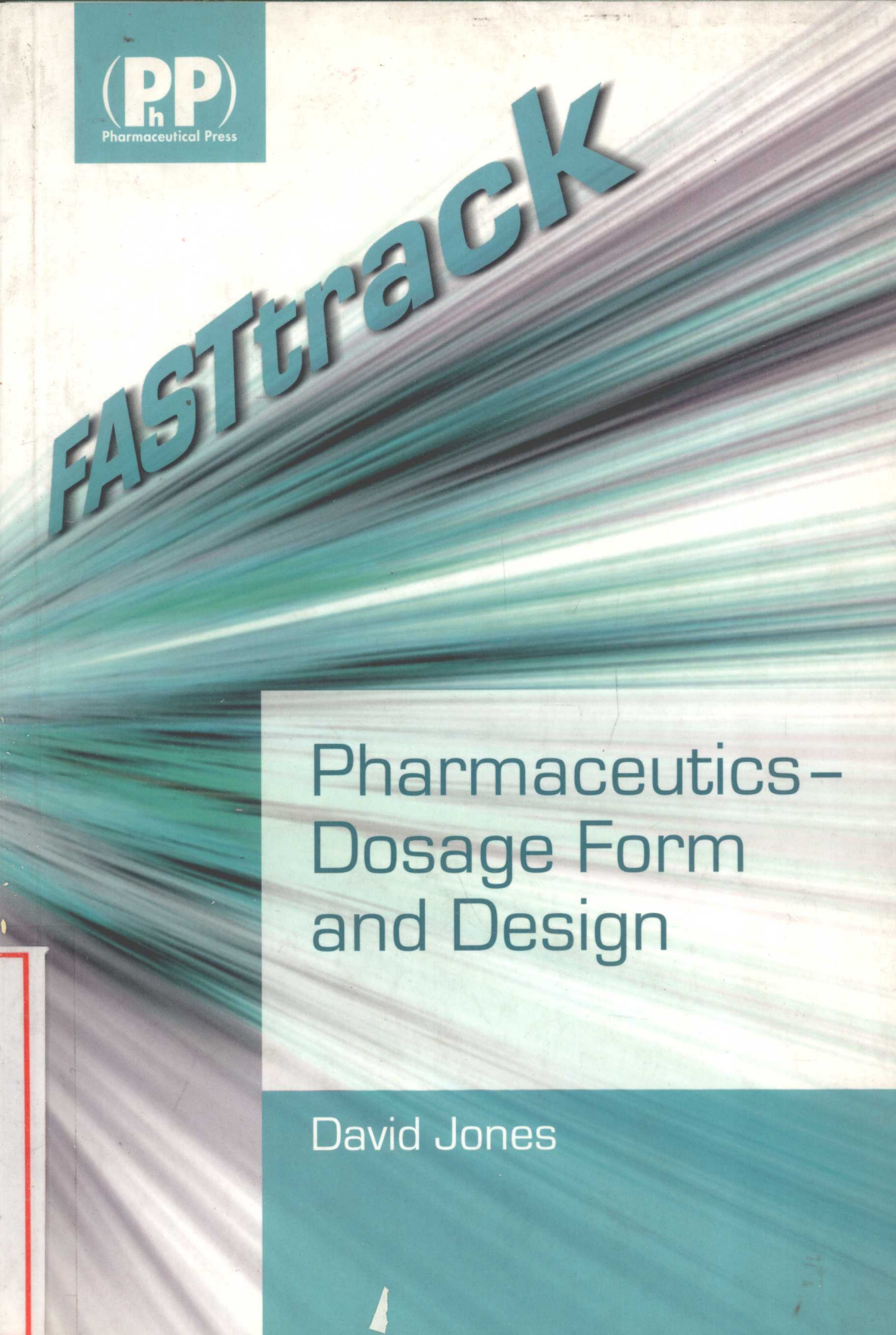
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Pharmaceutics – Dosage Form and Design
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Pharmaceutics – Dosage Form and Design

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Pharmaceutical Press
London • Chicago

Dedicated to my mother May, my late father Fred,
my wife Linda and our children Dary and Holly.

