alternative to sucrose, in inhibiting the growth of bacteria commonly present in infected wounds. Polyethylene glycol was added to the pastes as a lubricant and hydrogen peroxide was included in the formulation as a preservative. To simulate the dilution that the pastes invariably experience as a result of fluid being drawn into the wound, serum was added to the formulations in varying amounts. Figure 3.3 illustrates the effects of these sucrose pastes on the colony-forming ability of Proteus mirabilis and shows the reduction in efficiency of the pastes as a result of dilution and the consequent increase of their water activity (see Fig. 3.4). It is clear that P. mirabilis was susceptible to the antibacterial activity of the pastes, even when they were diluted by 50%. It was reported that although $a_{
m w}$ may not be maintained at less



Figure 3.3 The effects of sucrose pastes diluted with serum on the colony-forming ability of *P. mirabilis*. Reproduced from reference 6 with permission.

than 0.86 (the critical level for inhibition of growth of *S. aureus*) for more than 3 hours after packing of the wound, nevertheless clinical experience had shown that twice-daily dressing was adequate to remove **infected** slough from dirty wounds within a few days.

3.3.4 Chemical potential

Properties such as volume, enthalpy, free energy and entropy, which depend on the quantity of substance, are called *extensive* properties. In contrast, properties such as temperature, density and refractive index, which are independent of the amount of material, are referred to as *intensive* properties. The quantity denoting the rate of increase in the magnitude of an extensive property with increase in the number of moles of a substance added to the system at constant temperature

Activity and chemical potential



Figure 3.4 Effects on a_w of adding xylose (solid symbols) and sucrose paste (open symbols) to serum. Reproduced from reference 6 with permission.

and pressure is termed a *partial molar quantity*. Such quantities are distinguished by a bar above the symbol for the particular property. For example,

$$\left. \frac{\partial V}{\partial n_2} \right|_{T,P,n_1} = \overline{V}_2 \tag{3.41}$$

Note the use of the symbol ∂ to denote a partial change which, in this case, occurs under conditions of constant temperature, pressure and number of moles of solvent (denoted by the subscripts outside the brackets).

In practical terms the partial molar volume, \overline{V} , represents the change in the total volume of a large amount of solution when one additional mole of solute is added – it is the effective volume of 1 mole of solute in solution.

Of particular interest is the partial molar free energy, \overline{G} , which is also referred to as the *chemical potential*, μ , and is defined for component 2 in a binary system by

$$\left(\frac{\partial G}{\partial n_2}\right)_{T, P, n_1} = \overline{G}_2 = \mu_2 \tag{3.42}$$

Partial molar quantities are of importance in the consideration of open systems, that is those involving transference of matter as well as energy. For an open system involving two components

67

$$dG = \left(\frac{\partial G}{\partial T}\right)_{P, n_1, n_2} dT + \left(\frac{\partial G}{\partial P}\right)_{T, n_1, n_2} dP + \left(\frac{\partial G}{\partial n_1}\right)_{T, P, n_2} dn_1 + \left(\frac{\partial G}{\partial n_2}\right)_{T, P, n_1} dn_2$$
(3.43)

At constant temperature and pressure equation (3.43) reduces to

 $dG = \mu_1 \, dn_1 + \mu_2 \, dn_2 \tag{3.44}$

:.
$$G = \int dG = \mu_1 n_1 + \mu_2 n_2$$
 (3.45)

The chemical potential therefore represents the contribution per mole of each component to the total free energy. It is the effective free energy per mole of each component in the mixture and is always less than the free energy of the pure substance.

It can readily be shown (see Box 3.5) that the chemical potential of a component in a two-phase system (for example, oil and water), at equilibrium at a fixed temperature and pressure, is identical in both phases. Because of the need for equality of chemical potential at equilibrium, a substance in a system which is not at equilibrium will have a tendency to diffuse spontaneously from a phase in which it has a high chemical potential to another in which it has a low chemical potential. In this respect the chemical *potential* resembles electrical *potential*; hence its name is an apt description of its nature.

Chemical potential of a component in solution

Where the component of the solution is a *non-electrolyte*, its chemical potential in dilute solution at a molality *m*, can be calculated from

$$\mu_2 = \mu^{\Theta} + RT \ln m$$

where

 $\mu^{\circ} = \mu_2^{\circ} + RT \ln M_1 - RT \ln 1000$

and M_1 = molecular weight of the solvent.

(3.47)

Box 3.5 Chemical potential in two-phase systems

Consider a system of two phases, a and b, in equilibrium at constant temperature and pressure. If a small quantity of substance is transferred from phase a to phase b, then, because the overall free energy change is zero, we have

$$\mathrm{d}G_{\mathrm{a}} + \mathrm{d}G_{\mathrm{b}} = 0 \tag{3.46}$$

where dG_a and dG_b are the free energy changes accompanying the transfer of material for each phase. From equation (3.44),

$$dG_a = \mu_a dn_a$$
 and $dG_b = \mu_b dn_b$

and thus

 $\mu_a dn_a + \mu_b dn_b = 0$

A decrease of dn moles of component in phase a leads to an increase of exactly dn moles of this component in phase b, that is

$$dn_{a} = -dn_{b} \tag{3.48}$$

Substitution of equation (3.48) into equation (3.47) leads to the result

$$\mu_{\rm o} = \mu_{\rm b} \tag{3.49}$$

In general, the chemical potential of a component is identical in all the phases of a system at equilibrium at a fixed temperature and pressure.

Box 3.6 Chemical potential of a component in solution

Nonelectrolytes

In dilute solutions of nonvolatile solutes, Raoult's law (see section 2.3,1) can usually be assumed to be obeyed and the chemical potential of the solute is given by equation (3.50):

$$\mu_2 = \mu_2^{\forall} + RI \ln x_2 \tag{3.50}$$

It is usually more convenient to express solute concentration as molality, m, rather than mole fraction, using

$$x_2 = \frac{mM_1}{1000}$$

where M_1 = molecular weight of the solvent. Thus

 $\mu_2 = \mu^{\oplus} + RT \ln m$ (3.51)

where

 $\mu^{\circ} = \mu_2^{\circ} + RT \ln M_1 - RT \ln 1000$

At higher concentrations, the solution generally exhibits significant deviations from Raoult's law and mole fraction must be replaced by activity:

 $\mu_2 = \mu_2^{\Theta} + RT \ln a_2$ (3.52)

 $\mu_2 = \mu_2^{\oplus} + RT \ln \gamma_2 + RT \ln x_2$ (3.53)

Electrolytes

The chemical potential of a strong electrolyte, which may be assumed to be completely dissociated in solution, is equal to the sum of the chemical potentials of each of the component ions. Thus

$$\mu_{+} = \mu_{+}^{\circ} + RT \ln a_{+}$$
 (3.54)
and

and therefore

 $\mu_{-} = \mu_{-}^{\ominus} + RT \ln a$ (3.55)

$$\mu_2 = \mu_2^{\Theta} + RT \ln \alpha \tag{3.56}$$

where $\mu_2^{\scriptscriptstyle \ominus}$ is the sum of the chemical potentials of the ions, each in their respective standard state, i.e.

$$\mu_{2}^{e} = \nu_{+}\mu_{+}^{e} + \nu_{-}\mu_{-}^{e}$$

where ν_+ and ν_- are the number of cations and anions, respectively, and a is the activity of the electrolyte as given in section 3.3.2.

For example, for a 1:1 electrolyte, from equation (3.26),

$$a = a_{\pm}^2$$

Therefore

 $\mu_2 = \mu_2^{\circ} + 2RT \ln a_{\perp}$ From equation (3.33),

$$\therefore \mu_2 = \mu_2^{\oplus} + 2RT \ln m_V$$

In the case of *strong electrolytes*, the chemical potential is the sum of the chemical potentials of the ions. For the simple case of a 1 : 1 electrolyte, the chemical potential is given by

 $\mu_2 = \mu_2^{\Theta} + 2RT \ln m\gamma_{\pm}$

The derivations of these equations are given in Box 3.6.

3.4 Osmotic properties of drug solutions

A nonvolatile solute added to a solvent affects not only the magnitude of the vapour pressure above the solvent but also the freezing point and the boiling point to an extent that is proportional to the relative number of solute molecules present, rather than to the weight concentration of the solute. Properties that are dependent on the number of molecules in solution in this way are referred to as *colligative* properties, and the most important of such properties from a pharmaceutical viewpoint is the osmotic pressure.

3.4.1 Osmotic pressure

Whenever a solution is separated from a solvent by a membrane that is permeable only to solvent molecules (referred to as a semipermeable membrane), there is a passage of solvent across the membrane into the solution. This is the phenomenon of *osmosis*. If the solution is totally confined by a semipermeable membrane and immersed in the solvent, then a pressure differential develops across the membrane, which is referred to as the osmotic *pressure*. Solvent passes through the membrane because of the inequality of the chemical potentials on either side of the membrane. Since the chemical potential of a solvent molecule in solution is less than that in pure solvent, solvent will spontaneously enter the solution until this inequality is removed. The equation which relates the osmotic pressure of the solution, Π , to the solution concentration

is the van't Hoff equation:

$$\Pi V = n_2 R T \tag{3.57}$$

On application of the van't Hoff equation to the drug molecules in solution, consideration must be made of any ionisation of the molecules, since osmotic pressure, being a colligative property, will be dependent on the total number of particles in solution (including the free counterions). To allow for what was at the time considered to be anomalous behaviour of electrolyte solutions, van't Hoff introduced a correction factor, *i*. The value of this factor approaches a number equal to that of the number of ions, ν , into which each molecule dissociates as the solution is progressively diluted. The ratio i/ν is termed the *practical osmotic coefficient*, ϕ .

For nonideal solutions, the activity and osmotic pressure are related by the expression

$$\ln a_1 = \frac{-\nu m M_1}{1000} \phi \tag{3.58}$$

where M_1 is the molecular weight of the solvent and *m* is the molality of the solution. The relationship between the osmotic pressure and the osmotic coefficient is thus

$$\Pi = \left(\frac{RT}{\overline{V}_1}\right) \frac{\nu m M_1}{1000} \phi \tag{3.59}$$

where \overline{V}_1 is the partial molal volume of the solvent.

