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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 in 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.

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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

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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

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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.

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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.

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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.

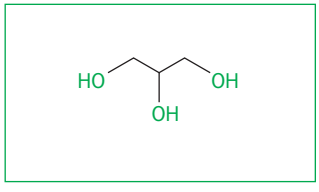

Figure 1.1 Structural formula of glycerol.

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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.

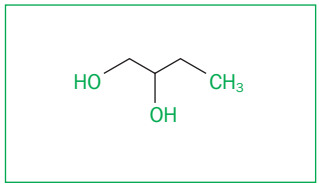

Figure 1.2 Structural formula of propylene glycol.

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.

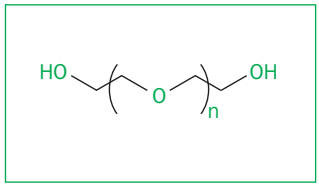

Figure 1.3 Structural formula of poly(ethylene glycol).

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.

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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

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drug–polymer complex would prevent drug absorption across biological membranes.

Common excipients in pharmaceutical solutions

There are several excipients that are commonly employed in the formulation of pharmaceutical solutions. These include: (1) buffers; (2) sweetening agents; and (3) viscosity-enhancing agents.

Buffers

Buffers are employed within pharmaceutical solutions to control the pH of the formulated product and, in so doing, optimise the physicochemical performance of the product. Typically pH control is performed:

- to maintain the solubility of the therapeutic agent in the formulated product. The solubility of the vast number of currently available drugs is pH-dependent and, therefore, the solubility of the therapeutic agent in the formulation may be compromised by small changes in pH
- to enhance the stability of products in which the chemical stability of the active agent is pH-dependent.

The concentration (and hence buffer capacity) of buffer salts employed in the formulation of oral solutions should be selected to offer sufficient control of the pH of the formulation but yet should be overcome by biological fluids following administration. This latter property is particularly appropriate for parenteral formulations to ensure that there is no irritation or damage following injection.

Examples of buffer salts used in pharmaceutical solutions include:

- acetates (acetic acid and sodium acetate): circa 1–2%
- citrates (citric acid and sodium citrate): circa 1–5%
- phosphates (sodium phosphate and disodium phosphate): circa 0.8–2%.

It must be remembered that the buffer system used in solution formulations should not adversely affect the solubility of the therapeutic agent, e.g. the solubility of drugs may be affected in the presence of phosphate salts.

Sweetening agents

Sweetening agents are employed in liquid formulations designed for oral administration specifically to increase the palatability of the therapeutic agent. The main sweetening agents employed in oral preparations are sucrose, liquid glucose, glycerol, sorbitol, saccharin sodium and aspartame. The use of artificial sweetening agents in formulations is increasing and, in many formulations,

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saccharin sodium is used either as the sole sweetening agent or in combination with sugars or sorbitol to reduce the sugar concentration in the formulation. The use of sugars in oral formulations for children and patients with diabetes mellitus is to be avoided.

Viscosity-enhancing agents

The administration of oral solutions to patients is usually performed using a syringe, a small-metered cup or a traditional 5-ml spoon. The viscosity of the formulation must be sufficiently controlled in order to ensure the accurate measurement of the volume to be dispensed. Furthermore, increasing the viscosity of some formulations may increase the palatability. Accordingly there is a viscosity range that the formulation should exhibit to facilitate this operation. Certain liquid formulations do not require the specific addition of viscosity-enhancing agents, e.g. syrups, due to their inherent viscosity.

The viscosity of pharmaceutical solutions may be easily increased (and controlled) by the addition of non-ionic or ionic hydrophilic polymers. Examples of both of these categories are shown below:

- non-ionic (neutral) polymers
  - cellulose derivatives, e.g.:
    - methylcellulose
    - hydroxyethylcellulose
    - hydroxypropylcellulose
  - polyvinylpyrrolidone
- ionic polymers
  - sodium carboxymethylcellulose (anionic)
  - sodium alginate (anionic).

Full details of the physicochemical properties of these polymers are provided in later chapters.

