



Lecture 2

Solutions (Part 2)

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- Coloring agents



Excipients for Oral Solutions

Introduction

Vehicle

Solubilizing agents

Complexing agents

Introduction

Excipients in pharmaceutical formulations are physiologically inert compounds that are included in the formulation to:

1. Facilitate the administration of the dosage form, e.g. pourability, palatability.
2. Protect the formulation from issues regarding physical and chemical stability.
3. Enhance the solubility of the therapeutic agent.



Vehicle

Purified Water

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 incompatibilities between dissolved solids and the medicinal agents being added.

The use of tap water is permitted in washing, in extraction of crude vegetable drugs, in preparation of certain products for external use, and when the difference between tap water and purified water is of no consequence.



Vehicle

Purified Water

The main features of Purified Water USP are as follows:

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



Vehicle

Alcohol USP

Alcohol USP contains between 94.9 and 96.0% v/v ethyl alcohol (ethanol) and is most commonly used as a co-solvent, both as a single co-solvent and with other co-solvents, e.g. glycerol (to reduce the amount of alcohol required).

Alcohol is often preferred because of its miscibility with water and its ability to dissolve many water-insoluble ingredients, including drug substances, flavorants, and antimicrobial preservatives.



Vehicle

Alcohol USP

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, particularly for children.

For OTC oral products intended for children under 6 years of age, the recommended alcohol content limit is 0.5%; for products intended for children 6 to 12 years of age, the recommended limit is 5%; and for products recommended for children over 12 years of age and for adults, the recommended limit is 10%.

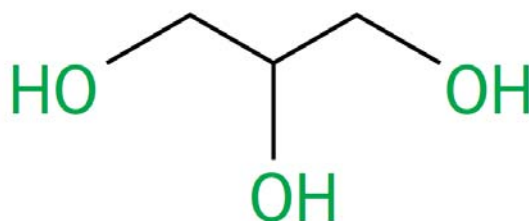


Vehicle Glycerol

Co-solvents are employed with water to increase the solubility of the therapeutic agent within the formulation.

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)

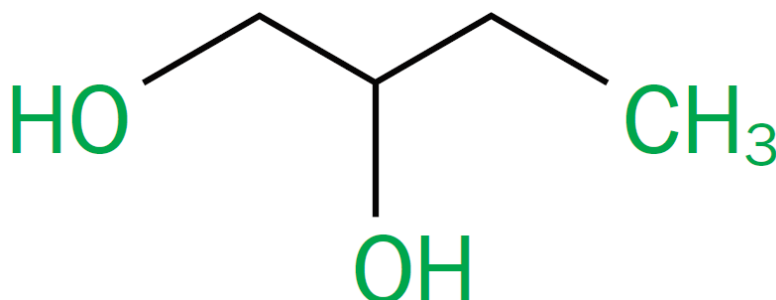
It has similar co-solvency properties to ethanol.



Vehicle Propylene Glycol USP

Propylene Glycol USP is an odourless, colourless, viscous liquid diol that contains two hydroxyl groups

It is used in pharmaceutical preparations as a co-solvent, generally as a replacement for glycerin.



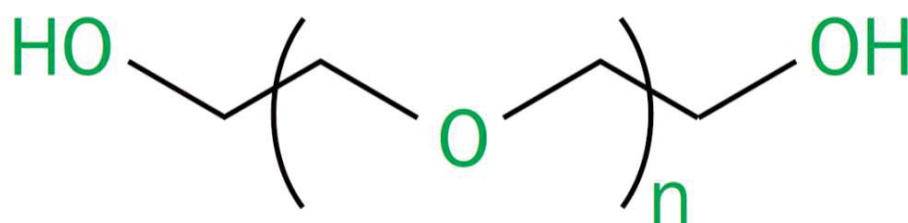
Vehicle

Poly(ethylene glycol) (PEG)

PEG 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.



Solubilizing agents

Surface Active 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 such as ***solubilization by surface active agents*** and ***complexation***.