3.4.2 Osmolality and osmolarity

The experimentally derived osmotic pressure is frequently expressed as the *osmolality* ξ_{m} , which is the mass of solute which, when dissolved in 1 kg of water, will exert an osmotic pressure, Π' , equal to that exerted by 1 mole of an ideal unionised substance dissolved in 1 kg of water. The unit of osmolality is the osmole (abbreviated as osmol), which is the amount of substance that dissociates in solution to form one mole of osmotically active particles, thus 1 mole of glucose (not ionised) forms 1 osmole of solute, whereas 1 mole of NaCl forms 2 osmoles (1 mole of Na⁺ and 1 mole of

Cl⁻). In practical terms, this means that a 1 molal solution of NaCl will have (approximately) twice the osmolality (osmotic pressure) as a 1 molal solution of glucose.

According to the definition, $\xi_m = \Pi/\Pi'$. The value of Π' may be obtained from equation (3.59) by noting that for an ideal unionised substance $\nu = \phi = 1$, and since *m* is also unity, equation (3.59) becomes

$$\Pi' = \left(\frac{RT}{\overline{V}_1}\right) \frac{M_1}{1000}$$

Thus

$$\xi_{\rm m} = \nu m \phi \tag{3.60}$$

EXAMPLE 3.3 Calculation of osmolality

A 0.90% w/w solution of sodium chloride (mol. wt. = 58.5) has an osmotic coefficient of 0.928. Calculate the osmolality of the solution.

Answer

Osmolality is given by equation (3.60) as

 $\xi_{\rm m} = \nu m \phi$

so

 $\xi_{\rm m} = 2 \times \frac{9.0}{58.5} \times 0.928 = 286 \text{ mosmol kg}^{-1}$

Pharmaceutical labelling regulations sometimes require a statement of the osmolarity; for example, the USP 27 requires that sodium chloride injection should be labelled in this way. *Osmolarity* is defined as the mass of solute which, when dissolved in 1 litre of solution, will exert an osmotic pressure equal to that exerted by 1 mole of an ideal unionised substance dissolved in 1 litre of solution. The relationship between osmolality and osmolarity has been discussed by Streng *et al.*⁷

Table 3.1 lists the osmolalities of commonly used intravenous fluids.

3.4.3 Clinical relevance of osmotic effects

Osmotic effects are particularly important from a physiological viewpoint since bio-

fluids	
Solution	Tonicity (mosmol kg ⁻¹)
Vamin 9	700 *
Vamin 9 Glucose	1350
Vamin14	1145
Vamin 14 Electrolyte-free	810
Vamin 18 Electrolyte-free	1130
Vaminolact	510
Vitrimix KV	1130
Intralipid 10% Novum	300
Intralipid 20%	350
Intralipid 30%	310
Intrafusin 22	1400
Hyperamine 30	1450
Gelofusine	279°
Hyperamine 30	1450
Lipofundin MCT/LCT 10%	345°
Lipofundin MCT/LCT 20%	380°
Nutriflex 32	1400°
Nutriflex 48	2300°
Nutriflex 70	2100°
Sodium Bicarbonate Intravenous Infu	sion BP
8.4% w/v	2000°
4.2% w/v	1000°

Table 3.1 Tonicities (osmolalities) of introvenous

^a Osmolarity (mosmol dm⁻³).

logical membranes, notably the red blood cell membrane, behave in a manner similar to that of semipermeable membranes. Consequently, when red blood cells are immersed in a solution of greater osmotic pressure than that of their contents, they shrink as water passes out of the cells in an attempt to reduce the chemical potential gradient across the cell membrane. Conversely, on placing the cells in an aqueous environment of lower osmotic pressure, the cells swell as water enters and eventually lysis may occur. It is an important consideration, therefore, to ensure that the effective osmotic pressure of a solution for injection is approximately the same as that of blood serum. This effective osmotic pressure, which is termed the tonicity, is not always identical to the osmolality because it is concerned only with those solutes in solution that can exert an effect on the passage of water through the biological membrane. Solutions that have the same tonicity as blood serum are

said to be *isotonic* with blood. Solutions with a higher tonicity are *hypertonic* and those with a lower tonicity are termed *hypotonic* solutions. Similarly, in order to avoid discomfort on administration of solutions to the delicate membranes of the body, such as the eyes, these solutions are made isotonic with the relevant tissues.

The osmotic pressures of many of the products of Table 3.1 are in excess of that of plasma (291 mosmol dm⁻³). It is generally recommended that any fluid with an osmotic pressure above 550 mosmol dm-3 should not be infused rapidly as this would increase the incidence of venous damage. The rapid infusion of marginally hypertonic solutions (in the range 300-500 mosmol dm⁻³) would appear to be clinically practicable; the higher the osmotic pressure of the solution within this range, the slower should be its rate of infusion to avoid damage. Patients with centrally inserted lines are not normally affected by limits on tonicity as infusion is normally slow and dilution is rapid.

Certain oral medications commonly used in the intensive care of premature infants have very high osmolalities. The high tonicity of enteral feedings has been implicated as a cause of necrotising enterocolitis (NEC). A higher frequency of gastrointestinal illness including

NEC has been reported⁸ among premature infants fed undiluted calcium lactate than among those fed no supplemental calcium or calcium lactate eluted with water or formula. White and Harkavy⁹ have discussed a similar case of the development of NEC following medication with calcium glubionate elixir. These authors have measured osmolalities of several medications by freezing point depression and compared these with the osmolalities of analogous intravenous (i.v.) preparations (see Table 3.2). Except in the case of digoxin, the osmolalities of the i.v. preparations were very much lower than those of the corresponding oral preparations despite the fact that the i.v. preparations contained at least as much drug per millilitre as did the oral forms. This striking difference may be attributed to the additives, such as ethyl alcohol, sorbitol and propylene glycol, which make a large contribution to the osmolalities of the oral preparations. The vehicle for the i.v. digoxin consists of 40% propylene glycol and 10% ethyl alcohol with calculated osmolalities of 5260 and 2174 mosmol kg⁻¹ respectively, thus explaining the unusually high osmolality of this i.v. preparation. These authors have recommended that extreme caution should be exercised in the administration of these oral preparations and perhaps any medication in a

Table 3.2 Measured and calculated osmo	lalities of drugs ^a		
Drug (route)	Concentration of drug	Mean measured osmolality (mosmol kg ⁻¹)	Calculated available milliosmoles in 1 kg of drug preparation ^b
Theophylline elixir (oral)	$80 \text{ mg}/15 \text{ cm}^3$	>3000	4980
Aminophylline (i.v.)	25 mg cm^{-3}	116	200
Calcium glubionate (oral)	115 mg/5 cm ³	>3000	2270
Calcium gluceptate (i.v.)	90 mg/5 cm ³	507	950
Digoxin elixir	25 mg dm ⁻³	>3000	4420
Digoxin (i.v.)	100 mg dm ⁻³	>3000	9620
Dexamethasone elixir (oral)	0.5 mg/5 cm ³	>3000	3980
Dexamethasone sodium phosphate (i.v.)	4 mg cm^{-3}	284	312

° Reproduced from reference 9.

^b This would be the osmolality of the drug if the activity coefficient were equal to 1 in the full-strength preparation. The osmolalities of serial dilutions of the drug were plotted against the concentrations of the solution, and a least-squares regression line was drawn. The value for the osmolality of the full-strength solution was then estimated from the line. This is the 'calculated available milliosmoles'.

syrup or elixir form when the infant is at risk from necrotising enterocolitis. In some cases the osmolality of the elixir is so high that even mixing with infant formula does not reduce the osmolality to a tolerable level. For example, when a clinically appropriate dose of dexamethasone elixir was mixed in volumes of formula appropriate for a single feeding for a 1500 g infant, the osmolalities of the mixes increased by at least 300% compared to formula alone (see Table 3.3).

Volatile anaesthetics

The aqueous solubilities of several volatile anaesthetics can be related to the osmolarity of the solution.¹⁰ The inverse relationship between solubility (expressed as the liquid/gas partition coefficient) of those anaesthetics and the osmolarity is shown in Table 3.4.

These findings have practical applications for the clinician. Although changes in serum

osmolarity within the physiological range (209–305 mosmol dm⁻³) have only a small effect on the liquid/gas partition coefficient, changes in the serum osmolarity and the concentration of serum constituents at the extremes of the physiological range may significantly decrease the liquid/gas partition coefficient. For example, the blood/gas partition coefficient of isoflurane decreases significantly after an infusion of mannitol. This may be attributed to both a transient increase in the osmolarity of the blood and a more prolonged decrease in the concentration of serum constituents caused by the influx of water due to the osmotic gradient.

Rehydration solutions

An interesting application of the osmotic effect has been in the design of rehydration solutions. During the day the body moves many litres of fluid from the blood into the

Drug (dose)	Volume of drug (cm ³) + volume of formula (cm ³)	Mean measured osmolality (mosmol kg ⁻¹)
Infant formula	-	292
Theophylline elixir, 1 mg kg ⁻¹	0.3 + 15	392
	0.3 + 30	339
Calcium glubionate syrup, 0.5 mmol kg ⁻¹	0.5 + 15	378
	0.5 + 30	330
Digoxin elixir, 5 µg kg ⁻¹	0.15 + 15	347
	0.15 + 30	322
Dexamethasone elixir, 0.25 mg kg ⁻¹	3.8 + 15	1149
0.0	3.8 + 30	791

Table 3.4	Liquid/gas partition	n coefficients of	anaesthetics ir	n four	aqueous solutions at 37°Cª
-----------	----------------------	-------------------	-----------------	--------	----------------------------

Solution	Osmolarity	Partition coefficient			
	(mosinor din -)	Isoflurane	Enflurane	Halothane	Methoxyflurane
Distilled H ₂ O Normal saline Isotonic heparin (1000 U cm ⁻³)	0 308 308	0.626 ± 0.05 0.590 ± 0.01 0.593 ± 0.01	0.754 ± 0.06 0.713 ± 0.01 0.715 ± 0.01	0.859 ± 0.02 0.825 ± 0.02 -	4.33 ± 0.5 4.22 ± 0.30 4.08 ± 0.22
Mannitol (20%)	1098	0.476 ± 0.023	0.575 ± 0.024	0.747 ± 0.03	3.38 ± 0.14
Reproduced from referen	nce 10		1 and 1 and 1		

intestine and back again. The inflow of water into the intestine, which aids the breakdown of food, is an osmotic effect arising from the secretion of Cl⁻ ions by the crypt cells of the intestinal lining (see section 9.2.2) into the intestine. Nutrients from the food are taken up by the villus cells in the lining of the small intestine. The villus cells also absorb Na⁺ ions, which they pump out into the extracellular spaces, from where they return to the circulation. As a consequence of this flow of Na⁺, water and other ions follow by osmotic flow and hence are also transferred to the blood. This normal functioning is disrupted by diarrhoea-causing microorganisms which either increase the Cl⁻-secreting activity of the crypt cells or impair the absorption of Na+ by the villus cells, or both. Consequently, the fluid that is normally returned to the blood across the intestinal wall is lost in watery stool. If untreated, diarrhoea can eventually lead to a severe decline in the volume of the blood, the circulation may become dangerously slow, and death may result.