Antioxidants

Antioxidants are included in pharmaceutical solutions to enhance the stability of therapeutic agents that are susceptible to chemical degradation by oxidation. Typically antioxidants are molecules that are redox systems that exhibit higher oxidative potential than the therapeutic agent or, alternatively, are compounds that inhibit free radical-induced drug decomposition. Typically in aqueous solution antioxidants are oxidised (and hence degraded) in preference to the therapeutic agent, thereby protecting the drug from decomposition. Both water-soluble and water-insoluble antioxidants are commercially available, the choice of these being performed according to the nature of the formulation. Examples of antioxidants that are commonly used

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for aqueous formulations include: sodium sulphite, sodium metabisulphite, sodium formaldehyde sulphoxylate and ascorbic acid. Examples of antioxidants that may be used in oil-based solutions include: butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA) and propyl gallate. Typically antioxidants are employed in low concentrations (< 0.2% w/w) and it is usual for the concentration of antioxidant in the finished product to be markedly less than the initial concentration, due to oxidative degradation during manufacture of the dosage form. Antioxidants may also be employed in conjunction with chelating agents, e.g. ethylenediamine tetraacetic acid, citric acid, that act to form complexes with heavy-metal ions, ions that are normally involved in oxidative degradation of therapeutic agents.

Preservatives

Preservatives are included in pharmaceutical solutions to control the microbial bioburden of the formulation. Ideally, preservatives should exhibit the following properties:

- possess a broad spectrum of antimicrobial activity encompassing Gram-positive and Gram-negative bacteria and fungi
- be chemically and physically stable over the shelf-life of the product
- have low toxicity.

A wide range of preservatives is available for use in pharmaceutical solutions for oral use, including the following (values in parentheses relate to the typical concentration range used in oral solutions):

- benzoic acid and salts (0.1–0.3%)
- sorbic acid and its salts (0.05–0.2%)
- alkyl esters of parahydroxybenzoic acid (0.001–0.2%). Usually a combination of two members of this series is employed in pharmaceutical solutions, typically methyl and propyl parahydroxybenzoates (in a ratio of 9:1). The combination of these two preservatives enhances the antimicrobial spectrum.

Factors affecting preservative efficacy in oral solutions

The activity of a preservative is dependent on the correct form of the preservative being available in the formulation at the required concentration to inhibit microbial growth (termed the minimum inhibitory concentration: MIC). Unfortunately, in many solution formulations, the concentration of preservative within the formulation may be affected by the presence of other excipients and by formulation pH. Factors that directly affect the efficacy of

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preservatives in oral solutions include: (1) the pH of the formulation; (2) the presence of micelles; and (3) the presence of hydrophilic polymers.

The pH of the formulation. In some aqueous formulations the use of acidic preservatives, e.g. benzoic acid, sorbic acid, may be problematic.

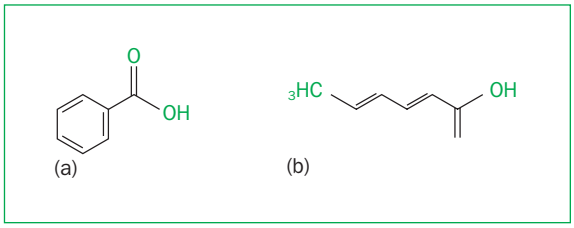

Figure 1.4 Structural formula of (a) benzoic acid and (b) sorbic acid.

The antimicrobial properties are due to the unionised form of the preservative; the degree of ionisation being a function of the pH of the formulation. The activity of the unionised form of the acid in this respect is due to the ability of this form to diffuse across the outer membrane of the microorganism and eventually into the cytoplasm. The neutral conditions within the cytoplasm enable the preservative to dissociate, leading to acidification of the cytoplasm and inhibition of growth.

The fraction of acidic preservative at a particular pH may be calculated using a derived form of the Henderson–Hasselbalch equation, as follows:

$$Fraction = \left(\frac{1}{(1+10^{pH-pKa})}\right)$$

The use of this equation may be illustrated in the following example:

Worked example

Example 2.1

Assuming that the MIC for the unionised form of an acidic preservative (pKa 4.2) is 0.0185 mg/ml, calculate the required concentration to preserve an oral solution that has been buffered to pH 4.7.

The Henderson–Hasselbalch equation may be employed, as described above, to determine the fraction of unionised acid within the formulation.

$$Fraction = \left(\frac{1}{(1+10^{4.7-4.2})}\right) = 0.24$$

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The required concentration is then calculated by dividing the MIC for the unionised form of the preservative by the fraction of unionised preservative present, i.e. $\left(\frac{0.0185}{0.24}\right) - 0.07$ mg/ml.

