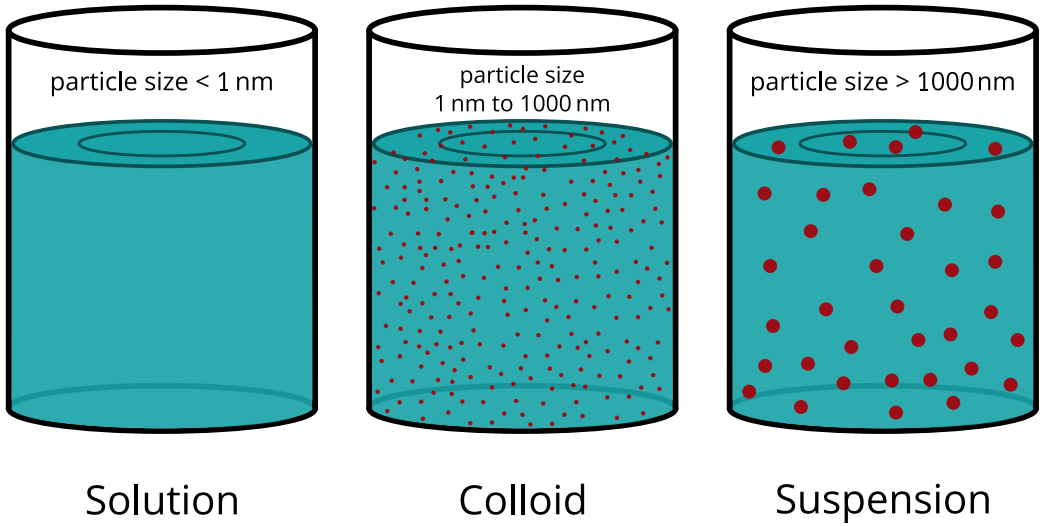
Suspensions

Introduction

- Suspensions contain **one or more insoluble** medicaments in a **vehicle**, with other additives such as preservatives, flavours, colours, buffers and stabilizers.
- Most pharmaceutical suspensions are aqueous, but an oily vehicle is sometimes used.
- Suspensions may be used for **oral administration, inhalation, topical application, as ophthalmic preparations, for parenteral administration and as aerosols.**



Introduction

- A pharmaceutical suspension may be defined as a **disperse system** in which one substance (**the disperse phase**) is distributed in particulate form throughout another (**the continuous phase**).
- Most are classified as a **coarse suspension**, which is a dispersion of particles with a mean diameter >1 μm.
- A **colloidal suspension** is a dispersion of particles with a mean diameter <1 μm.
- Suspended solids slowly separate on standing, but redispersion may be difficult if they form a compacted sediment.

Pharmaceutical applications of suspensions

- Drugs with low solubility in the continuous phase can be formulated as suspensions
- **Patient acceptability** – a liquid form rather than a solid dosage form
- Drugs that have an unpleasant taste in their soluble form can be made into insoluble derivatives, and formulated as a suspension, which will **be more palatable**, e.g. chloramphenicol (soluble) and chloramphenicol palmitate (insoluble)
- In oral suspensions, the drug is delivered in finely divided form, therefore optimal **dissolution** occurs in the gastrointestinal (GI) fluids and hence the **rate of absorption is increased**

Pharmaceutical applications of suspensions

- Insoluble forms of drugs may **prolong the action of a drug** by preventing rapid degradation in the continuous phase
- If the drug is unstable when in contact with the vehicle, suspensions should be **prepared immediately prior to handing out** to the patient.
- For example, in ampicillin suspension, water is added to powder or granules prior to giving out to the patient. A **14-day expiry date** is given, if the product is to be kept in the fridge

Pharmaceutical applications of suspensions

- Drugs which degrade in aqueous solution may be suspended in a **non-aqueous phase,** e.g. tetracycline hydrochloride has been suspended in a fractionated coconut oil for ophthalmic use
- **Bulky, insoluble powders** can be formulated as a suspension so that they are easier to take, e.g. kaolin, chalk and magnesium trisilicate
- **Intramuscular, intra-articular or subcutaneous injections** are often formulated as suspensions to prolong the release of the drug
- Lotions containing insoluble solids are formulated to **leave a thin coating of medicament on the skin**. Examples are Calamine Lotion BP and Sulphur Lotion Compound BPC.