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Preface

Pharmaceutical formulation involves the rational design and manufacture of dosage forms to ensure that the required biological and physical performances of the therapeutic agent are attained. The formulation scientist is therefore expected to have knowledge of several scientific disciplines, including physical pharmaceutics, pharmaceutical chemistry and biopharmaceutics. Pharmaceutical formulation may therefore be correctly viewed as an essential and unique component of the pharmaceutical sciences and, accordingly, the Pharmacy undergraduate degree. Due to the interdisciplinary nature, pharmaceutical formulation is often considered difficult by many students and challenging to all students. This textbook aims to ease the perceived difficulties of this subject and, hopefully, illustrate the significance of pharmaceutical formulation and the unique role of the pharmacist in the development of medicines.

The contents of this text have been designed to cover the vast majority of dosage forms that graduate pharmacists will encounter when they enter professional practice. In particular, the text aims to deliver the essential information concerning the formulation of these dosage forms in a format that will hopefully aid the understanding and hence remove the complexities of the various topics. The reader will observe that, in addition to the required theoretical aspects, each chapter contains information regarding the types (and physicochemical properties) of excipients that are used in the formulation of dosage forms. It is the author's opinion that this information is essential to ensure that the reader is able to traverse the information gap between the theory and practice of dosage form design. In understanding the physicochemical properties of excipients (and indeed therapeutic agents), the student will be able to optimise the prepared dosage form and, in addition, will be able to answer examination questions with the appropriate depth required to attain a high grade.

Each chapter describes a category of dosage form and, whilst the exact details change, it may be observed that the format of the chapters is similar. This will assist students in understanding and recalling the required information. The formulations of liquids and suspensions for oral administration, including the required theoretical aspects, are presented in Chapters 1 and 2. In Chapters 3 and 4 the theoretical aspects and formulations of products that contain disperse phases are described. Whilst these products are mostly administered topically, the formulation of emulsions for oral administration is also described. Chapter 5 describes parenteral formulations and, in particular, illustrates strategies for the successful formulation of parenteral solutions, suspensions and emulsions (including the considerations of osmolality and sterility and methods to attain sterility).

The formulation of ocular (and related) dosage forms is described in Chapter 6. In addition to the description of ocular formulations, this chapter concisely describes the biological demands of these formulations and, in so doing, highlights the effects of formulation type on the biological performance of the preparation. Chapter 7 examines the formulation of suppositories and pessaries, describing the various formulation strategies for these dosage forms and highlighting their biological demands. The formulation of respiratory dosage forms, namely metered-dose inhalers, dry-powder inhalers and solutions for nebulisation, is presented in Chapter 8. In addition to the description of the typical excipients, this chapter specifically highlights formulation factors that affect deposition of particles within the respiratory tract. It is worth noting that in Chapters 6–8 the biological aspects of drug delivery to the eye, nose, rectum, vagina and respiratory tract are described, as such information is required to ensure the design of formulations that provide optimal biological performance.

Finally, Chapters 9 and 10 describe the formulation of solid-dosage forms (tablets and capsules) with particular emphases on the excipients and methods used to prepare them, the different types of tablets and capsules, the tableting process, tableting defects and, finally, the film coating of tablets. The size of these chapters reflects the greater clinical usage of these dosage forms.

Writing this textbook presented many challenges to the author. Above all, I hope that, after completing this text, readers will gain a comprehensive understanding of pharmaceutical formulation that will enable them to formulate dosage forms and, importantly, give advice on this topic to other healthcare professionals, who are frequently unaware of the complexities of this topic.

It has been my great pleasure and privilege to have lectured on all of the topics described in this textbook to enthusiastic undergraduate and postgraduate students of pharmacy in both Northern Ireland and New Zealand. I am grateful to them, as their numerous questions and suggestions have informed the content of this textbook. I am also indebted to Professor Michael S. Roberts (University of Queensland) who, at the commencement of my academic career, inspired my enthusiasm for, and helped me navigate through, the scientific complexities of physical pharmaceutics and pharmaceutical formulation. His contribution to my career has been invaluable. My gratitude is also given to Dr Ryan Donnelly and Dr Gavin Andrews, both of the School of Pharmacy, Queen's University of Belfast, for the many hours that they spent proof-reading this text and for their comments on how its content and presentation could be improved. Finally I am sincerely grateful for the love, encouragement and support of my mother May, my late Father Fred, my wife Linda and our children, Dary and Holly, without which this academic journey would not have been possible. This book is dedicated to them.