In practice an overage is added and therefore the actual concentration of preservative required would be 0.1–0.15 mg/ml.

As the reader will observe, the pKa of the preservative is a vital determinant within the above calculations. Organic acids, e.g. benzoic acid, sorbic acid, have pKa values that are circa 4.2 and therefore, in solution formulations whose pH is neutral, a high concentration of preservative will be required to ensure that the required concentration of the unionised species is obtained. If the above calculation is repeated for an oral solution at pH 7.2, the following result is obtained:

$$Fraction = \left(\frac{1}{(1+10^{7.2-4.2})}\right) = 0.00001$$

Therefore, the required preservative concentration is $\left(\frac{0.0185}{0.00001}\right) = 1850$ mg/ml.

Importantly, the preservative efficacies of parabens (alky esters of parahydroxybenozoic acid) and the phenolics are generally not affected by formulation pH (within a pH range between 4.0 and 8.0) due to the high pKa of the organic hydroxyl group. The structures of these preservatives are shown in Figure 1.5.

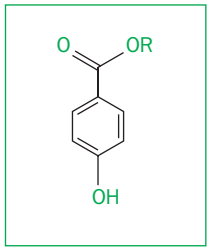

Figure 1.5 Structural formula for the parahydroxybenzoate esters (Parabens, where R refers to an alkyl group).

The presence of micelles

The role of micelles for the solubilisation of lipophilic therapeutic agents was described above. If the preservative exhibits lipophilic properties (e.g. the unionised form of acidic preservatives, phenolics, parabens), then partition of these species into the micelle may occur, thereby decreasing the available (effective) concentration of preservative in solution. An equilibrium is established, as depicted in Figure 1.6.

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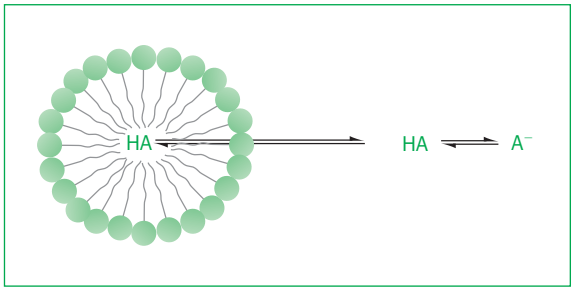

Figure 1.6 Diagrammatic illustration of the equilibrium of an acidic preservative in the presence of micelles. HA and A^- refer to the unionised and ionised states of the preservative.

To correct this problem, the preservative concentration must be increased to ensure that the free concentration within the formulation is ≥ MIC of the preservative.

The presence of hydrophilic polymers

It has been shown that the free concentration of preservative in oral solution formulations is reduced in the presence of hydrophilic polymers, e.g. polyvinylpyrrolidone, methylcellulose. This is due to the ability of the preservative to interact chemically with the dissolved polymer. As described above, this problem is addressed by increasing the concentration of preservative in the formulation. In certain circumstances the preservative may be incompatible with hydrophilic polymers in the formulation due to an electrostatic interaction. Therefore, cationic hydrophilic polymers should not be used in conjunction with acidic preservatives in oral solution formulations.

Flavours and colourants

Unfortunately the vast majority of drugs in solution are unpalatable and therefore, the addition of flavours is often required to mask the taste of the drug substance. Taste-masking using flavours is a difficult task; however, there are some empirical approaches that may be taken to produce a palatable formulation.

- The four basic taste sensations are salty, sweet, bitter and sour. It has been proposed that certain flavours should be used to mask these specific taste sensations. In particular:
  - Flavours that may be used to mask a salty taste include:
    - butterscotch
    - apricot
    - peach
    - vanilla
    - wintergreen mint.
  - Flavours that may be used to mask a bitter taste include:
    - cherry
    - mint
    - anise.

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- Flavours that may be used to mask a sweet taste include:
  - vanilla
  - fruit and berry.
- Flavours that may be used to mask a sour taste include:
  - citrus flavours
  - raspberry.