Properties of a good pharmaceutical suspension

- In preparing a pharmaceutically elegant product, several desirable properties are sought:

I. There is **ready redispersion** of any sediment which accumulates on storage

II. After gentle shaking, the medicament **stays in suspension long enough** for a dose to be accurately measured

III. The suspension is **pourable**

IV. Particles in suspension are **small and relatively uniform in size**, so that the product is free from a gritty texture.

Formulation of suspensions

- The three steps that can be taken to ensure formulation of an elegant pharmaceutical suspension are:

1. **Control particle size**. On a small scale, this can be done using a mortar and pestle, to grind down ingredients to a fine powder
2. **Use a thickening agent** to increase viscosity of the vehicle, by using suspending or viscosity-increasing agents
3. **Use a wetting agent**.

Electrical double layer

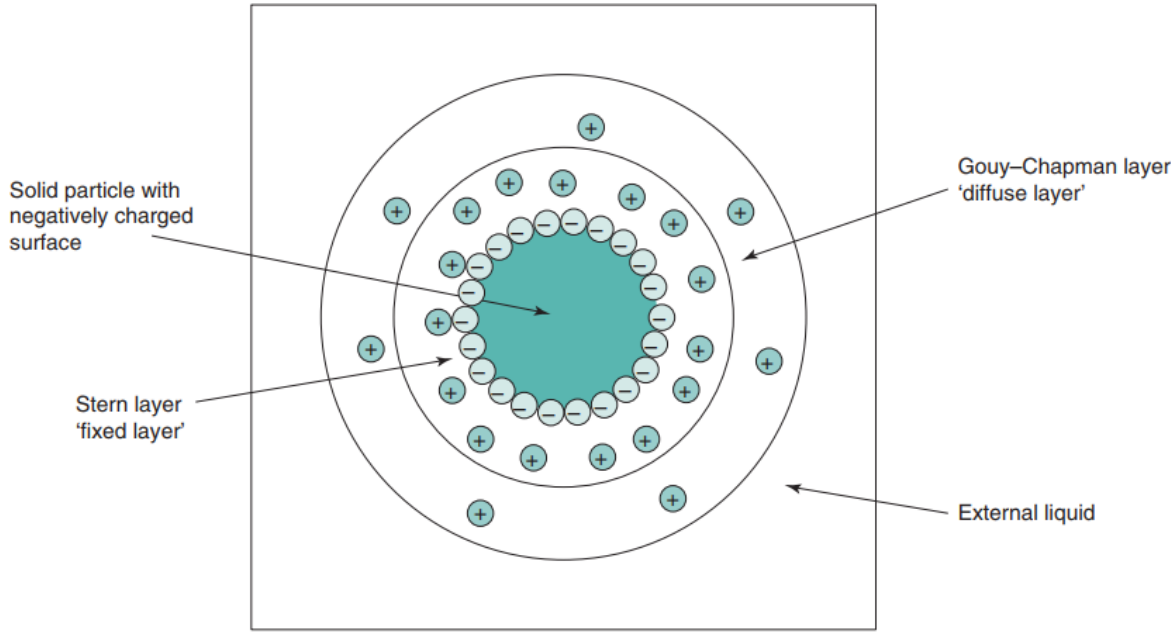
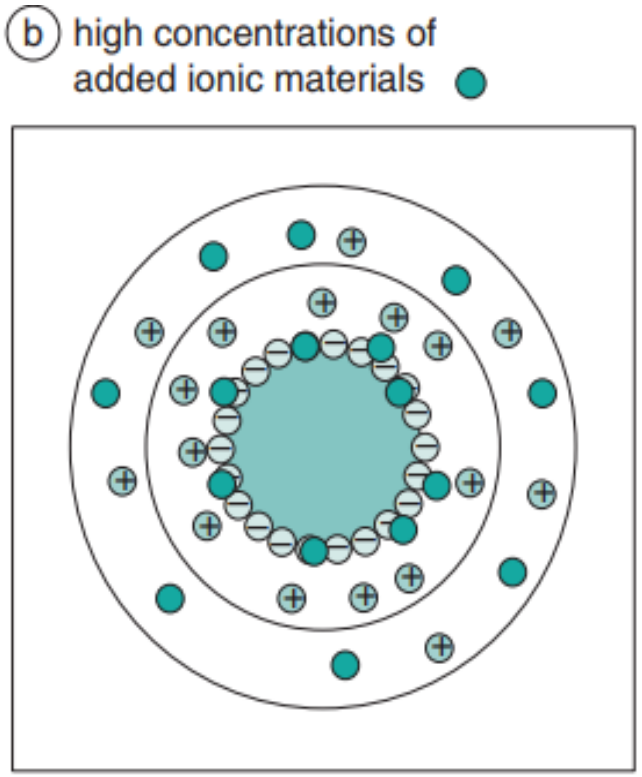
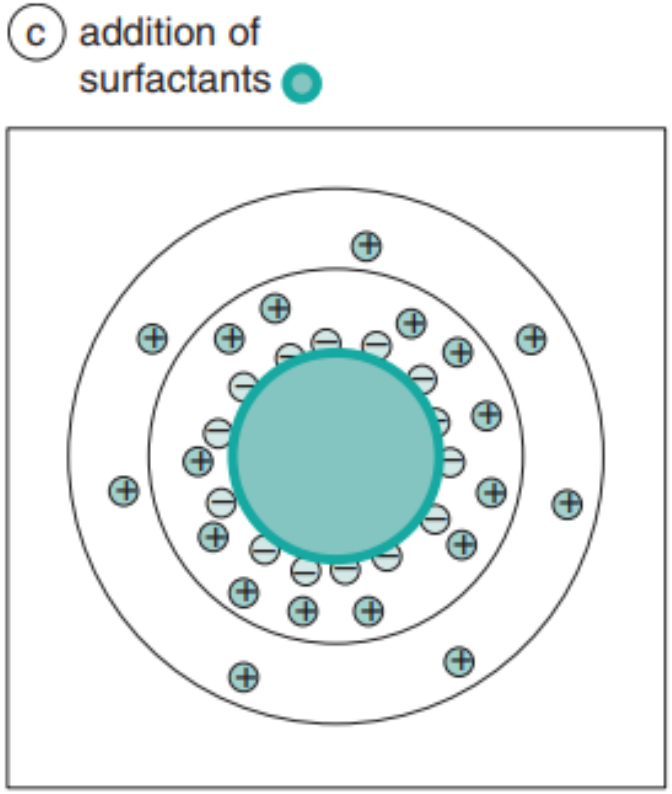