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.



Solubilizing agents

Critical Micelle Concentration

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).



Solubilizing agents

Solubilization by micelle

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.



Solubilizing agents

Solubilization by micelle

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.



Complexing Agents

Complexation refers to the interaction of a poorly soluble therapeutic agent with an organic molecule, e.g. 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 drug–polymer complex would prevent drug absorption across biological membranes.





Other Excipients

Buffers

Sweetening agents

Viscosity enhancing agent

Antioxidant

Preservatives

Flavoring agents

Coloring agents

Buffers pH Control

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:

1. 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

2. to enhance the stability of products in which the chemical stability of the active agent is pH-dependent.



Buffers

Buffer Capacity

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.



Buffers

Examples

Examples of buffer salts used in pharmaceutical solutions include:

- Acetates (acetic acid and sodium acetate): 1–2%
- Citrates (citric acid and sodium citrate): 1–5%
- Phosphates (sodium phosphate and disodium phosphate): 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, 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.



Viscosity Enhancing Agents

The viscosity of pharmaceutical solutions may be easily increased (and controlled) by the addition of non-ionic or ionic hydrophilic polymers:

Non-ionic (neutral) polymers

- cellulose derivatives, e.g.:
 - methylcellulose
 - hydroxyethylcellulose
 - hydroxypropylcellulose
- polyvinylpyrrolidone

Ionic polymers

- sodium carboxymethylcellulose (anionic)
- sodium alginate (anionic).



Antioxidants

Principle

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 which 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 made according to the nature of the formulation.



Antioxidants

Examples

Examples of antioxidants that are commonly used for aqueous formulations include: sodium sulphite, sodium metabisulphite, sodium formaldehyde sulfoxylate and ascorbic acid.

Examples of antioxidants that may be used in oil-based solutions include: butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA) and propyl gallate.

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

Ideal Properties

Preservatives are included in pharmaceutical solutions to control the microbial bioburden of the formulation.

Ideally, preservatives should exhibit the following properties:

1. Possess a broad spectrum of antimicrobial activity encompassing Gram-positive and Gram-negative bacteria and fungi
2. Be chemically and physically stable over the shelf-life of the product
3. Have low toxicity.



Preservatives

Examples

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 its 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.



Preservatives

Factors Affecting Preservatives

The effective 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 preservatives in oral solutions include:

- (1) pH of the formulation
- (2) Presence of micelles
- (3) Presence of hydrophilic polymers

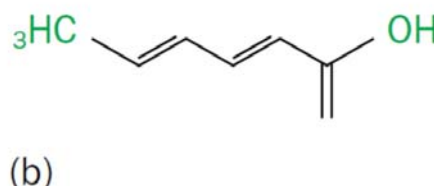
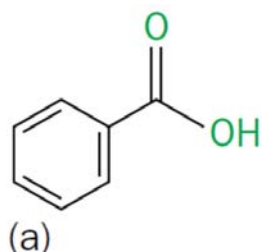


Preservatives

Factors Affecting Preservatives

pH of the formulation

In some aqueous formulations the use of acidic preservatives, e.g. benzoic acid (a), sorbic acid (b), may be problematic.



Preservatives

Factors Affecting Preservatives

pH of the formulation

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.



Preservatives

Factors Affecting Preservatives

pH of the formulation

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

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



Preservatives

Factors Affecting Preservatives

pH of the formulation

Example:

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.

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



Preservatives

Factors Affecting Preservatives

pH of the formulation

The required concentration is then calculated:

$$\frac{0.0185}{X} = \frac{0.24}{1} \Rightarrow X = 0.07 \text{ mg/ml}$$

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



Preservatives

Factors Affecting Preservatives

pH of the formulation

The pKa of the preservative is a vital determinant within the above calculations.