- Usually a combination of flavours is used to achieve the optimal taste-masking property.
- Certain excipients may added to oral solution formulations, referred to as *flavour adjuncts* (e.g. menthol, chloroform) that add flavour to the formulation but, in addition, act to desensitise the taste receptors. In so doing these agents augment the taste-masking properties of conventional flavours.

Colours are pharmaceutical ingredients that impart the preferred colour to the formulation. When used in combination with flavours, the selected colour should 'match' the flavour of the formulation, e.g. green with mint-flavoured solutions, red for strawberry-flavoured formulations. Although the inclusion of colours is not a prerequisite for all pharmaceutical solutions, certain categories of solution (e.g. mouthwashes/gargles) are normally coloured.

Types of pharmaceutical solutions

Pharmaceutical solutions for oral administration

There are three principal types of solution formulations that are administered orally: *oral solutions, oral syrups* and *oral elixirs*. In addition, other solution formulations are employed for a local effect, e.g. mouthwashes/gargles and enemas. Details of these are provided in the following sections.

Tips

The formulation of solutions for oral administration often requires the inclusion of several excipients.
It is important that each excipient included in the formulation is necessary and justified.
All excipients must be physically and chemically compatible (with each other and with the therapeutic agent).

Oral solutions

Oral solutions are administered to the gastrointestinal tract to provide systemic absorption of the therapeutic agent. Due to the resilience of the gastrointestinal environment, oral solutions may be formulated over a broad pH range. However, unless there are issues regarding the solubility or stability of the therapeutic agent, the usual pH of oral solutions is circa 7.0. Typically the following classes of excipients are used in the formulation of oral solutions.

- buffers (e.g. citrate, phosphate)
- preservatives (e.g. parabens, benzoic acid, sorbic acid)

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- antioxidants (water-soluble antioxidants are used, e.g. sodium metabisulphite 0.01–1.0% w/w)
- flavours and colours (the colour should be selected to complement the flavour of the formulation)
- viscosity-modifying agents (to affect the pourability of the formulation. For this purpose hydrophilic polymers are used, e.g. sodium alginate, hydroxyethylcellulose).

The reader should note that, to be classified as a solution, all components of the formulation (including the therapeutic agent) should be soluble, with no evidence of precipitation.

Oral syrups

Syrups are highly concentrated, aqueous solutions of sugar or a sugar substitute that traditionally contain a flavouring agent, e.g. cherry syrup, cocoa syrup, orange syrup, raspberry syrup. An unflavoured syrup is available that is composed of an aqueous solution containing 85% sucrose. Therapeutic agents may either be directly incorporated into these systems or may be added as the syrup is being prepared. If the former method is employed, it is important to ensure that the therapeutic agent is soluble within the syrup base.

It should also be remembered that the choice of syrup vehicle must be performed with due consideration to the physicochemical properties of the therapeutic agent. For example, cherry syrup and orange syrup are acidic and therefore the solubility of acidic or some zwitterionic therapeutic agents may be lowered and may result in precipitation of the drug substance. Under these circumstances, the physical stability of the preparation will have been compromised and the shelf-life of the product will have been exceeded. The use of acidic syrups may additionally result in reduced chemical stability for acid-labile therapeutic agents.

The major components of syrups are as follows:

- *Purified water*
- *Sugar (sucrose) or sugar substitutes (artificial sweeteners).* Traditionally syrups are composed of sucrose (usually between 60 and 80%) and purified water. Due to the inherent sweetness and moderately high viscosity of these systems, the addition of other sweetening agents and viscosity-modifying agents is not required. In addition, the high concentration of sucrose and associated unavailability of water (termed low water activity) ensures that the addition of preservatives is not required. As the concentration of sucrose is reduced from the upper limit (e.g. through dilution), the addition of preservatives may be required.

  In some formulations, other non-sucrose bases may replace traditional syrup. One of the most popular is Sorbitol

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Solution USP, which contains 64% w/w sorbitol (a polyhydric alcohol: Figure 1.7), although other alternatives are available that are based on mixtures of sorbitol and glycerin. These non-sucrose bases may be mixed with traditional syrups, if required, in the formulation of oral syrups that possess a low concentration of sucrose in comparison to traditional syrups.