Fig. 26.1 • The electrical double layer: a single solid particle in a liquid medium.





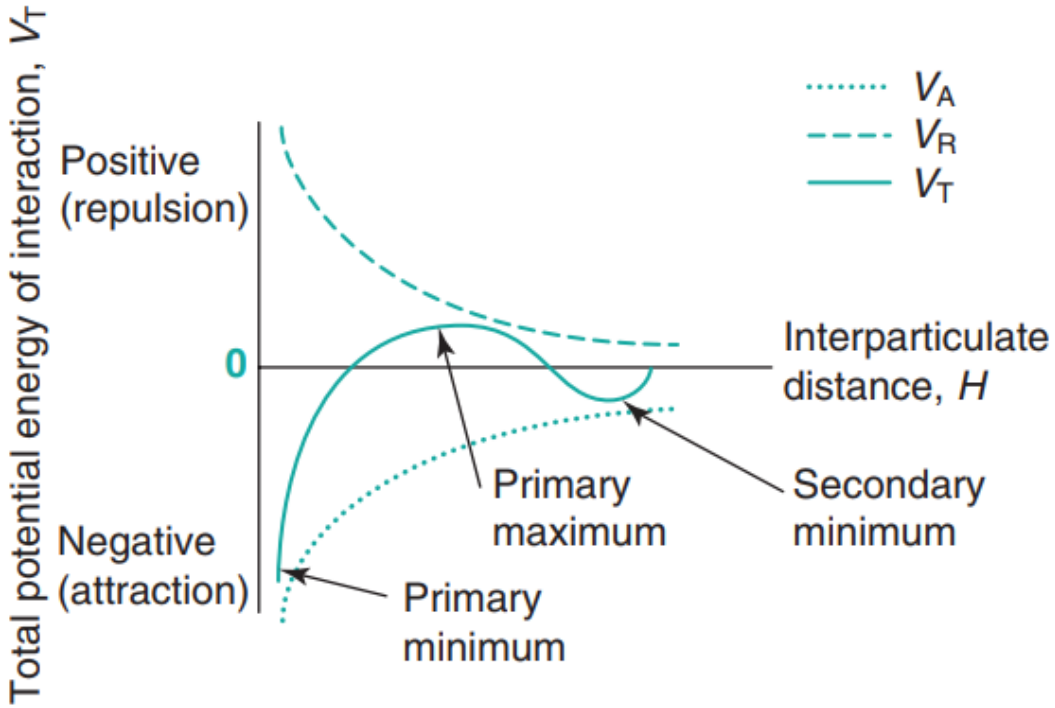


Fig. 26.3 • The energy of interaction between two similar particles, as described by the Derjaguin–Landau–Verwey–Overbeek theory.

Problems encountered when formulating insoluble solids into a suspension

1. Sedimentation

- The factors affecting the rate of sedimentation of a particle are described in **Stokes' equation**:
- where y = velocity of a spherical particle of radius r, and density ρ1, in a liquid of density ρ2, and viscosity η, and where g is the acceleration due to gravity.

$$y = \frac{2gr^2(\rho_1 - \rho_2)}{9\eta}$$

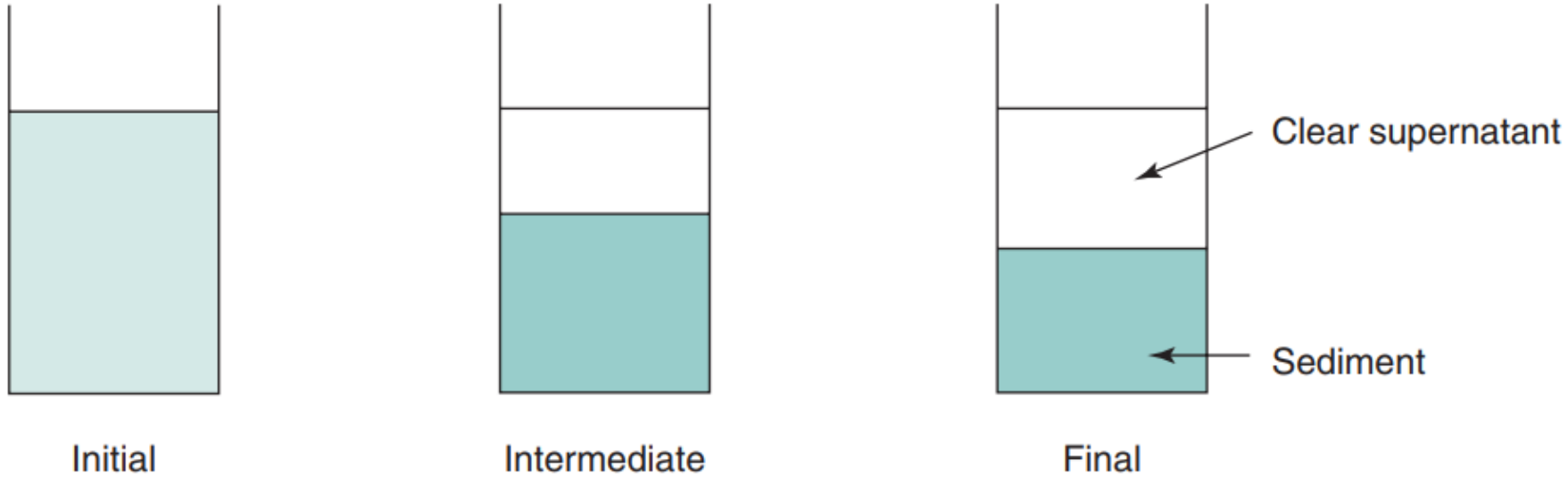


Fig. 26.6 • The sedimentation behaviour of a flocculated suspension. *Pale blue* indicates the initial suspension, *dark*