David S. Jones
March 2008

About the author

DAVID JONES gained a BSc (first-class honours) in Pharmacy (1985), a PhD in Pharmaceutics (1988) and, in 2006, a DSc. He registered with the Pharmaceutical Society of Northern Ireland in 1989 and took up a lectureship in Pharmaceutics in the School of Pharmacy, University of Otago, New Zealand. In 1992 he was appointed as the Head of Formulations at Norbrook Laboratories. In 1994, he was appointed to a lectureship in Pharmaceutics and was subsequently promoted to a senior lectureship (1997) and to a personal Chair (in Biomaterial Science) in 1999. His research concerns the characterisation, formulation and engineering of pharmaceutical materials/dosage forms and biomedical devices.

He is the author of two textbooks, six patents and over 350 research papers/communications. Professor Jones is both a Chartered Engineer and a Chartered Chemist and is a Fellow of the Institute of Materials, Minerals and Mining, a Fellow of the Royal Statistical Society, a Fellow of the Royal Society of Chemistry and a Member of the Institute of Engineers in Ireland. He is the editor of the *Journal of Pharmacy and Pharmacology.*

Contents

chapter 1
Pharmaceutical solutions for oral administration

Overview

In this chapter we will:

- examine the types and uses of pharmaceutical solutions as oral drug delivery systems
- provide an overview of the advantages and disadvantages of pharmaceutical solutions as oral drug delivery systems
- describe the formulation considerations for orally administered pharmaceutical solutions.

General description

KeyPoints

- Pharmaceutical solutions are extensively used as dosage forms for the oral administration of therapeutic agents.
- Pharmaceutical solutions are homogeneous, i.e. the therapeutic agent(s) and excipients are dissolved in the vehicle.
- Pharmaceutical solutions for oral administration are non-sterile dosage forms.

Pharmaceutical solutions may be generally defined as liquid preparations in which the therapeutic agent and the various excipients are dissolved in the chosen solvent system. Pharmaceutical solutions may contain a range of excipients, each with a defined pharmaceutical purpose. Examples of these include:

- the vehicle, usually purified water
- co-solvents, e.g. propylene glycol, glycerin, alcohol
- agents specifically to enhance the solubility of the therapeutic agent in the vehicle, e.g. surface-active agents
- preservatives, e.g. parahydroxybenzoate esters (methylhydroxybenzoate and propylhydroxybenzoate), boric acid and borate salts, sorbic acid and sorbate salts, phenolics
- sweeteners, e.g. glucose, saccharin, aspartame
- rheology (viscosity) modifiers, e.g. hydrophilic polymers (cellulose derivatives, alginic acid, polyvinylpyrrolidone)
- antioxidants, e.g. sodium formaldehyde sulphoxylate, butylated hydroxyanisole, butylated hydroxytoluene
- colours
- flavours
- buffers to regulate the pH of the formulation, e.g. citrate buffer.

The specific roles of each of these formulation excipients will be described later in this chapter.

Advantages and disadvantages of pharmaceutical solutions for oral administration

Advantages

- Therapeutic agents can easily be administered orally to individuals who have difficulty in swallowing, e.g. elderly patients, infants.
- The therapeutic agent is dissolved in the formulation and is therefore immediately available for absorption. Providing the drug does not precipitate within the gastrointestinal tract, the bioavailability of pharmaceutical solutions is greater than that of oral solid-dosage forms.
- Taste-masking of bitter therapeutic agents may be readily achieved.

Disadvantages

- Pharmaceutical solutions for oral administration are unsuitable for therapeutic agents that are chemically unstable in the presence of water.
- The poor solubility of certain therapeutic agents may prohibit their formulation as pharmaceutical solutions. The reader should note that certain techniques are available to enhance the solubility of poorly soluble drugs. These will be highlighted later in this chapter.
- Pharmaceutical solutions are expensive to ship and are bulky for the patient to carry due to the associated mass of the product.

