Solutions and parenteral products

Alton

Chapter

3,5,6,25,43

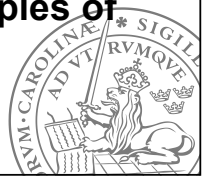
Questions for exam

How to send in questions

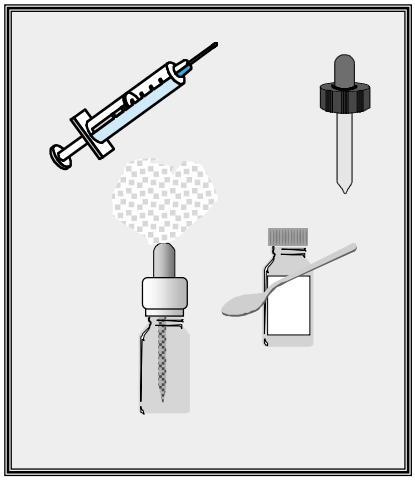
eval.ced.lu.se/eval/pub/267463/default.asp

Good examples for yesterdays lectures

- **How can you use the Classification of drug substances as a guideline to determine what type of drug formulation to develop?**
- **Discuss with each other other examples of good questions**



Formulations that are solutions



- Injectabilia
  - Free of particles
  - Sterile, osmolality
- Eyedrops
  - Viscosity
- Nasal sprays and nebulizers
  - Drop size
  - Viscosity
- Oral solutions
  - Taste and viscosity
- Topical solutions

Why use solutions?

- Fast uptake - No release concerns
- The delivery route demands a solution
- Easy to administrate to unconscious patients or patients with problems to swallow
- Easy to individualise dose

What characterises solutions

Colligative properties
- Osmolality
- Freeze point depression
- Vapour pressure

Ionic strength
- Osmolality
- Electrostatic
- Stability of the active components

pH
- Solubility
- Irritation
- Stability of the active components

Flow properties: rheology
- Injectability
- Bioavailability
- Stability of dispersions and foams

Surface tension
- Bioavailability
- Stability of dispersions and foams

organoleptic properties
- Taste
- Mouth feel

Other characteristics
- Colour
- Transparency

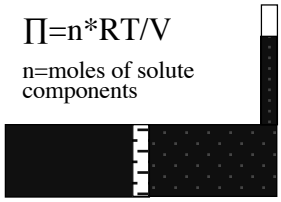
Osmolality

Definition

The osmotic pressure of a solution is the external force that needs to be applied to prevent dilution of the solution by entry of solution

$\Pi = n*RT/V$

n=moles of solute components



Osmotic differences can cause
- Haemolysis
- Exomosis
- Skin irritation

•**Hypotonic solutions< blood**
•**Hypertonic solutions>blood**
•**Isotonic solutions= blood** 240 to 340 mOmsm.

Ionic strength

Definition

$$I = \frac{1}{2}\sum C_i * z_i^2$$

If you have a buffer what will change its ionic strength?

Ionic strength effects electrostatics and thus:

- **The structure of polymers**
- **Adsorption**
- **Solubility**
- **The stability of colloidal solutions and foams**

pH

Effects on active components

- **Stability**
- **Uptake**

Effects on other excipients

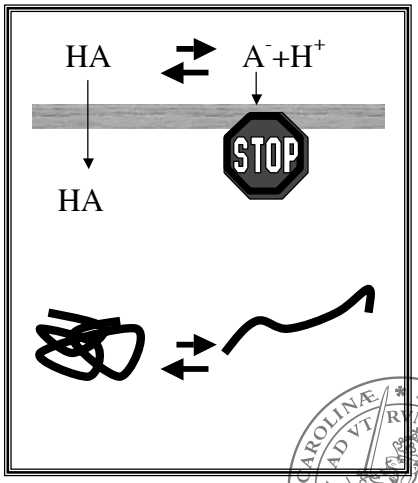
- **Influence on electrostatics**
- **Stability**

Effects on patient

- **Skin irritation**
- **Pain**

Effects microbiology

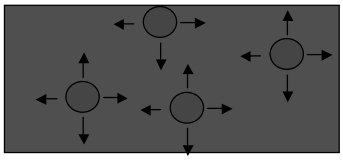
Effects osmolality



Surface tension and surface free energy

Definition

The amount of work needed to increase the surface area by one unit.