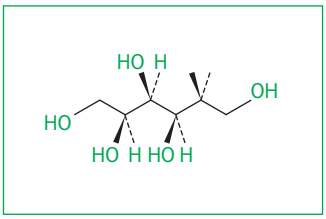

Figure 1.7 Structural formula of sorbitol.

More recently, many products have been formulated as medicated sugar-free syrups due to the glycogenetic and cariogenic properties of sucrose. For the afore-mentioned reasons, all medicinal products designed for administration to children and to diabetic patients must be sugar-free. Syrup substitutes must therefore provide an equivalent sweetness, viscosity and preservation to the original syrups. To achieve these properties artificial sweeteners (typically saccharin sodium, aspartame), non-glycogenetic viscosity modifiers (e.g. methylcellulose, hydroxyethylcellulose) and preservatives (e.g. sodium benzoate, benzoic acid and parahydroxybenzoate esters) are included.

- *Preservatives.* As highlighted above, preservatives are not required in traditional syrups containing high concentrations of sucrose. Conversely, in sugar-free syrups, syrups in which sucrose has been substituted at least in part by polyhydric alcohol and in traditional syrups that contain lower concentrations of sucrose, the addition of preservatives is required. Typical examples of commonly used preservatives include:
  - Mixtures of parahydroxybenzoate esters (usually methylhydroxybenzoate and propylhydroxybenzoate in a ratio of 9:1). The typical concentration range is 0.1–0.2% w/v. It is important to note that the preservative efficacy of these preservatives may be decreased in the presence of hydrophilic polymers (generally employed to enhance viscosity), due to an interaction of the preservative with the polymer. This effect is negated by increasing the overall preservative concentration. Other preservatives that are employed include benzoic acid (0.1–0.2%) or sodium benzoate (0.1–0.2%).

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- *Flavours.* These are employed whenever the unpalatable taste of a therapeutic agent is apparent, even in the presence of the sweetening agents. The flavours may be of natural origin (e.g. peppermint, lemon, herbs and spices) and are available as oils, extracts, spirits or aqueous solutions. Alternatively, a wide range of synthetic flavours are available that offer advantages over their natural counterparts in terms of purity, availability, stability and solubility.
  Certain flavours are also associated with a (mild) therapeutic activity. For example, many antacids contain mint due to the carminative properties of this ingredient. Alternatively other flavours offer a taste-masking effect by eliciting a mild local anaesthetic effect on the taste receptors. Examples of flavours in this category include peppermint oil, chloroform and menthol.
  The concentration of flavour in oral syrups is that which is required to provide the required degree of taste-masking effectively.
- *Colours.* These are generally natural or synthetic water-soluble, photo-stable ingredients that are selected according to the flavour of the preparation. For example, mint-flavoured formulations are commonly a green colour, whereas in banana-flavoured solutions a yellow colour is commonly employed. Such ingredients must not chemically or physically interact with the other components of the formulation.

Oral elixirs

An elixir is a clear, hydroalcoholic solution that is formulated for oral use. The concentration of alcohol required in the elixir is unique to each formulation and is sufficient to ensure that all of the other components within the formulation remain in solution. For this purpose other polyol co-solvents may be incorporated into the formulation. The presence of alcohol in elixirs presents a possible problem in paediatric formulations and, indeed, for those adults who wish to avoid alcohol. The typical components of an elixir are as follows:

- *Purified water.*
- *Alcohol.* This is employed as a co-solvent to ensure solubility of all ingredients. As highlighted above, the concentration of alcohol varies depending on the formulation. Generally the concentration of alcohol is greater than 10% v/v; however, in some preparations, the concentration of alcohol may be greater than 40% v/v.
- *Polyol co-solvents.* Polyol co-solvents, e.g. propylene glycol, glycerol, may be employed in pharmaceutical elixirs to enhance the solubility of the therapeutic agent and associated excipients. The inclusion of these ingredients enables the

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concentration of alcohol to be reduced. As before, the concentration of co-solvents employed is dependent on the concentration of alcohol present, the type of co-solvent used and the solubility of the other ingredients in the alcohol/co-solvent blend. The reader is directed to the pharmacopoeial monographs to observe the concentration of co-solvents in specific examples of the pharmaceutical elixirs. Two examples in the USP that illustrate the range of concentrations of co-solvents are Phenobarbital Elixir and Theophylline Elixir (Tables 1.1 and 1.2).