Oral rehydration therapy

Treatment of dehydration by oral rehydration therapy (ORT) is based on the discovery that the diarrhoea-causing organisms do not usually interfere with the carrier systems which bring sodium and glucose simultaneously into the villus cells from the intestinal cavity. This 'cotransport' system only operates when both sodium and glucose are present. The principle behind ORT is that if glucose is mixed into an electrolyte solution it activates the co-transport system, causing electrolyte and then water to pass through the intestinal wall and to enter the blood, so minimising the dehydration.

ORT requires administration to the patient of small volumes of fluid throughout the day (to prevent vomiting); it does not reduce the duration or severity of the diarrhoea, it simply replaces lost fluid and electrolytes. Let us examine, using the principles of the osmotic effect, two possible methods by which the process of fluid uptake from the intestine might be speeded up. It might seem reasonable to suggest that more glucose should be added to the formulation in an attempt to

enhance the co-transport system. If this is done, however, the osmolarity of the glucose will become greater than that of normal blood, and water would now flow from the blood to the intestine and so exacerbate the problem. An alternative is to substitute starches for simple glucose in the ORT. When these polymer molecules are broken down in the intestinal lumen they release many hundreds of glucose molecules, which are immediately taken up by the co-transport system and removed from the lumen. The effect is therefore as if a high concentration of glucose were administered, but because osmotic pressure is a colligative property (dependent on the number of molecules rather than the mass of substance), there is no associated problem of a high osmolarity when starches are used. The process is summarised in Fig. 3.5. A similar effect is achieved by the addition of proteins, since there is also a co-transport mechanism whereby amino acids (released on breakdown of the proteins in the intestine) and Na⁺ ions are simultaneously taken up by the villus cells.

This process of increasing water uptake from the intestine has an added appeal since the source of the starch and protein can be cereals, beans and rice, which are likely to be available in the parts of the world where problems arising from diarrhoea are most prevalent. Food-based ORT offers additional advantages: it can be made at home from low-cost ingredients and can be cooked, which kills the pathogens in water.

3.4.4 Preparation of isotonic solution

Since osmotic pressure is not a readily measurable quantity, it is usual to make use of the relationship between the colligative properties and to calculate the osmotic pressure from a more easily measured property such as the freezing point depression. In so doing, however, it is important to realise that the red blood cell membrane is not a perfect semipermeable membrane and allows through small molecules such as urea and ammonium chloride. Therefore, although the quantity of each substance required for an isotonic



Figure 3.5 How osmosis affects the performance of solutions used in oral rehydration therapy (ORT).

solution may be calculated from freezing point depression values, these solutions may cause cell lysis when administered.

It has been shown that a solution which is isotonic with blood has a freezing point depression, $\Delta T_{\rm f}$, of 0.52°C. One has therefore to adjust the freezing point of the drug solution to this value to give an isotonic solution. Freezing point depressions for a series of compounds are given in reference texts^{1,11}

Eyenovia Exhibit 1053, Page 37 of 55

75

and it is a simple matter to calculate the concentration required for isotonicity from these values. For example, a 1% NaCl solution has a freezing point depression of 0.576°C. The percentage concentration of NaCl required to make isotonic saline solution is therefore $(0.52/0.576) \times 1.0 = 0.90\%$ w/v.

With a solution of a drug, it is not of course possible to alter the **drug** concentration in this manner, and an adjusting substance must be added to achieve isotonicity. The quantity of adjusting substance can be calculated as shown in Box 3.7

Box 3.7 Preparation of isotonic solutions

If the drug concentration is x g per 100 cm³ solution, then

 $\Delta T_{\rm f}$ for drug solution = $x \times (\Delta T_{\rm f} \text{ of } 1\% \text{ drug solution}) = a$

Similarly, if w is the weight in grams of adjusting substance to be added to 100 cm³ of drug solution to achieve isotonicity, then

 $\Delta T_{\rm f} \text{ for adjusting solution}$ $= w \times (\Delta T_{\rm f} \text{ of } 1\% \text{ adjusting substance})$ $= w \times b$ For an isotonic solution, $a + (w \times b) = 0.52$ $\therefore w = \frac{0.52 - a}{b}$ (3.61)

EXAMPLE 3.4 Isotonic solutions

Calculate the amount of sodium chloride which should be added to 50 cm^3 of a 0.5% w/v solution of lidocaine hydrochloride to make a solution isotonic with blood serum.

Answer

From reference lists, the values of *b* for sodium chloride and lidocaine hydrochloride are 0.576°C and 0.130°C, respectively.

From equation (3.61) we have

 $a = 0.5 \times 0.130 = 0.065$

Therefore,

ı

$$v = \frac{0.52 - 0.065}{0.576} = 0.790 \text{ g}$$

Therefore, the weight of sodium chloride to be added to 50 cm^3 of solution is 0.395 g.

3.5 Ionisation of drugs in solution

Many drugs are either weak organic acids (for example, acetylsalicylic acid [aspirin]) or weak organic bases (for example, procaine), or their salts (for example, ephedrine hydrochloride). The degree to which these drugs are ionised in solution is highly dependent on the pH. The exceptions to this general statement are the nonelectrolytes, such as the steroids, and the quaternary ammonium compounds, which are completely ionised at all pH values and in this respect behave as strong electrolytes. The extent of ionisation of a drug has an important effect on its absorption, distribution and elimination and there are many examples of the alteration of pH to change these properties. The pH of urine may be adjusted (for example by administration of ammonium chloride or sodium bicarbonate) in cases of overdosing with amfetamines, barbiturates, narcotics and salicylates, to ensure that these drugs are completely ionised and hence readily excreted. Conversely, the pH of the urine may be altered to prevent ionisation of a drug in cases where reabsorption is required for therapeutic reasons. Sulfonamide crystalluria may also be avoided by making the urine alkaline. An understanding of the relationship between pH and drug ionisation is of use in the prediction of the causes of precipitation in admixtures, in the calculation of the solubility of drugs and in the attainment of optimum bioavailability by maintaining a certain ratio of ionised to unionised drug. Table 3.5 shows the nominal pH values of some body fluids and sites, which are useful in the prediction of the percentage ionisation of drugs in vivo.

3.5.1 Dissociation of weakly acidic and basic drugs and their salts

According to the Lowry-Brønsted theory of acids and bases, an acid is a substance which

and sites"	
Site	Nominal pH
Aqueous humour	7.21
Blood, arterial	7.40
Blood, venous	7.39
Blood, maternal umbilical	7.25
Cerebrospinal fluid	7.35
Duodenum	5.5
Faeces ^b	7.15
lleum, distal	8.0
Intestine, microsurface	5.3
Lacrimal fluid (tears)	7.4
Milk, breast	7.0
Muscle, skeletal ^c	6.0
Nasal secretions	6.0
Prostatic fluid	6.45
Saliva	6.4
Semen	7.2
Stomach	1.5
Sweat	5.4
Urine, temale	5.8
Urine, male	5.7
Vaginal secretions, premenopause	4.5
Vaginal secretions, postmenopause	7.0

Table 3.5 Nominal pH values of some body fluids

° Reproduced from D. W. Newton and R. B. Kluza, Drug Intell. Clin. Pharm., 12, 547 (1978).

^b Value for normal soft, formed stools, hard stools tend to be more

alkaline, whereas watery, unformed stools are acidic.

^c Studies conducted intracellularly in the rat.

will donate a proton and a base is a substance which will accept a proton. Thus the dissociation of acetylsalicylic acid, a weak acid, could be represented as in Scheme 3.1. In this equilibrium, acetylsalicylic acid acts as an acid, because it donates a proton, and the

acetylsalicylate ion acts as a base, because it accepts a proton to yield an acid. An acid and base represented by such an equilibrium is said to be a conjugate acid-base pair.

Scheme 3.1 is not a realistic expression, however, since protons are too reactive to exist independently and are rapidly taken up by the solvent. The proton-accepting entity, by the Lowry-Brønsted definition, is a base, and the product formed when the proton has been accepted by the solvent is an acid. Thus a second acid-base equilibrium occurs when the solvent accepts the proton, and this may be represented by

$$H_2O + H^+ \rightleftharpoons H_3O^+$$

The overall equation on summing these equations is shown in Scheme 3.2, or, in general,

$$HA + H_2O \Longrightarrow A^- + H_3O^+$$

By similar reasoning, the dissociation of benzocaine, a weak base, may be represented by the equilibrium

$$NH_2C_6H_5COOC_2H_5 + H_2O$$

base 1 acid 2

 \Rightarrow NH₃⁺C₆H₅COOC₂H₅ + OH⁻ acid 1 base 2

or, in general,

$$B + H_2 O \rightleftharpoons BH^+ + OH^-$$

Comparison of the two general equations shows that H₂O can act as either an acid or a base. Such solvents are called amphiprotic solvents.