Drug solubility

In pharmaceutical solutions both the therapeutic agent and the excipients are legally required to be present in solution over the shelf-life of the formulated product. As a result pharmaceutical solutions are termed homogeneous. One of the major challenges to the pharmaceutical scientist is the attainment of homogeneity in the formulation, due primarily to, in many cases, the limited aqueous solubility of the therapeutic agent. Initially there are possible scenarios regarding the formulation of pharmaceutical solutions of a therapeutic agent for oral administration:

- The aqueous solubility of the therapeutic agent is high at the selected pH of the formulation. Under these circumstances the therapeutic agent may be readily incorporated into the vehicle and formulated as an oral solution.
- The aqueous solubility of the therapeutic agent is moderate at the selected pH of the formulation, i.e. the aqueous solubility is less than the requested concentration of therapeutic agent. Under these circumstances the solubility of the therapeutic

agent in the formulation must be enhanced using co-solvents and related methods.

- The aqueous solubility of the therapeutic agent is low at the selected pH of the formulation. The difference between the aqueous solubility of the therapeutic agent and the required concentration is too great to be bridged by the use of co-solvents and related methods or the concentration of co-solvents or surfactants in the solubilised formulation may be toxic when administered orally. The drug may therefore be formulated as an alternative-dosage form, e.g. a suspension.

Prior to discussing the solubility of therapeutic agents and formulation strategies to modify this property, it is worth considering the process of drug dissolution. The dissolution of a therapeutic agent in water involves several key molecular steps: the removal of a molecule of the drug from the solid state, the formation of a cavity within the solvent and the accommodation of the drug molecule into the formed cavity. This process involves the breakage of solute–solute and solvent–solvent bonds (endothermic processes) and the formation of a bond between the solute and the solvent (with the subsequent liberation of energy). Dissolution occurs whenever the Gibb's free energy (ΔG) of the process is negative and involves a balance between the enthalpy of dissolution (ΔH) and the associated entropy (ΔS) at the temperature of dissolution (T), as defined below:

$$\Delta G = \Delta H - T\Delta S$$

Factors affecting the solubility of therapeutic agents

The solubility properties of drug molecules in a particular solvent system are sometimes difficult to predict and have been reported to be dependent, at least in part, on several physicochemical properties, including molecular weight, volume, radius of gyration, density, number of rotatable bonds, hydrogen bond donors and hydrogen bond acceptors. Furthermore, the properties of the solid state, e.g. crystal habit, crystalline/amorphous properties, will also affect the solubility of the therapeutic agent.

There are some empirical relationships between the physicochemical properties and the solubility of therapeutic agents that influence formulation strategies, as follows:

- The solubilities of a chemically related series of therapeutic agent are inversely related to their melting points. Therefore, as the melting point of the therapeutic agent is increased, the solubility would be expected to decrease.
- The solubility of a therapeutic agent is directly affected by both the type of chemical substituent groups and the substituent position. The solubility of therapeutic agents

containing hydrophilic groups (e.g. OH, COO^-, ammonium ion) will accordingly be greater than those containing lipophilic substituent groups, e.g. methyl, ethyl, ethoxy or chlorine groups.

- The solubilities of therapeutic agents that are either acids or bases (representing the vast majority of drug substances) are pH-dependent. The solubility of acids and bases increases as the degree of ionisation increases and may be easily calculated using the following equation (where S refers to the solubility of the drug and S_o is the intrinsic solubility, i.e. the solubility of the unionised form of the drug).

$$pK - pKa = \log\left(\frac{S - S_o}{S_o}\right) \qquad \text{for acids}$$

$$pH - pKa - \log\left(\frac{S_o}{S - S_o}\right) \qquad \text{for bases}$$

From these equations two invaluable conclusions may be drawn:

- At pH values *above* the pKa, the solubility of acidic drugs *increases.*
- At pH values *below* the pKa, the solubility of basic drugs *increases.*

In simple terms the solubility of acidic compounds increases as the pH of the solution is increased (above the pKa) and the solubility of basic compounds increases as the pH is lowered below the pKa.

Determination of the solubility properties of zwitterionic compounds, i.e. those that exhibit both acidic and basic properties, is more complicated than for simple acids or bases. However, in common with simple acids and bases, the solubility of zwitterionic therapeutic agents is affected by pH. At basic pH values the therapeutic agent behaves primarily as an acid whereas at low pH values the molecule behaves as a base. The pH range at which the therapeutic agent exhibits minimal solubility lies between the pKa values of the acidic and basic groups.