Table 1.1 Phenobarbital Elixir

Phenobarbital (therapeutic agent)	0.4% w/v
Orange oil (flavour)	0.025% v/v
Propylene glycol (co-solvent)	10% v/v
Alcohol	20% v/v
Sorbitol solution (sweetener)	60% v/v
Colour	As required
Purified water	ad 100%

Table 1.2 Theophylline Elixir

Theophylline (therapeutic agent)	0.53% w/v
Citric acid (pH regulation)	1.0% w/v
Liquid glucose (sweetening agent)	4.4% w/v
Syrup (sweetening agent)	13.2% v/v
Saccharin sodium (sweetening agent)	0.5% w/v
Glycerin (co-solvent)	5.0% v/v
Sorbitol solution (co-solvent)	32.4% v/v
Alcohol	20% v/v
Lemon oil (flavour)	0.01% w/v
FDC yellow no. 5 (colour)	0.01% w/v
Purified water	ad 100%

- *Sweetening agents.* The concentration of sucrose in elixirs is less than that in syrups and accordingly elixirs require the addition of sweetening agents. The types of sweetening agents used are similar to those used in syrups, namely syrup, sorbitol solution and artificial sweeteners such as saccharin sodium (Figure 1.8).
  It should be noted, however, that the high concentration of alcohol prohibits the incorporation of high concentrations of sucrose due to the limited solubility of this sweetening agent in the elixir vehicle. To obviate this problem, saccharin

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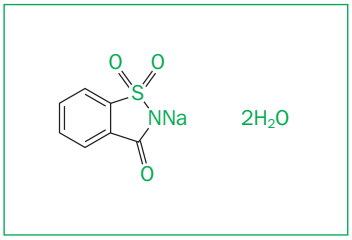
Figure 1.8 Structural formula of saccharin sodium (dihydrate).



sodium, an agent which is used in small quantities and which exhibits the required solubility profile in the elixir, is employed.

- *Flavours and colours.* All pharmaceutical elixirs contain flavours and colours to increase the palatability and enhance the aesthetic qualities of the formulation. The presence of alcohol in the formulation allows the pharmaceutical scientist to use flavours and colours that may perhaps exhibit inappropriate solubility in aqueous solution. For example, it may be observed that in the two formulations cited above, essential oils were used as the flavouring agents. As before, the selected colour should optimally match the chosen flavour.
- *Ancillary comments*

– Preservatives are not required in pharmaceutical elixirs that contain greater than circa 12% v/v alcohol, due to the antimicrobial properties of this co-solvent.
– Due to the volatile nature of some of the components of elixirs, elixirs should be packaged in tight containers and not stored at high temperatures.
– The addition of viscosity-enhancing agents, e.g. hydrophilic polymers, may be required to optimise the rheological properties of elixirs.

Tips

The choice of liquid type for oral administration (solution, elixir or linctus) is often dependent on the physicochemical properties of the therapeutic agent. For example, if the drug has a bitter taste, linctuses are often used.
It should be noted that linctuses are now commonly formulated as sugar-free preparations.
The use of elixirs is not common.

Miscellaneous oral solutions

In addition to conventional solutions, syrups and elixirs, there are other solution-based dosage forms that are administered orally, in particular *linctuses* and *mouthwashes/gargles*. These two subcategories are briefly described below.

Linctuses

Linctuses are viscous preparations that contain the therapeutic agent dissolved in a vehicle composed of a high percentage of sucrose and, if required, other sweetening agents. These formulations are administered

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orally and are primarily employed for the treatment of cough, due to their soothing actions on the inflamed mucous membranes. Linctuses may also be formulated as sugar-free alternatives in which sucrose is replaced by sorbitol and the required concentration of sweetening agent.

Mouthwashes and gargles

Mouthwashes/gargles are designed for the treatment of infection and inflammation of the oral cavity. Formulations designed for this purpose employ water as the vehicle, although a co-solvent, e.g. alcohol, may be employed to solubilise the active agent. The use of alcohol as a co-solvent may act to enhance the antimicrobial properties of the therapeutic agent. Other formulation components are frequently required to enhance the palatability and acceptability of the preparation. These include preservatives, colours, flavouring agents and non-cariogenic sweetening agents.

