**Oral Solutions**

- Oral liquids containing one or more active ingredients dissolved in a suitable vehicle

**Formulation of oral solutions**

- Check solubility of drug
- If decide to formulate as a solution will have to dissolve drug in the vehicle
- Ideal solvent is water
  - Freely available, cheap, non-toxic
  - Purified water
- BUT not all drugs are soluble in water
- Stability issues – some drugs are not stable in aqueous solution
- pH dependent solubility and stability

**Improving aqueous solubility**

- Cosolvency
  - Ethanol, glycerol, propylene glycol, syrup
- pH control
  - Weak acids, weak bases
  - Consider pH-dependent stability
  - Preservative activity
- Solubilization
- Complexation
- Chemical modification

**Formulation Additives**

- Buffers
  - Carbonate, citrate, phosphate, lactate, gluconate, tartrate
- Colours
- Flavours, sweetening agents
- Preservatives
- Antioxidants

**Colours**

- Soluble in water – dyes (insoluble in water – pigments)
  - See list in *Handbook of Pharmaceutical Excipients*
  - For extemporaneous preparation: amaranth solution 0.2 – 1 % v/v

**Flavouring agents**

<table>
<thead>
<tr>
<th>Taste of product</th>
<th>Suitable masking flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salty</td>
<td>Apricot, butterscotch, liquorice, peach, vanilla</td>
</tr>
<tr>
<td>Bitter</td>
<td>Anise, chocolate, mint, passion fruit, wild cherry</td>
</tr>
<tr>
<td>Sweet</td>
<td>Vanilla, fruits, berries</td>
</tr>
<tr>
<td>Sour</td>
<td>Citrus fruits, liquorice, raspberry</td>
</tr>
</tbody>
</table>
**Flavours, sweetening agents**

- [For extemporaneous dispensing]:
  - Syrup (~20% v/v – 60% v/v)
  - Orange syrup (~10 - 20% v/v)
  - Raspberry syrup (~10 - 20% v/v)
  - Conc. raspberry juice (~2.5 - 5% v/v)
  - Concentrated peppermint emulsion (~2.5% v/v)
  - Sorbitol (oral solns.: 20-35% w/v; oral susps.: 70% w/v)
  - Saccharin (0.02 – 0.5% w/v)
  - Sodium cyclamate (0.01 – 0.15% w/v)
  - Anise water (0.5% v/v)
  - Conc. camphor water (1% v/v)
  - Liquorice liquid extract (5% v/v)
  - Glycerol (up to 20% in alcoholic elixirs)

**Preservatives**

- Chemical agents that prevent growth of microorganisms in the product, thereby rendering it safe in use and increasing its shelf life.
- Microorganisms may cause several problems as, e.g., undesired visible growth or chemical changes of the product. Contamination by microorganisms may also be associated with health hazards.
- Preservatives are typically used in liquid products that do not have extreme pH values or a high concentration of surfactants. E.g., products with a pH between 3 and 10 generally require preservative(s) to avoid growth.

**Preservatives contd.**

- Chloroform water
  - Double strength
  - Single strength
- Chloroform spirit
- Appropriate volumes should be used such that final concentration of chloroform in the preparation is 0.25% v/v

**Chloroform water, chloroform spirit**

- Chloroform spirit
  - Chloroform 50ml
  - Ethanol (90%) to 1000ml
- Chloroform water
  - Chloroform 2.5ml
  - Water to 1000ml
- Double strength chloroform water
  - Chloroform 5ml
  - Water to 1000ml

Concentrated chloroform water 10% v/v chloroform, i.e. 20 x conc. of double strength chloroform water

[1998] Peppermint water for 4 day old infant with colic, 3.75 ml peppermint emulsion + 75 ml DSCW – make up to 150 ml with water