Scheme 3.2

Eyenovia Exhibit 1053, Page 39 of 55

Salts of weak acids or bases are essentially completely ionised in solution. For example, ephedrine hydrochloride (salt of the weak base ephedrine, and the strong acid HCl) exists in aqueous solution in the form of the conjugate acid of the weak base, $C_6H_5CH(OH)CH(CH_3)$ $N^+H_2CH_3$, together with its Cl⁻ counterions. In a similar manner, when sodium salicylate (salt of the weak acid salicylic acid, and the strong base NaOH) is dissolved in water, it ionises almost entirely into the conjugate base of salicylic acid, $HOC_6H_5COO^-$, and Na⁺ ions.

The conjugate acids and bases formed in this way are, of course, subject to acid-base equilibria described by the general equations above.

3.5.2 The effect of pH on the ionisation of weakly acidic or basic drugs and their salts

If the ionisation of a weak acid is represented as described above, we may express an equilibrium constant as follows:

$$K_a = \frac{a_{\rm H_3O^+} \times a_{\rm A^-}}{a_{\rm HA}}$$
(3.62)

Assuming the activity coefficients approach unity in dilute solution, the activities may be replaced by concentrations:

$$K_{a} = \frac{[H_{3}O^{+}][A^{-}]}{[HA]}$$
(3.63)

 K_a is variously referred to as the *ionisation* constant, dissociation constant, or acidity constant for the weak acid. The negative logarithm of K_a is referred to as pK_a , just as the negative logarithm of the hydrogen ion concentration is called the pH. Thus

$$pK_a = -\log K_a \tag{3.64}$$

Similarly, the *dissociation constant* or *basicity constant* for a weak base is

$$K_{\rm b} = \frac{a_{\rm OH^-} \times a_{\rm BH^+}}{a_{\rm B}} \approx \frac{[\rm OH^-] \, [\rm BH^+]}{[\rm B]}$$
(3.65)

and

$$pK_{\rm b} = -\log K_{\rm b} \tag{3.66}$$

lonisation of drugs in solution

77

The pK_a and pK_b values provide a convenient means of comparing the strengths of weak acids and bases. The lower the pK_a , the stronger the acid; the lower the pK_b , the stronger is the base. The pK_a values of a series of drugs are given in Table 3.6. pK_a and pK_b values of conjugate acid–base pairs are linked

Box 3.8 The degree of ionisation of weak acids and bases

Weak acids

Taking logarithms of the expression for the dissociation constant of a weak acid (equation 3.63)

$$-\log K_{a} = -\log [H_{3}O^{+}] - \log \frac{[A^{-}]}{[HA]}$$

which can be rearranged to

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$
(3.70)

Equation (3.70) may itself be rearranged to facilitate the direct determination of the molar percentage ionisation as follows:

$$[HA] = [A^{-}] \text{ antilog}(pK_{a} - pH)$$

Therefore,

percentage ionisation =
$$\frac{[A^-]}{[HA] + [A^-]} \times 100$$

percentage ionisation = $\frac{100}{1 + \text{antilog} (pK_a - pH)}$ (3.71)

Weak bases

An analogous series of equations for the percentage ionisation of a weak base may be derived as follows. Taking logarithms of equation (3.65) and rearranging gives

$$-\log K_b = -\log [OH^-] - \log \frac{[BH^+]}{[B]}$$

Therefore,

$$pH = pK_w - pK_b - \log \frac{[BH^+]}{[B]}$$
 (3.72)

Rearranging to facilitate calculation of the percentage* ionisation leads to

percentage ionisation =
$$\frac{100}{1 + antilog(pH - pK_w + pK_b)}$$
(3.73)

Compound	-	V	<u> </u>			
Compound	p	K _a	Compound		pK _o	
	Acid	Base		Acid	Base	
Acebutolol	-	9.2	Diamorphine		7.6	
Acetazolamide	-	7.2, 9.0	Diazepam	_	3.4	
Acetylsalicylic acid	3.5	-	Diclofenac	4.0	-	
Aciclovir		2.3, 9.3	Diethylpropion	_	87	
Adrenaline	9.9	8.5	Diltigzem		8.0	
Adriamycin	-	8.2	Diphenhydramine		0.0	
Allopurinol	9.4 (10.2) ^b	-	Disopyramide		2.1	
Alphaprodine	-	8.7	Dithranol		0.4	
Alprenolol	-	9.6	Doxenin		7.4	
Amikacin	_	8.1	Doxorubicin		0.0	
p-Aminobenzoic acid	49	2.4	Doxerveline	-	8.2, 10.2	
Aminophylline		5.0	Englandi	1.1	3.4, 9.3	
Amitriptyline	5.29/ 100	0.0	Englight	_	5.5	
Amiodarone		7.4	Enoxacin	6.3	8.6	
Amovicillin	247404	0.0	Ergometrine	-	6.8	
Ampicillin	2.4, 7.4, 7.0	7.0	Ergotamine	-	6.4	
Anomorphiss	2.5	7.2	Erythromycin	-	8.8	
Apomorphine	8.9	7.0	Famotidine		6.8	
Atenoioi	-	9.6	Fenoprofen	4.5		
Ascorbic acid	4.2, 11.6		Flucloxacillin	2.7	-	
Atropine	-	9.9	Flufenamic acid	3.9	-	
Azapropazone	<1.8	6.6	Flumequine	6.5	_	
Azathioprine	8.2		Fluorouracil	8.0. 13.0	_	
Benzylpenicillin	2.8	-	Fluphenazine	-	3981	
Benzocaine	-	2.8	Flurazepam	82	10	
Bupivacaine	-	8.1	Flurbiprofen	4.3	1.7	
Captopril	3.5	-	Eurosemide	3.0		
Cefadroxil	7.6	2.7	Glibenclamide	53	and the second	
Cefalexin	7.1	2.3	Guanethidino	0.0	11.0	
Cefaclor	7.2	27	Guanovan	-	11.9	
Celiprolol	-	97	Haloporidat	-	12.3	
Cetirizine	29	22.80	Havebashital	-	8.3	
Chlorambucil	4 5 11 91b	2.2, 0.0		8.3		
Chloramphenicol	4.0 (4.7)	5.5	nyaraiazine		0.5, 7.1	
Chlorcyclizine		0.0	louproren	4.4	1	
Chlordiazenovide		0.2	Imipromine	-	9.5	
Chloroquino	-	4.8	Indometacin	4.5	-	
Chlorothiazido		0.1, 9.9	Isoniazid	2.0, 3.9	-	
Chlorohonamine	0.5	9.5	Ketoproten	4.0	÷	
Chlorenamine	-	9.0	Labetalol	7.4	9.4	
Chlorenen i		9.3	Levodopa	2.3, 9.7, 13.	4 –	
Chlorpropamide	-	4.9	Lidocaine	-	7.94 (26°C),	
	-	8.8			7.55 (36°C)	
	-	6.8	Lincomycin		7.5	
	-	8.3	Maprotiline	-	10.2	
lindamycin	-	7.5	Meclofenamic acid	4.0	-	
Cocaine	-	8.5	Metoprolol	-	97	
Codeine	-	8.2	Methadone	1	83	
Cyclopentolate	-	7.9	Methotrexate	3818	5.4	
Jaunomycin	-	8.2	Metronidazole	0.0, 4.0	5.0	
Desipramine	_	10.2	Minocycline	7.0	2.3	
Dextromethorphan	-	8.3	Minocycline	7.8	2.8, 5.0, 9.5 continued	

Table 3.6 (continue	ed)	t top i			
Compound	p	Ka	Compound	1 - 13	pK _a
	Acid	Base		Acid	Base
Minoxidil	-	4.6	Prazocin	-	6.5
Morphine	o.u (prienoi)		Prochlorporazino		0.0 3781
Nadolol	27	7./	Promozino		0.7,0.1
Natcillin	Z./	-	Promothazina	-	0.1
Nalidixic acia	0.4	7.9	Propranolol	_	2.1
Nalorphine		7.0	Quinidino	-	1283
Naloxone	-	0.1	Quinine	_	4.2, 0.5
Naltrexone	9.5	0.1	Ranitidino	-	4.2, 0.0
Naproxen	4.2	7.0	Satalal	83	2.7, 0.2
Nitroturanioin	10.8	3213116	Sulfadiazine	6.5	2.0
Nitrazepam	6.2	0.4	Sulfaquanidino	121	2.0
Norfloxacin	0.2	0.7	Sulfamorazino	71	2.0
Nortriptyline	1201	7./	Sulfathiazolo	7.1	2.5
Novobiocin	4.3, 7.1	63	Tamovifon	7.1	8.0
	0.1	0.5	Tomazonam		1.6
Oxonnic dela	0.0	0.5	Tonovicam	1.1	53
Oxprenoioi		9.5	Terfenadine	1.1	0.5
Oxycodone	72	2201	Tetracaine	1000	9.5
Oxytetracycline	7.5	0.0, 7.1	Tetracucline	77	3305
Pentazocine	-	0.0	Theophyllipo	8.6	3.5
Perniaine	-	8.5	Thiopental	7.5	0.0
Phenazocine	83	0.5	Timolol	7.5	0 2 18 81b
Phenyloin	0.5	20.81	Tolbutamido	53	7.2 (0.0)
Physosngmine	-	1.6.7.1	Triflupromazino	2.0	0.2
Pindolol		8.8	Trimethoprin	-	7.2
Pindoloi	-	5608	Valproato	5.0	1.2
Piperazine	23	5.0, 9.0	Veranamil	5.0	8.8
Polymywin R	2.5	80	Warfarin	5 1	0.0
r olymyxin b		0.7	a a di di di li	5.1	1.5

^a For a more complete list see: D. W. Newton and R. B. Kluza, Drug Intell. Clin. Pharm., 12, 547 (1978); G. C. Raymond and J. L. Born, Drug Intell. Clin. Pharm., 20, 683 (1986); D. B. Jack, Handbook of Clinical Pharmacokinetic Data, Macmillan, London, 1992; The Pharmaceutical Codex 12th edn, Pharmaceutical Press, London, 1994.