Effects:

- **Surface tension reduction is the driving force for adsorption to interfaces.**
- **Drop size of sprays**
- **Foam formation**
- **Formation and stabilisation of emulsion**
- **Wetting of powders**
- **Film coating**
- **Dissolution**

Solvents commonly used in pharmaceutical preparations

- **Water**
  - **Purified water (RO)**
  - **Water for injection (Distilled)**
    - **Pyrogen free and endotoxin free**
    - **Have low conductivity**
    - **Have low amounts of organic molecules**
- **Cosolvents**
  - **They increase solubility of other substances by lowering dielectric constant of water**
  - **Ethanol, propylenglycol, and glycerol**
- **Buffers**
- **Other solvents**
  - **Hydrophilic ones**
    - **Ethanol**
    - **DMSO**
    - **Propylene glycol**
    - **PEG**
  - **Hydrophobic ones**
    - **Oils**

Other additives to solutions

- **Preservatives**
  - **Phenol**
  - **Parabens**
  - **Benzoic acid**
- **Colours, flavours, perfumes, and sweetening agents**

Salty	Apricot, vanilla, liquorice
Bitter	Anise,chocolate, mint
Sweet	Vanilla, fruits, berries
Sour	Citrus fruits, liquorice

- **Reducing agents**
  - **Vitamin E**
  - **Ascorbic acid**
- **Density and rheological modifiers**
  - **Polymers**
- **Sequestering agents**
  - **EDTA**
- **Substances that effect the surface activity**
  - **Polymers**
  - **Surfactants**

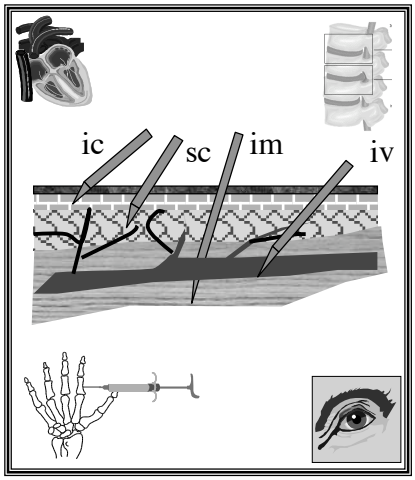
Chemical stability of solutions

- **Most common degradation pattern**
  - **Hydrolysis**
    - **pH**
    - **Ions**
  - **Oxidation**
    - **pH**
    - **Ions**
    - **Excipients**
  - **Aggregation**
    - **Concentration**

Tricks to increase chemical stability

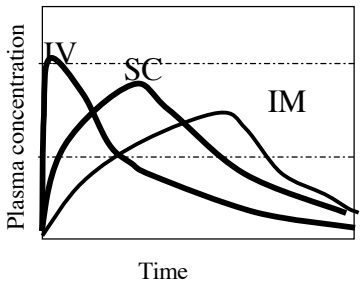
- **Choice of pH**
- **Antioxidants (reducing agents)**
  - **Sodium bisulphate**
  - **Ascorbic acid**
  - **Vitamin E**
- **Sequestering agents**
  - **EDTA**
- **Replacing air by an inert gas**

Injectabilia: routes of administration



- Intracutaneous or intradermal
- Subcutaneous or hypodermic
- Intramuscular
- Intravascular
- Intracardiac
- Intraspinal
- Intra-articular
- Ophthalmic

Pharmacokinetics of injectabilia



- **Simple solutions**
  - **IV>SC>IM**
- **Delayed release**
  - **Choice of the solvent: oil decreases release**
  - **Injection of suspensions**
  - **Controlled- release formulations**

Formulation: Patient compliance

- Choice of osmotic pressure of the formulation
  - IV: Isotonic or hypertonic
  - SC: Isotonic
  - IM: Hypertonic
- Skin irritation
  - Optimal pH≈7
  - For intrathecal, peridural and intracisternal injections pH 7.0-7.6
- Viscosity
  - Ease of injection

Formulation: Safety

Microbiological safety

- Bacterial infection
  - Single-dose products
    - Container integrity
    - Sterilisation procedure
  - Multiple-dose products
    - Container integrity
    - Sterilisation procedure
    - Bactericides
- Endotoxines
  - Quality control of excipients, including water

Particles

- Biological risks
  - Inflammatory response
  - Antigenic response
  - Occlusion of blood vessels
- Sources of particles
  - Excipients
  - Processes
  - Packing materials

Microbiological quality: sterile products

- 100% sterility: difficult to measure: Validation of process and suitable in process tests
- Authorities' definition of sterility is that there is a risk of finding one non sterile product out of a million
- If a product fail sterility testing it has failed if there is not an obvious reason to suspect analytical errors in that case retesting is allowed

Sterility testing - things to consider

- Risk of contamination during testing
  - Conduct the test in a clean room, LAF bench or isolator
  - Test of the medium
- Risk that antibacterial substances influence preservative tests:
  - Inactivating these by heat for example
  - Filtrating the sample and testing the filter
  - Validate that no interference exists

Microbiologic quality- endotoxin and pyrogen tests

Definitions

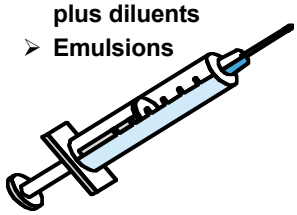
- Pyrogen
  - A pyrogen substance gives rise to an elevated body temperature when injected.
- Endotoxins
  - Lipopolysaccharides from the cell walls of Gram-negative bacteria. These are often pyrogens