**Preservatives contd.**

- Ethanol ≥10% v/v
  - Benzyl alcohol -> 2.0% v/v (N.B. don’t use in newborns – fatal adverse reactions).
  - Optimum activity at pH less than 5
- Glycerol (Glycerin) ≥20% w/v
  - Propylene glycol 15-30% w/v
  - Used as sweetening agent in alcoholic elixirs (up to 20%)
  - Also used as solvent/co-solvent

**2. Paediatric Paracetamol Oral Solution B.P.**

**M. 25 ml**

**Label N.P.**

**DEFINITION**

- Paediatric Paracetamol Oral Solution is a solution containing 2.4% w/v of Paracetamol in a suitable flavoured vehicle.
- Paediatric Paracetamol Oral Solution should not be diluted.
Step 1: solubility of paracetamol?

- Martindale: “Sparingly soluble in water; freely soluble in alcohol; very slightly soluble in dichloromethane.”
- Sparingly soluble: 1 in 30 to 1 in 100
  - 2.4% w/v = 2.4 g in 100 ml or 0.6 g in 25 ml
  - To dissolve 0.6 g need ~60 ml water!!
- Freely soluble: 1 in 1 to 1 in 10
  - To dissolve 0.6 g need ~6 ml alcohol (24% v/v)
  - Use alcohol as co-solvent
- Pharmaceutical Codex: “Soluble, at 20°, in 70 parts of water, in 7 parts of alcohol, in 13 parts of acetone, in 40 parts of glycerol and in 9 parts of propylene glycol…”
  - Could use propylene glycol as co-solvent
  - To dissolve 0.6 g need 5.4 ml propylene glycol

Ethanol in liquid preparations intended for children


**TABLE 1. Volume (Milliliters) of Ethanol Preparation Predicted to Produce a Blood Ethanol Concentration of 25 mg/100 ml**

<table>
<thead>
<tr>
<th>% Ethanol</th>
<th>Age (Weight)</th>
<th>2yr</th>
<th>4yr</th>
<th>6yr</th>
<th>8yr</th>
<th>10yr</th>
<th>12yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>1.524</td>
<td>2.432</td>
<td>3.192</td>
<td>4.104</td>
<td>4.964</td>
<td>5.776</td>
<td></td>
</tr>
<tr>
<td>5.0</td>
<td>912</td>
<td>1,216</td>
<td>1,796</td>
<td>2,092</td>
<td>2,432</td>
<td>2,888</td>
<td></td>
</tr>
<tr>
<td>7.5</td>
<td>695</td>
<td>851</td>
<td>1,094</td>
<td>1,386</td>
<td>1,662</td>
<td>1,952</td>
<td></td>
</tr>
<tr>
<td>10.0</td>
<td>456</td>
<td>590</td>
<td>728</td>
<td>926</td>
<td>1,121</td>
<td>1,444</td>
<td></td>
</tr>
<tr>
<td>12.5</td>
<td>365</td>
<td>486</td>
<td>638</td>
<td>821</td>
<td>973</td>
<td>1,155</td>
<td></td>
</tr>
<tr>
<td>15.0</td>
<td>294</td>
<td>399</td>
<td>513</td>
<td>611</td>
<td>716</td>
<td>803</td>
<td></td>
</tr>
<tr>
<td>20.0</td>
<td>228</td>
<td>304</td>
<td>400</td>
<td>513</td>
<td>608</td>
<td>722</td>
<td></td>
</tr>
<tr>
<td>25.0</td>
<td>162</td>
<td>243</td>
<td>319</td>
<td>410</td>
<td>496</td>
<td>578</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 2. Volume (Milliliters) of Ethanol Preparation Predicted to Produce a Potential Lethal Dose**

<table>
<thead>
<tr>
<th>Ethanol</th>
<th>2yr</th>
<th>4yr</th>
<th>6yr</th>
<th>8yr</th>
<th>10yr</th>
<th>12yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
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<tr>
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<td>1,662</td>
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<td>319</td>
<td>410</td>
<td>496</td>
<td>578</td>
</tr>
</tbody>
</table>