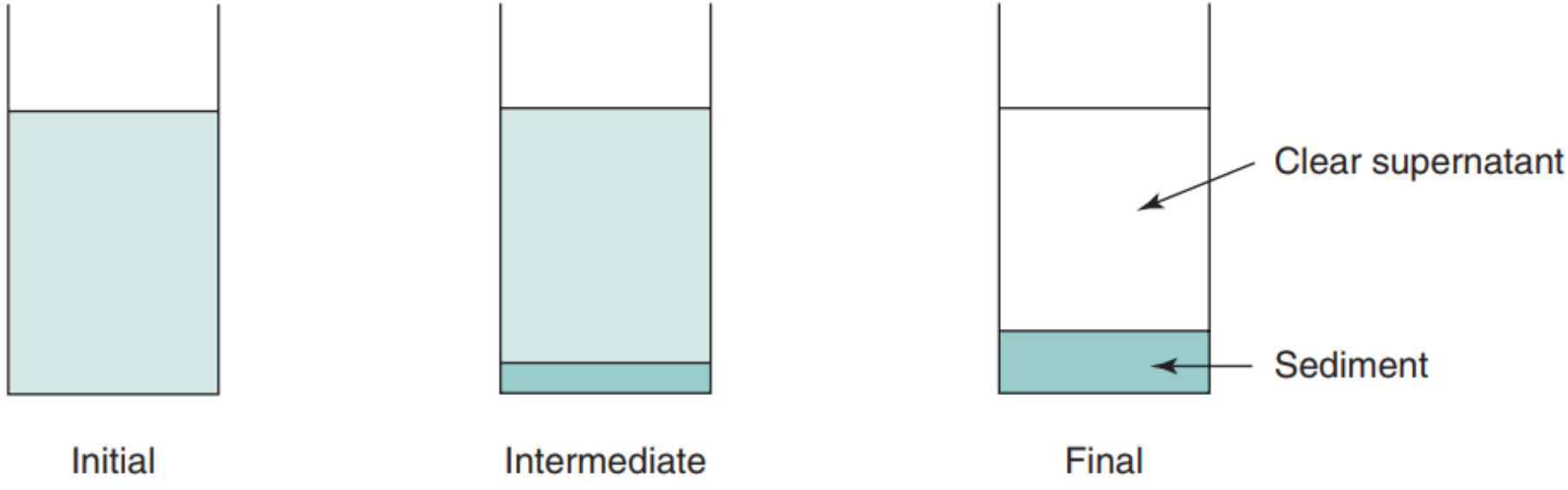


Fig. 26.7 • The sedimentation behaviour of a deflocculated suspension. *Pale blue* indicates the initial suspension, *dark blue* indicates the resulting sediment and *no colour* indicates an optically clear medium.

Problems encountered when formulating insoluble solids into a suspension

- The rate of fall of a suspended particle in a vehicle of a given density is **greater for larger particles** than it is for smaller particles.
- The greater the **difference in density** between the particles and vehicle, the greater will be the rate of descent.
- Increasing **the viscosity of the dispersion medium**, within limits, so that the suspension is still pourable, will reduce the rate of sedimentation of a solid drug.
- Thus, a decrease in settling rate in a suspension may be achieved by reducing the size of the particles and by increasing the density and the viscosity of the continuous phase.

Problems encountered when formulating insoluble solids into a suspension

2. Flocculation

- The natural tendency of particles towards aggregation.
- In a **deflocculated suspension**, the dispersed solid particles remain separate and settle slowly. However, the sediment that eventually forms is *hard to redisperse* and is described as a ‘cake’ or ‘clay’.
- In a **flocculated suspension**, individual particles aggregate into clumps or floccules in suspension. Because these flocs are larger than individual particles, sedimentation is more rapid, but the sediment is *loose* and *easily redispersible*.

Problems encountered when formulating insoluble solids into a suspension

- Excess flocculation may prevent ‘pourability’ due to its effect on rheological properties.
- The ideal is to use either a deflocculated system with a sufficiently high viscosity to prevent sedimentation, or controlled flocculation with a suitable combination of rate of sedimentation, type of sediment and pourability.

Problems encountered when formulating insoluble solids into a suspension

3. Wetting

- Air may be trapped in the particles of poorly wetted solids, which causes them to float to the surface of the preparation and prevents them from being readily dispersed throughout the vehicle.
- Wetting of the particles can be encouraged by reducing the interfacial tension between the solid and the vehicle, so that adsorbed air is displaced from solid surfaces by liquid.

Problems encountered when formulating insoluble solids into a suspension

- Hydrophilic colloids such as **acacia and tragacanth** can act as wetting agents. However, care should be taken when using these agents, as they can promote deflocculation.
- Intermediate HLB (hydrophilic–lipophilic balance) surfactants such as polysorbates and sorbitan esters are used for internal preparations.
- Solvents such as ethanol, glycerol and the glycols also facilitate wetting.
- Sodium lauryl sulphate and quillaia tincture are used in external preparations.