Formulation methods to enhance/optimise the solubility of therapeutic agents

The information described below may be employed to optimise the formulation of pharmaceutical solutions, remembering that the prerequisite for pharmaceutical solutions is the exclusive presence of dissolved therapeutic agent.

Appropriate selection of drug salt

The reader will be aware that the majority of therapeutic agents are commercially available to the pharmaceutical scientist in a range of salt forms, each form exhibiting a different aqueous solubility. The differences in solubility may be accredited, at least in part, to the crystal properties of the salt, which, in turn, affect the energy required to dissociate solute–solute bonds. Therefore, unless a specific salt form is specified or in the absence of a pharmaceutical approved salt of a therapeutic agent, the formulation scientist should select the salt that provides the required solubility in the dosage form.

Optimisation of the pH of the formulation

As mentioned above, the solubility of an ionised therapeutic agent is a function of both the pKa of the compound and the pH of the formulation. Importantly, the acceptable pH range of solutions for oral administration is large, ranging from circa 5 to 8 pH units. Therefore, a common formulation strategy involves the selection of a pH value for the formulation that optimises the ionisation and hence solubility of the therapeutic agent. Control of the pH in the formulation is achieved using a buffer that does not adversely affect the solubility of the therapeutic agent.

Use of co-solvents

Co-solvents are primarily liquid components that are incorporated into a formulation to enhance the solubility of poorly soluble drugs to the required level. In the formulation of pharmaceutical solutions for oral administration, aqueous solutions are preferred due to the lack of toxicity of water as the vehicle. However, if the solubility of the therapeutic agent renders this approach inappropriate, the incorporation of co-solvents within the formulation offers a pharmaceutically acceptable approach. Commonly employed co-solvents include glycerol, propylene glycol, ethanol and poly(ethylene glycol), details of which are provided in subsequent sections.

Prediction of the solubility of therapeutic agents in mixed solvent systems (the vehicle, water and the chosen co-solvent) is difficult, due to the effects of many variables on the solubility (as described previously). In practice the pharmaceutical scientist should measure the solubility of the chosen therapeutic agent in a series of mixed solvents to determine the most suitable solvent system for the given purpose. The final choice of the co-solvent system for a particular formulation involves consideration of the solubility of the therapeutic agent in the vehicle, the toxicity of the vehicle and the cost of the formulation. Indeed, it should be noted that the range of concentrations of each co-solvent used in oral formulations is primarily limited by concerns regarding toxicity.

Excipients used in pharmaceutical solutions for oral administration

Excipients in pharmaceutical formulations are physiologically inert compounds that are included in the formulation to facilitate the administration of the dosage form, e.g. pourability, palatability, to protect the formulation from issues regarding physical and chemical stability and to enhance the solubility of the therapeutic agent. Pharmaceutical solutions commonly contain a wide range of excipients, the details of which are provided below.

The vehicle

The preferred and most commonly used vehicle in solutions for oral administration is Purified Water USP, due to the low cost and low toxicity of this ingredient. Under normal circumstances tap (drinking) water should not be used due to the possibility of chemical imcompatibities within the formulation. The main features of Purified Water USP are as follows:

- It is prepared by distillation, ion exchange methods or by reverse osmosis.
- The solid residue (obtained after evaporation) is less than 1 mg per 100 ml of evaporated sample.
- It must not be used for the preparation of parenteral formulations.

In the case of parenteral formulations *Water for Injections BP* must be used, the specifications and use of which are described in Chapter 5.

Co-solvents

As defined previously, co-solvents are employed to increase the solubility of the therapeutic agent within the formulation. The main co-solvents that are used in the formulation of oral solutions are detailed below.

Glycerol

Glycerol (also termed glycerin) is an odorless, sweet liquid that is miscible with water and whose co-solvency properties are due to the presence of three hydroxyl groups (termed a triol) (Figure 1.1). It has similar co-solvency properties to ethanol.

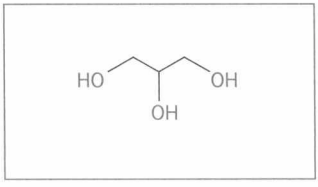

Figure 1.1 Structural formula of glycerol.