**Recommendations**

- Over the counter (OTC) liquid preparations should be limited to a maximum of 5% v/v ethanol
- Physician supervision is suggested for children less than 6 years using OTC preparations containing alcohol
- The amount of ethanol contained in any medicinal preparation should not be able to produce a blood concentration greater than 25 mg/100 ml after a single recommended dose and appropriate intervals between doses to prevent accumulation

IPHA Medicines Compendium

- Dozol syrup
  - 120mg/5ml paracetamol = 2.4% w/v
  - Macrogol 4000
  - Glycerol
  - Propylene glycol
  - Liquid sorbitol 70%
  - Liquid maltitol
  - Sodium cyclamate
  - Nipasept
  - Anatto extract (E160)
  - Ponceau 4R (E124)
  - Caramel flavour
  - Purified water

- Paralink Paracetamol Solution
  - 120mg/5ml paracetamol = 2.4% w/v
  - Polyethylene glycol 4000
  - (Macrogol 4000)
  - Glycerol
  - Propylene glycol
  - Ethanol (absolute alcohol)
  - Liquid sorbitol 70%
  - Liquid maltitol
  - Sodium cyclamate
  - Nipasept
  - Raspberry superbe
  - Purified water
Your formulation??

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>24 g</td>
</tr>
<tr>
<td>Colouring agent (e.g. Amaranth solution)</td>
<td>q.s.</td>
</tr>
<tr>
<td>Preservative (e.g. benzoic acid, chloroform - from chloroform spirit, single or double strength chloroform water)</td>
<td>q.s.</td>
</tr>
<tr>
<td>Flavouring agent/sweetening agent</td>
<td>q.s.</td>
</tr>
<tr>
<td>Cosolvent(s)</td>
<td>q.s.</td>
</tr>
<tr>
<td>Water to</td>
<td>1000 ml</td>
</tr>
</tbody>
</table>
Preservatives contd.

- Ethanol ≥10% v/v
- Benzyl alcohol → 2.0% v/v (N.B. don’t use in newborns – fatal adverse reactions). Optimum activity at pH less than 5
- Glycerol (Glycerin) >20% w/v
- Propylene glycol 15-30% w/v

Optimum activity at pH less than 5

Preservatives contd.

- Benzoic acid
  - Oral solns & susps: 0.01 - 0.1% w/v
  - Slightly soluble in water, freely soluble in EtOH
  - Greatest activity at pH ≤ 5
  - Benzoic acid solution B.P.
    - Benzoic acid 50 g
    - Propylene glycol 750 ml
    - Water to 1000 ml
- Sodium benzoate
  - Freely soluble in water, sparingly soluble in EtOH
  - 0.02 - 0.5% w/v
- Sorbic acid
  - 0.05 – 0.2% w/v
  - No antibacterial activity at pH > 6
- Potassium sorbate
  - 0.1 - 0.2% w/v

Preservatives contd.

- Parabens (Hydroxybenzoate)
  - Esters of 4-hydroxybenzoic acid, only differing in the ester group
  - Butylparaben
    - 0.006-0.05% w/v for oral solns. and susps.
  - Ethylparaben
    - 0.01-0.05% w/v for oral solns. and susps.
  - Methylparaben
    - 0.015-0.02% w/v for oral solns. and susps.
  - Propylparaben
    - 0.01-0.02% w/v for oral solns. and susps.

As a group effective over wide pH range (4-8) and have broad antimicrobial activity

Often used in combination – activity may be improved – additive effects (e.g. Nipasept)

Poor solubility – often used as sodium salt

Antioxidants

- Ascorbic acid and sodium ascorbate
  - 0.01 - 0.1% w/v
- Sodium metabisulphite
  - 0.01 - 0.1% w/v

Types of Oral Solutions

- Mixtures are oral liquids, usually aqueous preparations, containing one or more active ingredients dissolved or suspended in a suitable vehicle.
Types of Oral Solutions contd.