^b Values in parentheses represent alternative values from the literature.

by the expression

$$pK_a + pK_b = pK_w \tag{3.67}$$

where pK_w is the negative logarithm of the dissociation constant for water, K_w . K_w is derived from consideration of the equilibrium

$$H_2O + H_2O \Longrightarrow H_3O^+ + OH^-$$

where one molecule of water is behaving as the weak acid or base and the other is behaving as the solvent. Then

$$K = \frac{a_{\rm H_3O^*} \times a_{\rm OH^-}}{a_{\rm H_2O}^2} \approx \frac{[\rm H_3O^+] [\rm OH^-]}{[\rm H_2O]^2} \qquad (3.68)$$

The concentration of molecular water is considered to be virtually constant for dilute aqueous solutions. Therefore

$$K_{\rm w} = [{\rm H}_3 {\rm O}^+][{\rm O}{\rm H}^-]$$
 (3.69)

where the dissociation constant for water (*the ionic product*) now incorporates the term for molecular water and has the values given in Table 3.7.

Table 3.7 Ionic product for water				
Temperature (°C)	$K_{\rm w} \times 10^{14}$	pK _w		
0	0.1139	14.94		
10	0.2920	14.53		
20	0.6809	14.17		
25	1.008	14.00		
30	1.469	13.83		
40	2.919	13.54		
50	5.474	13.26		
60	9.614	13.02		
70	15.1	12.82		
80	23.4	12.63		

When the pH of an aqueous solution of the weakly acidic or basic drug approaches the pK_a or $pK_{b'}$ there is a very pronounced change in the ionisation of that drug. An expression that enables predictions of the pH dependence of the degree of ionisation to be made can be derived as shown in Box 3.8. The influence of pH on the percentage ionisation may be determined for drugs of known pK_a using Table 3.8.

EXAMPLE 3.5 Calculation of percentage ionisation

Calculate the percentage of cocaine existing as the free base in a solution of cocaine hydrochloride at pH 4.5, and at pH 8.0. The pK_b of cocaine is 5.6.

Answer

From equation (3.73): At pH 4.5:

percentage ionisation $= \frac{100}{1 + \text{antilog}(4.5 - 14.0 + 5.6)}$ $= \frac{100}{1.000126}$ = 99.99%

Thus the percentage existing as cocaine base = 0.01%.

At pH 8.0:

percentage ionisation $= \frac{100}{1 + \operatorname{antilog}(8.0 - 14.0 + 5.6)}$ $= \frac{100}{1.398}$ = 71.53%

Thus the percentage existing as cocaine base = 28.47%

If we carry out calculations such as those of Example 3.5 over the whole pH range for both acidic and basic drugs, we arrive at the graphs shown in Fig. 3.6. Notice from this figure that

• The basic drug is virtually completely ionised at pH values up to 2 units below its pK_a, and virtually completely unionised at pH values greater than 2 units above its pK_a.



Figure 3.6 Percentage ionisation of weakly acidic and weakly basic drugs as a function of pH.

Table 3.8 Pe	ercentage ionisation c		ompounas as a		
	At pH at	pove pK _a		At pH belo	ow pK _a
pH-pK _a	If anionic	If cationic	pKa – pH	If anionic	If cationic
60	99.999 90	0.000 099 9	0.1	44.27	55.73
5.0	99.999 00	0.000 999 9	0.2	38.68	61.32
10	99.990 0	0.009 999 0	0.3	33.39	66.61
-	-	-	0.4	28.47	71.53
-	-	100	0.5	24.03	75.97
3.5	99.968	0.031 6		-	-
3.4	99.960	0.039 8	.=.	-	-
3.3	99.950	0,050 1	0.6	20.07	79.93
3.2	99.937	0.063 0	0.7	16.63	83.37
3.1	99.921	0.079 4	0.8	13.70	86.30
-	-	-	0.9	11.19	88.81
-	-	-	1.0	9.09	90.91
3.0	99.90	0.099 9	_	-	-
2.9	99.87	0.1257		- 7.04	- 02.44
2.8	99.84	0.100.1	1.1	7.30	92.04
2./	99.60	0.199 1	1.2	J.93 4 77	94.07
2.0	77.7J	0.230 3	1.5	3.83	96.17
-	-	3	1.4	3.07	96.93
2.5	99.68	0.315.2	-	-	-
2.0	99.60	0.396 6	_	-	-
2.3	99.50	0.498 7	1.6	2.450	97.55
2.2	99.37	0.627 0	1.7	1.956	98.04
2.1	99.21	0.787 9	1.8	1.560	98.44
-	-	-	1.9	1.243	98.76
-	-	-	2.0	0.990	99.01
2.0	99.01	0.990	-	-	-
1.9	98.76	1.243	-	-	-
1.8	98.44	1.560	2.1	0.787 9	99.21
1.7	98.04	1.956	2.2	0.627 0	99.37
1.6	97.55	2.450	2.3	0.498 /	99.50
	-	-	2.4	0.396 6	99.60
- 1.5	-	- 2.07	2.5	0.315 2	99.08
1.5	90.93	3.07	-	-	-
13	90.17	1 77	2.6	0 250 5	99.75
1.0	94.07	5.93	2.0	0.199.1	99.80
1.1	92.64	7.36	2.8	0.158 2	99.84
			2.9	0.125 7	99.87
1.0	90.91	9.09	3.0	0.099 9	99.90
0.9	88.81	11.19	-		20
0.8	86.30	13.70	3.1	0.079 4	99.921
0.7	83.37	16.63	3.2	0.063 0	99.937
0.6	79.93	20.07	3.3	0.050 1	99.950
100	- :		3.4	0.039 8	99.960
0.5	75.97	24.03	3.5	0.031 6	99.968
0.4	71.53	28.47	-	-	-
0.3	66.61	33.39	4.0	0.009 999 0	99.990 0
0.2	61.32	38.68	5.0	0.000 999 9	99.999 00
0.1	55./3	44.2/	6.0	0.000 099 9	99.999 90
0	50.00	50.00	-	-	100

- The acidic drug is virtually completely unionised at pH values up to 2 units below its pK_a and virtually completely ionised at pH values greater than 2 units above its pK_a.
- Both acidic and basic drugs are exactly 50% ionised at their pK_a values.

3.5.3 Ionisation of amphoteric drugs

Ampholytes (amphoteric electrolytes) can function as either weak acids or weak bases in aqueous solution and have pK_a values corresponding to the ionisation of each group. They may be conveniently divided into two categories – ordinary ampholytes and zwitterionic ampholytes – depending on the relative acidity of the two ionisable groups.^{12, 13}

Ordinary ampholytes

In this category of ampholytes, the pK_a of the acidic group, pK_a^{acidic} , is higher than that of the basic group, pK_a^{basic} , and consequently the first group that loses its proton as the pH is increased is the basic group. Table 3.6 includes several examples of this type of ampholyte. We will consider, as a simple example, the ionisation of *m*-aminophenol (I), which has $pK_a^{\text{acidic}} = 9.8$ and $pK_a^{\text{basic}} = 4.4$.

The steps of the ionisation on increasing pH are shown in the following equilibria:

$$NH_{3}^{+}C_{6}H_{4}OH \rightleftharpoons NH_{2}C_{6}H_{4}OH \rightleftharpoons NH_{2}C_{6}H_{5}O$$

This compound can exist as a cation, as an unionised form, or as an anion depending on the pH of the solution, but because the difference between pK_a^{acidic} and pK_a^{basic} is >2, there will be no simultaneous ionisation of the two groups and the distribution of the species will be as shown in Fig. 3.7. The ionisation pattern will become more complex, however, with drugs in which the difference in pK_a of the two



Structure | *m*-Aminophenol



Figure 3.7 Distribution of ionic species for the ordinary ampholyte *m*-aminophenol.

Redrawn from A. Pagliara, P.-A. Carrupt, G. Caron, P. Gaillard and B. Testa, Chem. Rev., 97, 3385 (1997).

groups is much smaller because of overlapping of the two equilibria.

Zwitterionic ampholytes

This group of ampholytes is characterised by the relation $pK_a^{acidic} < pK_a^{basic}$. The most common examples of zwitterionic ampholytes are the amino acids, peptides and proteins. There are essentially two types of zwitterionic electrolyte depending on the difference between the pK_a^{acidic} and pK_a^{basic} values, ΔpK_a

Large ΔpK_a . The simplest type to consider is that of compounds having two widely separated pK_a values, for example glycine. The pK_a values of the carboxylate and amino groups on glycine are 2.34 and 9.6, respectively and the changes in ionisation as the pH is increased are described by the following equilibria:

$$HOOCCH_2NH_3^+ \rightleftharpoons ^-OOCCH_2NH_3^+ \Leftrightarrow ^-OOCCH_2NH_2^+$$

Over the pH range 3–9, glycine exists in solution predominantly in the form $^{-}OOCCH_2NH_3^+$ Such a structure, having both positive and negative charges on the same molecule, is referred to as a zwitterion and can react both as an acid,

$$^{-}OOCCH_2NH_3^+ + H_2O \rightleftharpoons ^{-}OOCCH_2NH_2 + H_2O$$

or as a base,

$$^{-}$$
OOCCH₂NH₃⁺ + H₂O \rightleftharpoons
 \rightleftharpoons HOOCCH₂NH₂⁺ + OH

This compound can exist as a cation, as a zwitterion, or as an anion depending on the pH of the solution. The two pK_a values of glycine are >2 pH units apart and hence the distribution of the ionic species will be similar to that shown in Fig. 3.7.

At a particular pH, known as the *isoelectric* pH or *isoelectric point*, pH_i , the effective net charge on the molecule is zero. pH_i can be calculated from

$$pH_i = \frac{pK_a^{acidic} + pK_a^{basic}}{2}$$

Small ΔpK_a . In cases where the two pK_a values are $\ll 2$ pH units apart there is overlap of the ionisation of the acidic and basic groups, with the result that the zwitterionic electrolyte can exist in four different electrical states – the cation, the unionised form, the zwitterion, and the anion (Scheme 3.3).