Testing pyrogens

- Testing products on rabbits
- The Limulus Amoebocyte Lysate test (LAL)- measures gel formation in the lyses products of the amoebocyte cells of the giant horseshoe crab

Things to consider regarding formulation of parenteral products

- **Types**
  - **Solution**
  - **Suspension**
  - **Reconstructed solution, a powder (often lyophilised) plus diluents**
  - **Emulsions**



- **Volume of injection**
  - **IV**
    - **Injection of max 20 ml**
    - **Infusion of min 250 ml**
  - **SC and IM**
    - **Small volumes**
- **Single- or multi dose- container**
  - **A multi-dose container requires use of bactericides**
- **Excipients**
- **Type of packing material**

Solutions and suspension

Solutions

- **The simplest and thus preferred form**
- **Risk of low stability of the active compound**
- **Normally rapid uptake**
- **Important quality parameters**
  - **pH**
  - **Osmolality (ionic strength)**
  - **Sterility**
  - **Content and impurities**

Suspensions

- **Particles suspended in a solution**
- **Not thermodynamilly stable**
- **Used for substances of low solubility or for controlled released formulations**
- **Critical parameter the same as for solutions plus particle size**

Reconstituted powders + diluent

- Mainly for biotech products
  - Increase shelf-life stability
  - Most commonly formulated as a lyophilised powders
- Advantages of lyophilisation
  - Avoiding high temperatures
  - Providing a light porous powder
  - Rather easy to reconstitute
  - There is no concentration of the solution prior to drying
  - Can be produced under sterile conditions
- Disadvantages
  - A hygroscopic product
  - It is a slow process
  - It is expensive to adapt to non-aqueous solutions
- Critical factors
  - The amount of water remaining
  - Risk of aggregation
    - Include fillers such as Manitol, Trehalose to avoid this

Emulsions for injection

- **Emulsions are used for:**
  - **Delivery of oily substances via IV**
  - **Parenteral nutrition (Intralipid)**
  - **Delayed release**

Safety

- **The ideal sizes for emulsion droplets are 0.5-1.0 μm, equal to the size of chylomicra**
- **Should not be larger than 3 μm for IV**

Excipients for injectabilia and solutions

Common excipients

- **Solvents**
- **Buffers**
  - **Carbonates**
  - **Citrates**
  - **Phosphates**
- **Isotonic modifiers**
  - **Sodium chloride**
  - **Dextrose**

- **Special requirements on the excipients**
  - **Microbiology**
  - **Toxins**
- **Limitation on the excipients**
  - **Should not be used unless proven valuable**
  - **Few excipients are accepted for parenteral use**
  - **Few qualities of excipients conform to the standard set for parenteral use.**

Packing material and device

- **User compliance**
  - **Prefilled syringes**
  - **Multi- or single- dose containers**
  - **Pumps**
  - **Needle free delivery**
    - **Laws in some states in the US that benefits needle-free or safe needle delivery**

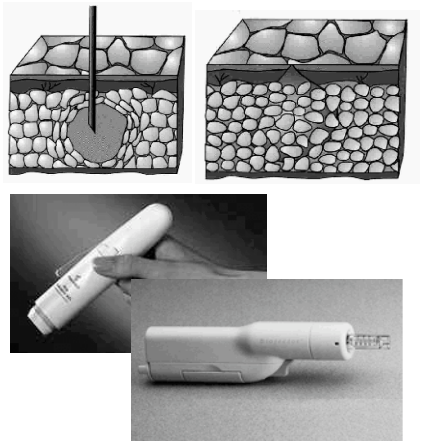
- **Safety**
  - **Integrity of the packing material**
  - **Avoiding contamination of the product from packing material**
  - **Stopping the sharing of needles**

Problems connected with needles

- Difficult for patients to use
- Dangerous for healthcare professionals employing them
- Risk of contamination, particularly in Third World countries
  - 16 million cases of Hep B
  - 4,5 million cases of Hep C
  - 150 000 million cases of HIV

One child dies every 10 s due to disease caused by contaminated needles

Needle free delivery



- Principles of needle-free injection
  - Solution or particles are accelerated to a speed sufficient to enable them to penetrate the skin
- Reason for development of needle free injection
  - Easier for patients to handle
  - Less pain and phobia
  - Avoids the use of contaminated needles
- The pharmacokinetics can be different from that of normal sc

- **Write down what you believe is important quality demands on a parenteral formulation?**

Terms to know from today's lecture

- **iv. = intravenous**
- **sc = subcutaneous**
- **im= intramuscular**
- **Hypotonic solutions< blood**
- **Hypertonic solutions>blood**
- **Isotonic solutions= blood**
- **Parenteral formulation: not administrated through the mouth**
- **Endotoxin and pyrogen: toxins that are especially dangerous for injectabilia**
- **Bactericides: substances that kills bacteria**