Organic acids, e.g. benzoic acid, sorbic acid, have pKa values of about 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:

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



Preservatives

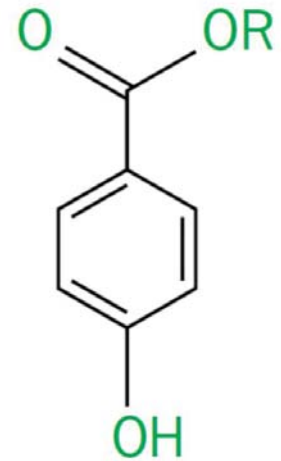
Factors Affecting Preservatives

pH of the formulation

Therefore, the required preservative concentration is

$$\frac{0.0185}{X} = \frac{0.00001}{1} \Rightarrow X = 1850 \text{ mg/ml}$$

Importantly, the preservative efficacies of parabens (alkyl esters of parahydroxybenzoic 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.

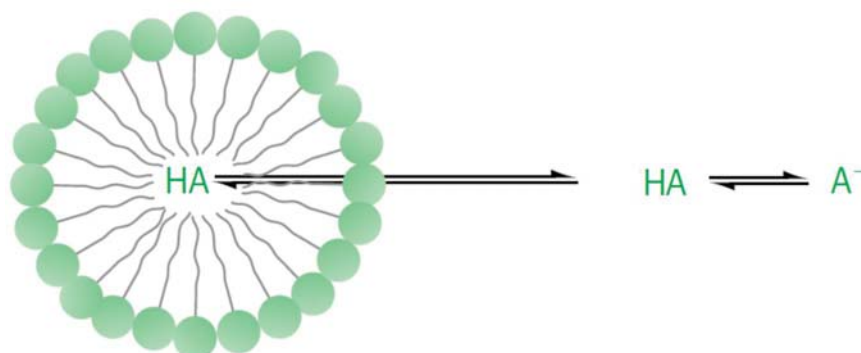


Preservatives

Factors Affecting Preservatives

Presence of Micelles

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.

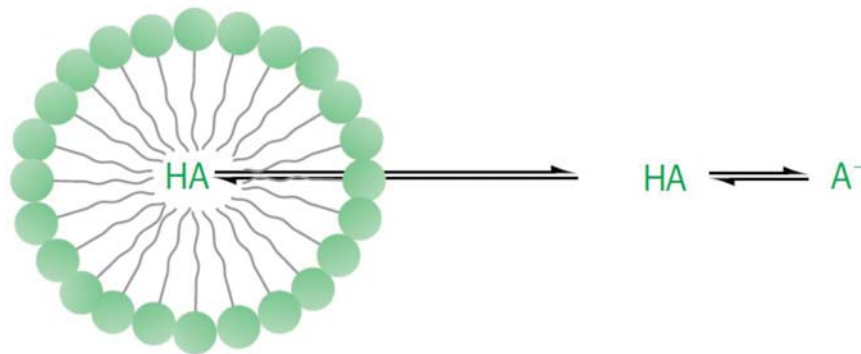


Preservatives

Factors Affecting Preservatives

Presence of Micelles

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



Preservatives

Factors Affecting Preservatives

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.

This problem is addressed by increasing the concentration of preservative in the formulation.



Preservatives

Factors Affecting Preservatives

Presence of hydrophilic polymers

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.



Flavoring Agents

Taste Making

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.



Flavoring Agents

Flavors

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:

Taste	Flavors
Salty	Apricot, Peach, Vanilla, Wintergreen mint
Bitter	Chocolate, Cherry, Mint, Anise
Sweet	Vanilla, fruit and berry
Sour	Citrus flavours, Raspberry



Flavoring Agents

Flavour Adjuncts

Usually a combination of flavours is used to achieve the optimal taste-masking property.

Certain excipients may be 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.



Coloring Agents

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.



References

Sinko, P. J. M. A. N. 2006. *Martin's physical pharmacy and pharmaceutical sciences: physical chemical and biopharmaceutical principles in the pharmaceutical sciences*, Philadelphia, Lippincott Williams & Wilkins.