In Scheme 3.3, (ABH)[±] is the zwitterion and, although possessing both positive and negative charges, is essentially neutral. The unionised form, (ABH), is of course also neutral and can be regarded as a tautomer of the zwitterion. Although only two dissociation constants K_a^{acidic} and K_a^{basic} (macrodissociation constants) can be determined experimentally, each of these is composed of individual microdissociation constants because of simultaneous ionisation of the two groups (see section 3.5.5). These microdissociation constants represent equilibria between the cation and zwitterion, the anion and the zwitterion, the cation and the unionised form, and the anion and the unionised form. At pHi, the unionised form and the zwitterion always coexist, but the ratio of the concentrations of each will vary depending on the relative magnitude of the microdissociation constants. The distribution of the ionic species for labetalol which has $pK_a^{acidic} = 7.4$ and $K_a^{basic} = 9.4$ is shown in Fig. 3.8.





Figure 3.8 Distribution of ionic species for the zwitterionic ampholyte labetalol.

Redrawn from A. Pagliara, P.-A. Carrupt, G. Caron, P. Gaillard and B. Testa, Chem. Rev., 97, 3385 (1997).

Examples of zwitterionic drugs with both large and small ΔpK_a values are given in Box 3. 9; others can be noted in Table 3.6.

3.5.4 Ionisation of polyprotic drugs

In the examples we have considered so far, the acidic drugs have donated a single proton. There are several acids, for example citric, phosphoric and tartaric acids, that are capable of donating more than one proton; these compounds are referred to as polyprotic or polybasic acids. Similarly, a polyprotic base is one capable of accepting two or more protons. Many examples of both types of polyprotic drugs can be found in Table 3.6, including the polybasic acids amoxicillin and fluorourocil, and the polyacidic bases pilocarpine, doxorubicin and aciclovir. Each stage of the dissociation may be represented by an equilibrium expression and hence each stage has a distinct pK_a or pK_b value. The dissociation of phosphoric acid, for example, occurs in three stages; thus:

$$\begin{split} H_{3}PO_{4} + H_{2}O \\ \rightleftharpoons H_{2}PO_{4}^{-} + H_{3}O^{+} & K_{1} = 7.5 \times 10^{-3} \\ H_{2}PO_{4}^{-} + H_{2}O \\ \rightleftharpoons HPO_{4}^{2-} + H_{3}O^{+} & K_{2} = 6.2 \times 10^{-8} \\ HPO_{4}^{2-} + H_{2}O \\ \rightleftharpoons PO_{4}^{3-} + H_{3}O^{+} & K_{2} = 2.1 \times 10^{-13} \end{split}$$





3.5.5 Microdissociation constants

The experimentally determined dissociation constants for the various stages of dissociation of polyprotic and zwitterionic drugs are referred to as macroscopic values. However, it is not always easy to assign macroscopic dissociation constants to the ionisation of specific groups of the molecule, particularly when the pK_a values are close together, as discussed in section 3.5.4. The diprotic drug morphine has macroscopic pK_a values of 8.3 and 9.5, arising from ionisation of amino and phenolic groups. Experience suggests that the first pK_a value is probably associated with the ionisation of the amino group and the second with that of the phenolic group; but it is not possible to assign the values of these groups unequivocally and for a more complete picture of the dissociation it is necessary to take into account all possible ways in which the molecule may be ionised and all the possible species present in solution. We may represent the most highly protonated form of morphine, ⁺HMOH, as +O, where the '+' refers to the protonated amino group and the



Scheme 3.4

O refers to the uncharged phenolic group. Dissociation of the amino proton only produces an uncharged form MOH, represented by OO, while dissociation of the phenolic proton gives a zwitterion ⁺HMO⁻, represented by '+-'. The completely dissociated form MO⁻ is represented as O-. The entire dissociation scheme is given in Scheme 3.4.

The constants K_1 , K_2 , K_{12} and K_{21} are termed microdissociation constants and are defined by

$$k_{1} = \frac{[+-][H_{3}O^{+}]}{[+O]} \qquad k_{2} = \frac{[OO][H_{3}O^{+}]}{[+O]}$$
$$k_{12} = \frac{[O-][H_{3}O^{+}]}{[+-]} \qquad k_{21} = \frac{[O-][H_{3}O^{+}]}{[OO]}$$

The micro- and macrodissociation constants are related by the following expressions:

$$K_1 = k_1 + k_2 \tag{3.74}$$

$$\frac{1}{K_2} = \frac{1}{k_{12}} + \frac{1}{k_{21}} \tag{3.75}$$

and

$$K_1 K_2 = k_1 k_{12} = k_2 k_{21} \tag{3.76}$$

Various methods have been proposed whereby the microdissociation constants for the morphine system may be evaluated.¹⁴ Other drugs for which microdissociation constants have been derived include the tetracyclines,¹⁵ doxorubicin,¹⁶ cephalosporin,¹⁷ dopamine¹⁸ and the group of drugs shown in Box 3.9.¹³

3.5.6 pK_a values of proteins

The pK_a values of ionisable groups in proteins and other macromolecules can be significantly different from those of the corresponding groups when they are isolated in solution. The shifts in pK_a values between native and denatured states or between bound and free forms of a complex can cause changes in binding constants or stability of the protein due to pH effects. For example, the acid denaturation of proteins may be a consequence of anomalous shifts of the pK_a values of a small number of amino acids in the native protein.¹⁹ Several possible causes of such shifts have been proposed. They may arise from interactions among ionisable groups on the protein molecule; for example, an acidic group will have its pK_a lowered by interactions with basic groups. Other suggested cases of shifts of pK_a include hydrogen-bonding interactions with nonionisable groups and the degree of exposure to the bulk solvent; for example, an acidic group will have its pK_a increased if it is fully or partially removed from solvent, but the effect may be reversed by strong hydrogen-bonding interactions with other groups.

The calculation of pK_a values of protein molecules thus requires a detailed consideration of the environment of each ionisable group, and is consequently highly complex. An additional complication is that a protein with N ionisable residues has 2^N possible ionisation states; the extent of the problem is apparent when it is realised that a moderately sized protein may contain as many as 50 ionisable groups.

3.5.7 Calculation of the pH of drug solutions

We have considered above the effect on the ionisation of a drug of buffering the solution at given pH values. When these weakly acidic or basic drugs are dissolved in water they will, of course, develop a pH value in their own right. In this section we examine how the pH of drug solutions of known concentration can be simply calculated from a knowledge of the pK_a of the drug. We will consider the way in which one of these expressions may be derived from the expression for the ionisation in solution; the derivation of the other expressions follows a similar route and you may wish to derive these for yourselves.

Weakly acidic drugs

We saw above that the dissociation of these types of drugs may be represented by equation (3.63). We can now express the concentrations of each of the species in terms of the degree of dissociation, α , which is a number with a value between 0 (no dissociation) and 1 (complete dissociation):

$$HA + H_2O \rightleftharpoons A^- + H_3O^+ (1 - \alpha)c \qquad \alpha c \qquad \alpha c$$

where *c* is the initial concentration of the weakly acidic drug in mol dm^{-3} .

Because the drugs are weak acids, α will be very small and hence the term $(1 - \alpha)$ can be approximated to 1. We may therefore write

$$K_{a} = \frac{\alpha^{2} c^{2}}{(1-\alpha)c} \approx \alpha^{2} c \qquad (3.77)$$

Therefore,

$$\alpha = \left(\frac{K_{\rm a}}{c}\right)^{1/2}$$

To introduce pH into the discussion we note that

$$\begin{aligned} \alpha c &= [H_3 O^+] = [H^+] \\ \therefore & [H^+] = (K_a c)^{1/2} \\ \therefore & -\log[H^+] = -\frac{1}{2}\log K_a - \frac{1}{2}\log c \\ pH &= \frac{1}{2}pK_a - \frac{1}{2}\log c \end{aligned}$$
(3.78)

We now have an expression which enables us to calculate the pH of any concentration of the weakly acidic drug provided that its pK_a value is known.

EXAMPLE 3.6 Calculation of the pH of a weak

acid

Calculate the pH of a 50 mg cm⁻³ solution of ascorbic acid (mol. wt = 176.1; $pK_a = 4.17$).

Answer

For a weakly acidic drug,

pH = $\frac{1}{2}$ pK_a - $\frac{1}{2}$ log c c = 50 mg cm⁻³ = 50 g dm⁻³ = 0.2839 mol dm⁻³ ∴ pH = 2.09 + 0.273 = 2.36

Weakly basic drugs

We can show by a similar derivation to that above that the pH of aqueous solutions of weakly basic drugs will be given by

$$pH = \frac{1}{2}pK_{w} + \frac{1}{2}pK_{a} + \frac{1}{2}\log c$$
 (3.79)

EXAMPLE 3.7 Calculation of the pH of a weakly basic drug

Calculate the pH of a saturated solution of codeine monohydrate (mol. wt. = 317.4) given that its $pK_a = 8.2$ and its solubility at room temperature is 1 g in 120 cm³ water.

Answer

Codeine is a weakly basic drug and hence its pH will be given by

 $pH = \frac{1}{2}pK_{w} + \frac{1}{2}pK_{a} + \frac{1}{2}\log c$

where c = 1 g in 120 cm³ = 8.33 g dm⁻³ = 0.02633 mol dm⁻³.

 \therefore pH = 7.0 + 4.1 - 0.790 = 10.31

Drug salts

Because of the limited solubility of many weak acids and weak bases in water, drugs of these types are commonly used as their salts; for example, sodium salicylate is the salt of a weak acid (salicylic acid) and a strong base (sodium hydroxide). The pH of a solution of this type of salt is given by

$$pH = \frac{1}{2}pK_{w} + \frac{1}{2}pK_{a} + \frac{1}{2}\log c$$
(3.80)

Alternatively, a salt may be formed between a weak base and a strong acid; for example, ephedrine hydrochloride is the salt of ephedrine and hydrochloric acid. Solutions of such drugs have a pH given by

$$pH = \frac{1}{2}pK_{a} - \frac{1}{2}\log c$$
 (3.81)

Finally, a salt may be produced by the combination of a weak base and a weak acid, as in the case of codeine phosphate. Solutions of such drugs have a pH given by

$$pH = \frac{1}{2}pK_{w} + \frac{1}{2}pK_{a} - \frac{1}{2}pK_{b}$$
(3.82)

87

Notice that this equation does not include a concentration term and hence the pH is independent of concentration for such drugs.