Alcohol USP (CH_3CH_2OH)

Alcohol USP contains between 94.9 and 96.0% v/v ethyl alcohol (ethanol) and is commonly used as a co-solvent, both as a single co-solvent and with other co-solvents, e.g. glycerol. The known pharmacological and toxicological effects of this co-solvent have compromised the use of alcohol in pharmaceutical preparations. As a result there are both labelling requirements for preparations that contain alcohol and upper limits with respect to the concentration of alcohol that may be used in formulations.

Propylene Glycol USP

Propylene Glycol USP is an odourless, colourless, viscous liquid diol that contains two hydroxyl groups (Figure 1.2). It is used in pharmaceutical preparations as a co-solvent, generally as a replacement for glycerin.

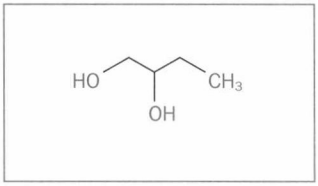

Figure 1.2 Structural formula of propylene glycol.

Poly(ethylene glycol) (PEG)

PEG (Figure 1.3) is a polymer composed of repeating units of the monomer ethylene oxide (in parenthesis). The physical state of the polymer is dependent on the number of repeat units (n) and hence on the molecular weight. Lower-molecular-weight grades (PEG 200, PEG 400) are preferred as co-solvents in pharmaceutical solutions.

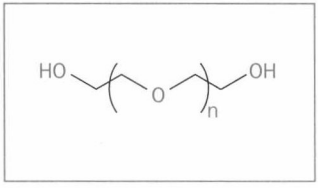

Figure 1.3 Structural formula of poly(ethylene glycol).

Miscellaneous agents used to enhance the solubility of therapeutic agents

In addition to the use of co-solvents, other pharmaceutical strategies are available to the pharmaceutical scientist to increase the solubility of therapeutic agents in the chosen vehicle. These include the use of surface-active agents and complexation, as detailed below.

Surface-active agents

Surface-active agents are chemicals that possess both hydrophilic (water-liking) and hydrophobic (water-disliking) regions. At dilute concentrations surface-active agents will orient at the interface between two phases (e.g. water/oil, water/air), with the hydrophilic and hydrophobic regions of the molecule being positioned to the hydrophilic and hydrophobic phases, respectively. As the concentration is increased, the interface will become saturated with surface-active agent and the molecules that are present in the bulk aqueous phase will orient themselves in an attempt to shield the hydrophobic regions of the surface-active agent. This orientation is referred to as a *micelle* and the concentration of surface-active agent at this occurs is termed the *critical micelle concentration* (CMC).

For further details regarding the physicochemical properties of surfactants, the reader should consult the companion text by David Attwood and Alexander T Florence (*FASTtrack: Physical Pharmacy* (London: Pharmaceutical Press; 2008). The use of surface-active agents for the solubilisation of poorly soluble drugs occurs exclusively in the presence of micelles and hence at concentrations of surface-active agents in excess of the CMC. In this the core of the micelle represents a hydrophobic region into which the poorly water-soluble drugs may partition. The location in the micelle is related to the chemical structure of the drug. For example, if the therapeutic agent is poorly soluble the molecule will locate exclusively within the micelle, whereas if the drug is water-insoluble but contains polar groups, the molecule will orient within the micelle, with the polar groups at the surface of the micelle and the hydrophobic region of the molecule located within the hydrophobic core of the micelle. In so doing the drug is solubilised within the colloidal micelles; due to their small size, the resulting solution appears homogeneous to the naked eye.

Tip

As the reader will have observed, there are several methods that may be used for the solubilisation of therapeutic agents. The choice of method should involve consideration of the stability of the formed solution, the pharmaceutical acceptability of the solubilisation strategy and cost.

Complexation

Complexation refers to the interaction of a poorly soluble therapeutic agent with an organic molecule, e.g. surface-active agents, hydrophilic polymers to generate a soluble intermolecular complex. One particular concern regarding the use of solution of drug complexes is the ability of the complex to dissociate following administration. This is particularly important in situations where the complexing agent is a hydrophilic polymer, as the high molecular weight of the