- **Elixirs** are clear, flavoured oral liquids containing one or more active ingredients dissolved in a vehicle that usually contains a high proportion of Sucrose or a suitable polyhydric alcohol or alcohols and may also contain Ethanol (96 per cent) or a Dilute Ethanol.
  - Polyhydric alcohol: alcohols containing >1 hydroxyl group – glycols e.g. propylene glycol \( CH_2CH(OH)CH_2OH \); polyethylene glycols (PEGs, macrogols) \( OHCH_2(CH_2CH_2O)_nCH_2OH \); glycerol \( CH_2OHCHOHCH_2OH \)

- **Linctuses** are viscous oral liquids that may contain one or more active ingredients in solution. The vehicle usually contains a high proportion of Sucrose, other sugars or a suitable polyhydric alcohol or alcohols. Linctuses are intended for use in the treatment or relief of cough, and are sipped and swallowed slowly without the addition of water.

Types of Oral Solutions contd.

**Oral Suspensions**

- Oral Suspensions are Oral Liquids containing one or more active ingredients suspended in a suitable vehicle. Suspended solids may slowly separate on standing but are easily redispersed.

Advantages of formulating products as oral suspensions

- Suspended insoluble powders easier to swallow than tablets/capsules
- Uniform dispersal of disperse phase for more effective absorption after dosing
- Good for bulky insoluble powders e.g. Kaolin B.P.
- Insoluble derivative may be more palatable than soluble equivalent
- Insoluble derivative may be more stable in suspension than equivalent soluble salt
  - Superior chemical stability of dispersed drugs in comparison to solutions

- If a drug is not very soluble can formulate as a suspension – a dispersion of finely divided insoluble solid particles (the disperse phase) in a fluid (the dispersion medium)
- The suspension must remain sufficiently homogeneous for at least a period between shaking the container and removing the required dose
- The sediment produced on storage must be easily resuspended by the use of moderate agitation

Stokes’ law

\[
v = \frac{(\rho_s - \rho_f) g d^2}{18 \eta}
\]

- \( v \): velocity of fall (rate of sedimentation)
- \( g \): acceleration due to gravity
- \( \rho_s \): density of sphere
- \( \rho_f \): density of liquid
- \( d \): diameter of sphere
- \( \eta \): viscosity of liquid
Ways of reducing rate of sedimentation

- Reduce particle size
  - Particle size may change on storage particularly if there is temperature fluctuation: solubility may increase as temp. increases, on cooling drug will crystallise out.

- Reduce density difference between particle and liquid
  - Increase liquid density
    - Add sucrose, sorbitol, glucose, glycerol or other soluble, non-toxic materials – density modifiers (may also be viscosity modifiers)

- Increase liquid viscosity
  - Add a thickening or suspending agent
Diffusible and indiffusible solids

- **Diffusible solid** – does not dissolve in the vehicle but may be mixed with vehicle so that, upon shaking, the powder is evenly diffused throughout the liquid for sufficient time to ensure uniform distribution in each dose. e.g. light kaolin, light magnesium carbonate (in Kaolin Mixture B.P.)
- **Indiffusible solid** – a solid is regarded as indiffusible when it does not remain evenly distributed in the vehicle long enough to ensure uniformity of the measured dose – the vehicle must therefore must be increased in viscosity – use a suspending agent

Ideal properties of suspending agents/thickeners/viscosity modifiers

- Must be able to readily and uniformly incorporate into substance to be suspended
- Should readily dispersed when added to water
- Shouldn’t interfere with dissolution or absorption of drug
- Should ensure uniform distribution of insoluble material
- Should be inert, non-toxic and free from incompatibilities
- Should be acceptable colour, odour and have a bland taste
- Free from microbial contamination
- Readily available and inexpensive

Suspending agents

- Polysaccharides
- Water-soluble celluloses
- Hydrated silicates
- Carbopol

Polysaccharides

- Acacia gum (gum arabic, from acacia tree)
  - Often used as a thickening agent for extemporaneously prepared oral suspensions (in a concentration of 5-15% w/v)
  - Soluble 1 in 2.7 water
  - Very sticky - not used for external preps.
  - Not very good for dense powders but often used in combination with other thickeners as in Compound Tragacanth Powder BP which contains acacia, tragacanth, starch and sucrose
  - Acacia muclilage becomes acidic on storage

Polysaccharides contd.