..... EXAMPLE 3.8 Calculation of the pH of drug salts

Calculate the pH of the following solutions

- (a) 5% oxycodone hydrochloride ($pK_a = 8.9$, mol. wt. = 405.9).
- (b) 600 mg of benzylpenicillin sodium ($pK_a =$ 2.76, mol. wt. = 356.4) in 2 cm^3 of water
 - for injection. chlorphenamine maleate
- (c) 100 mg cm⁻³ (mol. wt. = 390.8) in water for injection $(pK_b \text{ chlorphenamine} = 5.0, pK_a \text{ maleic}$ acid = 1.9).

Answer

(a) Oxycodone hydrochloride is the salt of a weak base and a strong acid, hence

 $pH = \frac{1}{2}pK_a - \frac{1}{2}\log c$

where $c = 50 \text{ g dm}^{-3} = 0.1232 \text{ mol dm}^{-3}$.

:. pH = 4.45 + 0.45 = 4.90

(b) Benzylpenicillin sodium is the salt of a weak acid and a strong base, hence

 $pH = \frac{1}{2}pK_{w} + \frac{1}{2}pK_{a} + \frac{1}{2}\log c$

where c = 600 mg in $2 \text{ cm}^3 = 0.842 \text{ mol}$ dm^{-3} .

 \therefore pH = 7.00 + 1.38 - 0.037 = 8.34

(c) Chlorphenamine maleate is the salt of a weak acid and a weak base, hence

> $pH = \frac{1}{2}pK_{w} + \frac{1}{2}pK_{a} - \frac{1}{2}pK_{b}$ \therefore pH = 7.00 + 0.95 - 2.5 = 5.45

3.5.8 Preparation of buffer solutions

A mixture of a weak acid and its salt (that is, a conjugate base), or a weak base and its conjugate acid, has the ability to reduce the large changes in pH which would otherwise result from the addition of small amounts of acid or alkali to the solution. The reason for the

buffering action of a weak acid HA and its ionised salt (for example, NaA) is that the A⁻ ions from the salt combine with the added H⁺ ions, removing them from solution as undissociated weak acid:

$$A^- + H_3O^+ \rightleftharpoons H_2O + HA$$

Added OH⁻ ions are removed by combination with the weak acid to form undissociated water molecules:

 $HA + OH^{-} \rightleftharpoons H_2O + A^{-}$

The buffering action of a mixture of a weak base and its salt arises from the removal of H⁺ ions by the base B to form the salt and removal of OH⁻ ions by the salt to form undissociated water:

$$B + H_3O^+ \rightleftharpoons H_2O + BH^+$$
$$BH^+ + OH^- \rightleftharpoons H_2O + B$$

The concentration of buffer components required to maintain a solution at the required pH may be calculated using equation (3.70). Since the acid is weak and therefore only very slightly ionised, the term [HA] in this equation may be equated with the total acid concentration. Similarly, the free A⁻ ions in solution may be considered to originate entirely from the salt and the term [A⁻] may be replaced by the salt concentration.

Equation (3.70) now becomes

$$pH = pK_a + \log \frac{[salt]}{[acid]}$$
(3.83)

By similar reasoning, equation (3.72) may be modified to facilitate the calculation of the pH of a solution of a weak base and its salt, giving

$$pH = pK_w - pK_b + \log \frac{[base]}{[salt]}$$
(3.84)

Equations (3.83) and (3.84) are often referred to as the Henderson-Hasselbalch equations.

EXAMPLE 3.9 Buffer solutions

Calculate the amount of sodium acetate to be added to 100 cm³ of a 0.1 mol dm⁻³ acetic acid solution to prepare a buffer of pH 5.20.

Answer

The pK_a of acetic acid is 4.76. Substitution in equation (3.83) gives

$$5.20 = 4.76 + \log \frac{[\text{salt}]}{[\text{acid}]}$$

The molar ratio of [salt]/[acid] is 2.754. Since 100 cm^3 of 0.1 mol dm⁻³ acetic acid contains 0.01 mol, we would require 0.027 54 mol of sodium acetate (2.258 g), ignoring dilution effects.

.........

Equations (3.83) and (3.84) are also useful in calculating the change in pH which results from the addition of a specific amount of acid or alkali to a given buffer solution, as seen from the following calculation in Example 3.10.

EXAMPLE 3.10 Calculation of the pH change in buffer solutions

Calculate the change in pH following the addition of 10 cm^3 of 0.1 mol dm⁻³ NaOH to the buffer solution described in Example 3.9.

Answer

The added 10 cm³ of 0.1 mol dm⁻³ NaOH (equivalent to 0.002 mol) combines with 0.001 mol of acetic acid to produce 0.001 mol of sodium acetate. Reapplying equation (3.83) using the revised salt and acid concentrations gives

$$pH = 4.76 + \log \frac{(0.02754 + 0.001)}{(0.01 - 0.001)} = 5.26$$

The pH of the buffer has been increased by only 0.06 units following the addition of the alkali.

Buffer capacity

The effectiveness of a buffer in reducing changes in pH is expressed as the buffer capacity, β . The buffer capacity is defined by the ratio

$$\beta = \frac{\mathrm{d}c}{\mathrm{d}(\mathrm{pH})} \tag{3.85}$$

where dc is the number of moles of alkali (or

acid) needed to change the pH of 1 dm^3 of solution by an amount d(pH). If the addition of 1 mole of alkali to 1 dm^3 of buffer solution produces a pH change of 1 unit, the buffer capacity is unity.

Equation (3.70) may be rewritten in the form

$$pH = pK_a + \frac{1}{2.303} \ln\left[\frac{c}{c_0 - c}\right]$$
(3.86)

where c_0 is the total initial buffer concentration and c is the amount of alkali added. Rearrangement and subsequent differentiation yield

$$c = \frac{c_0}{1 + \exp[-2.303(\text{pH} - \text{pK}_a)]}$$
(3.87)

Therefore,

$$\beta = \frac{dc}{d(pH)} = \frac{2.303 c_0 \exp[2.303 (pH - pK_a)]}{1 + \exp[2.303 \exp(pH - pK_a)]^2}$$
(3.88)

$$\beta = \frac{2.303 c_0 K_a [H_3 O^+]}{([H_3 O^+] + K_a)^2}$$
(3.89)

EXAMPLE 3.11 Calculation of buffer capacity

Calculate the buffer capacity of the acetic acid–acetate buffer of Example 3.9 at pH 4.0.

Answer

The total amount of buffer components in 100 cm^3 of solution = 0.01 + 0.02754 = 0.03754 moles. Therefore,

 $c_0 = 0.3754 \text{ mol dm}^{-3}$

 pK_a of acetic acid = 4.76. Therefore,

$$K_{a} = 1.75 \times 10^{-5}$$

The pH of the solution = 4.0. Therefore,

$$[H_3O^+] = 10^{-4}$$

Substituting in equation (3.89),

$$\beta = \frac{2.303 \times 0.3754 \times 1.75 \times 10^{-5} \times 10^{-4}}{(10^{-4} + 1.75 \times 10^{-5})^2}$$

= 0.1096

The buffer capacity of the acetic acid-acetate buffer is $0.1096 \text{ mol } dm^{-3}$ per pH unit.

Figure 3.9 shows the variation of buffer capacity with pH for the acetic acid-acetate buffer used in the numerical examples above $(c_0 = 0.3754 \text{ mol dm}^{-3})$ as calculated from equation (3.89). It should be noted that β is at a maximum when pH = pK_a (that is, at pH 4.76). When selecting a weak acid for the preparation of a buffer solution, therefore, the chosen acid should have a pK_a as close as possible to the pH required. Substituting pH = pK_a into equation (3.89) gives the useful result that the maximum buffer capacity is $\beta_{max} = 0.576c_0$, where c_0 is the total buffer concentration.

Buffer solutions are widely used in pharmacy to adjust the pH of aqueous solutions to that required for maximum stability or that needed for optimum physiological effect. Solutions for application to delicate tissues, particularly the eye, should also be formulated at a pH not too far removed from that of the appropriate tissue fluid, as otherwise irritation may be caused on administration. The pH of tears lies between 7 and 8, with an average value of 7.4. Fortunately, the buffer capacity of tears is high and, provided that the solutions to be administered have a low buffer capacity, a reasonably wide range of pH may be tolerated, although there is a difference in the



Figure 3.9 Buffer capacity of acetic acid-acetate buffer (initial concentration = $0.3754 \text{ mol dm}^{-3}$) as a function of pH.

irritability of the various ionic species that are commonly used as buffer components. The pH of blood is maintained at about 7.4 by primary buffer components in the plasma (carbonic acid-carbonate and the acid-sodium salts of phosphoric acid) and secondary buffer components (oxyhaemoglobin-haemoglobin and acid-potassium salts of phosphoric acid) in the erythrocytes. Values of 0.025 and 0.039 mol dm⁻³ per pH unit have been quoted for the buffer capacity of whole blood. Parenteral solutions are not normally buffered, or alternatively are buffered at a very low capacity, since the buffers of the blood are usually capable of bringing them within a tolerable pH range.

Universal buffers

We have seen from Fig. 3.9 that the buffer capacity is at a maximum at a pH equal to the pK_a of the weak acid used in the formulation of the buffer system and decreases appreciably as the pH extends more than one unit either side of this value. If, instead of a single weak monobasic acid, a suitable mixture of polybasic and monobasic acids is used, it is possible to produce a buffer which is effective over a wide pH range. Such solutions are referred to as universal buffers. A typical example is a mixture of citric acid ($pK_{a1} = 3.06$, $pK_{a2} = 4.78$, $pK_{a3} = 5.40$), Na_2HPO_4 (pK_a of conjugate acid $H_2PO_4^- = 7.2$), diethylbarbituric acid ($pK_{a1} = 7.43$) and boric acid ($pK_{a1} = 9.24$). Because of the wide range of pK_a values involved, each associated with a maximum buffer capacity, this buffer is effective over a correspondingly wide pH range (pH 2.4–12).