Enemas

Enemas are pharmaceutical solutions that are administered rectally and are employed to ensure clearance of the bowel, usually by softening the faeces or by increasing the amount of water in the large bowel (osmotic laxatives). Enemas may be aqueous or oil-based solutions and, in some formulations, the vehicle is the agent that promotes bowel evacuation, e.g. arachis oil retention enema. Aqueous formulations usually contain salts (e.g. phosphates) to alter the osmolality within the rectum, thereby increasing the movement of fluid to the rectal contents. Viscosity-enhancing agents, e.g. glycerol, may be included to aid retention of the formulation within the rectum and to reduce the incidence of seepage.

Multiple choice questions

1. Regarding weakly acidic drug molecules, which of the following statements are true?

a. The solubility of weak acids increases as the pH is decreased.

b. The solubility of weak acids increases as the pH is increased.

c. The solubility of weak acids in pharmaceutical formulations may be affected by the presence of counterions.

d. All weakly acidic therapeutic agents exhibit an isoelectric point.

2. Regarding weakly basic drug molecules, which of the following statements are true?

a. The solubility of weak bases increases as the pH is decreased.

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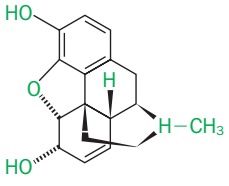
b. The solubility of weak bases increases as the pH is increased.
c. The solubility of weak bases in pharmaceutical formulations may be affected by the presence of counterions.
d. All weakly basic therapeutic agents exhibit an isoelectric point.

3. Regarding the following drug substance, which of the following statements are true?



a. The solubility of the above drug increases as the pH is decreased from pH 9 to pH 4.
b. The solubility of the above drug increases as the pH is increased from 7 to 9.
c. The above drug may be susceptible to oxidation.
d. The above drug exhibits an isoelectric point.

4. Regarding buffers for pharmaceutical solutions for oral administration, which of the following statements are true?
a. Citrate buffer is commonly used as a buffer for pharmaceutical solutions.
b. Buffers are required solely to control the stability of therapeutic agents.
c. Buffer salts may affect the solubility of therapeutic agents.
d. The buffer capacity of a buffer system is increased as the concentration of buffer components is increased.

5. Regarding the use of antioxidants in pharmaceutical solutions for oral administration, which of the following statements are true?
a. Antioxidants are required in all solution formulations.
b. Antioxidants reduce the rate of oxidation of the therapeutic agent.
c. BHT and BHA are examples of antioxidants that are included in aqueous solutions.
d. The efficacy of antioxidants may be improved in the presence of ethylenediaminetetraacetic acid (EDTA).

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6. Regarding the use of co-solvents for the formulation of pharmaceutical solutions for oral administration, which of the following statements are true?

a. Co-solvents are required in all pharmaceutical solution formulations.
b. Alcohols are commonly used as co-solvents in pharmaceutical solutions.
c. Glycerol may directly affect the pH of the formulation.
d. Co-solvents may affect the viscosity of the solution formulation.

7. Regarding the use of preservatives in pharmaceutical solutions for oral administration, which of the following statements are true?

a. Preservatives are required in all pharmaceutical solution formulations.
b. Preservatives are not required if the solution is manufactured under sterile conditions.
c. Esters of parahydroxybenzoic acid are used as preservatives for pharmaceutical solutions for oral administration.
d. Preservatives render pharmaceutical solutions for oral administration sterile.

8. Regarding pharmaceutical elixirs, which of the following statements are true?

a. Preservatives are required in all elixir formulations.
b. Elixirs generally require the addition of sweetening agents.
c. Elixirs generally contain $< 10\%$ alcohol USP.
d. Colours are required for all elixir formulations.

9. Regarding pharmaceutical linctuses, which of the following statements are true?

a. Preservatives are required in all linctus formulations.
b. Linctuses generally require the addition of synthetic sweetening agents.
c. Linctus formulations may contain high concentrations of sucrose.
d. Colours are required for all linctus formulations.

10. Regarding oral syrups, which of the following statements are true?

a. Preservatives are required in all oral syrups.
b. In certain syrups the concentration of sucrose may be $\leq 80\%$ w/w.
c. Sugar-free syrups require the inclusion of a viscosity-modifying agent.
d. Colours are required for all oral syrups.

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