- Xanthan gum (produced by fermentation of glucose or sucrose by the Xanthomonas campestris bacterium)
  - Widely used in oral and topical products
    - Good stability and viscosity over a wide temperature (10-60°C) and pH (3-12) range
    - Soluble in cold or warm water
    - Commercially available as Keltrol® (0.4%, 1% solution)

Extemporaneous preparation

The following formula applies.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light Kaolin or Light Kaolin (Natural)</td>
<td>200 g</td>
</tr>
<tr>
<td>Light Magnesium Carbonate</td>
<td>50 g</td>
</tr>
<tr>
<td>Sodium Bicarbonate</td>
<td>50 g</td>
</tr>
<tr>
<td>Concentrated Peppermint Emulsion</td>
<td>25 ml</td>
</tr>
<tr>
<td>Double Strength Chloroform Water</td>
<td>500 ml</td>
</tr>
<tr>
<td>Water Sufficient to produce</td>
<td>1000 ml</td>
</tr>
</tbody>
</table>

Kaolin Mixture B.P.
**Polysaccharides contd.**

- Tragacanth (from Astragalus gummifer, Astragalus tragacanthus)
  - Can be used for internal and external products
  - Practically insoluble in water but swells rapidly in 10 times its own weight of hot or cold water to produce viscous colloidal sols or semigels
  - Takes several days to hydrate fully and achieve maximum viscosity after dispersion in water
  - Thixotropic
  - Don’t add directly to water (clumps) – disperse first in alcohol
  - Tragacanth mucilage is prepared with alcohol and chloroform water (1.25% tragacanth) and the proportion used as a suspending agent is one-quarter of the volume of the mixture
  - Compound Tragacanth Powder BP is used in concentrations of 2-4% w/v
    - Acacia, starch, sucrose, tragacanth

**Water-soluble celluloses**

- Methylcellulose
  - Semisynthetic polysaccharide of the general formula 
    \[ \text{[C}_{x}\text{H}_{y}\text{O}_{z}\text{OH}]_{n} \]
  - Produced by the methylation of cellulose

  ![Cellulose](image1.png)
  ![Methylcellulose](image2.png)

- Hydroxyethylcellulose
  - Hydroxyethyl instead of methyl on cellulose chains
  - Soluble in both hot and cold water
  - Similar to methylcellulose

- Sodium carboxymethylcellulose
  - Clear solutions in hot and cold water
  - Anionic; incompatible with polyvalent cations, acid precipitates at low pH
  - Used at concentrations up to 1%

**Water-soluble celluloses contd.**

- Algic acid (prepared from kelp)
  - Algic acid – Swells in water but does not dissolve – absorbs 200-300 its own weight of water
  - Alginate mucilages must not be heated above 60 °C – depolymerization occurs with loss of viscosity
  - Sodium alginate is the most widely used salt (1-5% w/v) – anionic – will be incompatible with cationic materials; slowly soluble in water giving viscous colloidal solution

- Starch
  - Maize, rice, potato, corn
  - Slightly soluble to soluble in water
  - Rarely used alone
    - One of constituents of Compound Tragacanth Powder
    - Can be used with sodium carboxymethylcellulose

**Microcrystalline cellulose (Avicel™)**

- Purified, partially depolymerised cellulose
- Thixotropic
- Often used with other cellulose derivatives
Ora-plus®

- Water 97 %
- Sodium phosphate monobasic <1 %
- Sodium carboxymethylcellulose <1 %
- Microcrystalline cellulose <1 %
- Xanthan gum <1 %
- Carrageenan <1 %