3.6 Diffusion of drugs in solution

Diffusion is the process by which a concentration difference is reduced by a spontaneous flow of matter. Consider the simplest case of a solution containing a single solute. The solute will spontaneously diffuse from a region of high concentration to one of low concentration. Strictly speaking, the driving force for

Eyenovia Exhibit 1053, Page 52 of 55

diffusion is the gradient of chemical potential, but it is more usual to think of the diffusion of solutes in terms of the gradient of their concentration. Imagine the solution to be divided into volume elements. Although no individual solute particle in a particular volume element shows a preference for motion in any particular direction, a definite fraction of the molecules in this element may be considered to be moving in, say, the x direction. In an adjacent volume element, the same fraction may be moving in the reverse direction. If the concentration in the first volume element is greater than that in the second, the overall effect is that more particles are leaving the first element for the second and hence there is a net flow of solute in the x direction, the direction of decreasing concentration. The expression which relates the flow of material to the concentration gradient (dc/dx) is referred to as Fick's first law:

$$J = -D \frac{\mathrm{d}c}{\mathrm{d}x} \tag{3.90}$$

where *J* is the flux of a component across a plane of unit area and *D* is the diffusion coefficient (or diffusivity). The negative sign indicates that the flux is in the direction of decreasing concentration. *J* is in mol m⁻² s⁻¹, *c* is in mol m⁻³ and *x* is in metres; therefore, the units of *D* are m² s⁻¹.

The relationship between the radius, *a*, of the diffusing molecule and its diffusion coefficient (assuming spherical particles or molecules) is given by the *Stokes–Einstein equation* as

$$D = \frac{RT}{6\pi\eta a N_{\rm A}} \tag{3.91}$$

Table 3.9 shows diffusion coefficients of some p-hydroxybenzoate (paraben) preservatives and typical proteins in aqueous solution. Although the trend for a decrease of D with increase of molecular size (as predicted by equation 3.91) is clearly seen from the data of this table, it is also clear that other factors, such as branching of the p-hydroxybenzoate molecules (as with the isoalkyl derivatives) and the shape of the protein molecules, also affect the diffusion coefficients. The diffusion

 Table 3.9
 Effect of molecular weight on diffusion coefficient (25°C) in aqueous media

Compound	Molecular weight	D (10 ⁻¹⁰ m ² s ⁻¹)
p-Hydroxybenzoates ^a		
Methyl hydroxybenzoate	152.2	8.44
Ethyl hydroxybenzoate	166.2	7.48
n-Propyl hydroxybenzoate	180.2	6.81
lsopropyl hydroxybenzoate	180.2	6.94
n-Butyl hydroxybenzoate	194.2	6.31
Isobutyl hydroxybenzoate	194.2	6.40
n-Amyl hydroxybenzoate	208.2	5.70
Proteins ^b		
Cytochrome c (horse)	12 400	1.28
Lysozyme (chicken)	14 400	0.95
Trypsin (bovine)	24 000	1.10
Albumin (bovine)	66 000	0.46
° From reference 20		

therapeutic peptides and proteins.

coefficients of more complex molecules such as proteins will also be affected by the shape of the molecule, more asymmetric molecules having a greater resistance to flow.

The diffusional properties of a drug have relevance in pharmaceutical systems in a consideration of such processes as the dissolution of the drug and transport through artificial (e.g. polymer) or biological membranes. Diffusion in tissues such as the skin or in tumours is a process which relies on the same criteria as discussed above, even though the diffusion takes place in complex media.

Summary

- We have looked at the meaning of some of the terms commonly used in thermodynamics and how these are interrelated in the three laws of thermodynamics. In particular, we have seen that:
 - *Entropy* is a measure of the disorder or chaos of a system and that processes, such as the melting of a crystal, which result in an increased disorder are

accompanied by an increase in entropy. Since spontaneous processes always produce more disordered systems, it follows that the entropy change for these processes is always positive.

- During a spontaneous change at constant temperature and pressure, there is a decrease in the *free energy* until the system reaches an equilibrium state, when the free energy change becomes zero. The free energy is therefore a measure of the useful work that a system can do; when the system has reached equilibrium it has used up its free energy and consequently no longer has the ability to do any further work; thus *all spontaneous processes are irreversible*.
- There is a simple relation**ship betwee**n free energy change and the equilibrium constant for a reaction from which an equation has been derived for the change of equilibrium constant with temperature.
- If there are no interactions between the components of a solution (ideal solution) then the *activity* equals the concentration; in real solutions the ratio of the activity to the concentration is called the *activity coefficient*.
- The *chemical potential* is the effective free energy per mole of each component of a solution. In general, the chemical potential of a component is identical in all phases of a system at equilibrium at a fixed temperature and pressure.
- Parenteral solutions should be of approximately the same tonicity as blood serum; the amount of adjusting substance which must be added to a formulation to achieve isotonicity can be calculated using the

freezing point depressions of the drug and the adjusting substance.

- The strengths of weakly acidic or basic drugs may be expressed by their pK_a and pK_b values; the lower the pK_a the stronger is the acid; the lower the $pK_{\rm b}$ the stronger is the base. Acidic drugs are completely unionised at pH values up to 2 units below their pK_a and completely ionised at pH values greater than 2 units above their pK_a . Conversely, basic drugs are completely ionised at pH values up to 2 units below their pK_a and completely unionised when the pH is more than 2 units above their pK_a . Both types of drug are exactly 50% ionised at their pK_a values. Some drugs can donate or accept more than one proton and so may have several pK_a values; other drugs can behave as both acids and bases, i.e. they are amphoteric drugs. The pH of aqueous solutions of each of these types of drug and their salts can be calculated from their pK_a and the concentration of the drug.
- A solution of a weak acid and its salt (conjugate base) or a weak base and its conjugate acid acts as a buffer solution. The quantities of buffer components required to prepare buffers solutions of known pH can be calculated from the *Henderson–Hasselbalch equation*. The buffering capacity of a buffer solution is maximum at the pK_a of the weak acid component of the buffer. Universal buffers are mixtures of polybasic and monobasic acids that are effective over a wide range of pH.
 - The drug molecules in solution will spontaneously diffuse from a region of high chemical potential to one of low chemical potential; the rate of diffusion may be calculated from *Fick's law*.

References

- 1. *The Pharmaceutical Codex*, 12th edn, The Pharmaceutical Press, London, 1994
- P. W. Atkins. *Physical Chemistry*, 7th edn, Oxford University Press, 2001
- 3. D. J. Shaw and H. E. Avery. *Physical Chemistry*, Macmillan Education Limited, London, 1994
- J. H. Rytting, S. S. Davis and T. Higuchi. Suggested thermodynamic standard state for comparing drug molecules in structure-activity studies. *J. Pharm. Sci.*, 61, 816–8 (1972)
- J. H. B. Christian. In Water Activity: Influences on Food Quality (ed. L. B. Rockland and G. F. Stewart), Academic Press, New York, 1981, p. 825

- U. Ambrose, K. Middleton and D. Seal. In vitro studies of water activity and bacterial growth inhibition of sucrose-polyethylene glycol 400hydrogen peroxide and xylose-polyethylene glycol 400- hydrogen peroxide pastes used to treat infected wounds. Antimicrob. Agents Chemother., 35, 1799–803 (1991)
- W. H. Streng, H. E. Huber and J. T. Carstensen. Relationship between osmolality and osmolarity. J. Pharm. Sci., 67, 384–6 (1978)
- D. M. Willis, J. Chabot, I. C. Radde and G. W. Chance. Unsuspected hyperosmolality of oral solutions contributing to necrotizing enterocolitis in very-low-birth-weight infants. *Pediatrics*, 60, 535-8 (1977)
- K. C. White and K. L. Harkavy. Hypertonic formula resulting from added oral medications. *Am. J. Dis. Child.*, 136, 931–3 (1982)
- J. Lerman, M. M. Willis, G. A. Gregory and E. I. Eger. Osmolarity determines the solubility of anesthetics in aqueous solutions at 37°C. Anesthesiology, 59, 554-8 (1983)
- 11. The Merck Index, 12th edn, Merck, Rahway, NJ, 1996
- A. Pagliara, P.-A. Carrupt, G. Caron, et al. Lipophilicity profiles of ampholytes. Chem. Rev., 97, 3385-400 (1997)
- G. Bouchard, A. Pagliara, P.-A. Carrupt, et al. Theoretical and experimental exploration of the lipophilicity of zwitterionic drugs in 1,2-dichloroethane/water system. *Pharm. Res.*, 19, 1150–9 (2002)

- 14. P. J. Niebergall, R. L. Schnaare and E. T. Sugita. Spectral determination of microdissociation constants. J. Pharm. Sci., 61, 232 (1972)
- L. J. Leeson, J. E. Krueger and R. A. Nash. Structural assignment of the second and third acidity constants of tetracycline antibiotics. *Tetrahedron Lett.*, 18, 1155–60 (1963)
- R. J. Sturgeon and S. G. Schulman. Electronic absorption spectra and protolytic equilibriums of doxorubicin: direct spectrophotometric determination of microconstants. J. Pharm. Sci., 66, 958-61 (1977)
- W. H. Streng, H. E. Huber, J. L. DeYoung and M. A. Zoglio. Ionization constants of cephalosporin zwitterionic compounds. *J. Pharm. Sci.*, 65, 1034 (1976); 66, 1357 (1977)
- T. Ishimitsu, S. Hirose and H. Sakurai. Microscopic acid dissociation constants of 3,4-dihydroxyphenethylamine (dopamine). *Chem. Pharm. Bull.*, 26, 74–8 (1978)
- 19. B. Honig and A. Nicholls. Classical electrostatics in biology and chemistry. *Science*, 268, 1144–9 (1995)
- T. Seki, M. Okamoto, O. Hosoya and K. Juni. Measurement of diffusion coefficients of parabens by the chromatographic broadening method. J. Pharm. Sci. Technol., Jpn. 60, 114-7 (2000)
- N. Baden and M. Terazima. A novel method for measurement of diffusion coefficients of proteins and DNA in solution. *Chem. Phys. Lett.*, 393, 539-45 (2004)