Suspending agents

- Suspending agents **increase the viscosity of the vehicle**, thereby slowing down sedimentation.
- Most agents can form **thixotropic gels** which are semisolid on standing, but flow readily after shaking. Care must be taken when selecting a suspending agent for oral preparations, as

A. The acid environment of the stomach may alter the physical characteristics of the suspension

B. Some suspending agents may also bind to certain medicaments, making them less bioavailable.

- Suspending agents can be divided into five broad categories:.

1. Natural polysaccharide

- The main problem with these agents is their **natural variability between batches and microbial contamination.**
- **Tragacanth** is a widely used suspending agent.
- Tragacanth Powder requires to be dispersed with the insoluble powders before water is added to prevent clumping.
- Compound Tragacanth Powder BP contains tragacanth, acacia, starch and sucrose and so is easier to use.
- Other examples include **acacia gum, starch, agar, guar gum, carrageenan and sodium alginate**.

2. Semi-synthetic polysaccharides

- These are derived from the naturally occurring polysaccharide **cellulose**.
- Examples include **methylcellulose** (Cologel®, Celacol®), **hydroxyethylcellulose** (Natrosol 250®), **sodium carboxymethylcellulose** (Carmellose sodium) and **microcrystalline cellulose** (Avicel®).

3. Clays

- These are naturally occurring inorganic materials, which are mainly **hydrated silicates**.
- Examples include **bentonite** and **magnesium aluminium silicate** (Veegum®).

4. Synthetic thickeners

- These were introduced to **overcome the variable quality of natural products.**
- Examples include **carbomer** (Carboxyvinyl polymer, Carbopol®), colloidal **silicon dioxide** (Aerosil®, Cab-o-sil®) and **polyvinyl alcohol.**

5. Miscellaneous compounds

- **Gelatin** is used as a suspending and viscosity increasing agent.

Preservation of suspensions

- **Water** is the most common source of microbial contamination.
- **The naturally occurring additives** such as acacia and tragacanth may be sources of microbes and spores.
- Preservative action may be diminished because of **adsorption of the preservative onto solid particles of drug**, or interaction with suspending agents.
- Useful preservatives in extemporaneous preparations include **chloroform water, benzoic acid and hydroxybenzoates**.

The dispensing of suspensions

1. Crystalline and granular solids are finely powdered in the mortar.
2. The suspending agent should then be added and mixed thoroughly in the mortar.
3. Add a little of the liquid vehicle to make a paste and mix well until smooth and free of lumps.
4. Continue with gradual additions until the mixture can be poured into a tared bottle.
5. Further liquid is used to rinse all the powder into the bottle, where it is made up to volume.

Special labels and advice for suspensions

I. The most important additional label for suspensions is '**Shake well before use**', as some sedimentation of medicament would normally be expected. Shaking the bottle will *redisperse the medicament* and ensure that the patient can measure *an accurate dose*.

II. 'Store in a cool place'. Stability of suspensions may be adversely affected by both extremes and variations of temperature. Some suspensions, such as those made by reconstituting dry powders, may need to be stored in a refrigerator.

Inhalations

- The **volatile components** are adsorbed onto the **surface of a diffusible solid** to ensure uniform dispersion throughout the liquid.
- When hot water is added, the oils vaporize.
- Where quantities are not stated, 1 g of light magnesium carbonate is used for each 2 mL of oil (such as eucalyptus oil) or 2 g of volatile solid (such as menthol).
- An example of a traditional inhalation is menthol and eucalyptus inhalation.

Action and uses.

- Traditionally used, but no longer recommended, for the treatment of acute diarrhoea.

Formulation notes.

- Light kaolin is a diffusible solid; therefore no suspending agent is required.

Example 34.1

Prepare 150 mL Kaolin and Morphine Mixture BP.

	Master formula	For 150 mL
Light kaolin	2 g	30 g
Sodium bicarbonate	500 mg	7.5 g
Chloroform and morphine tincture	0.4 mL	6 mL
Water	to 10 mL	to 150 mL

Action and uses.

- Traditionally used, but no longer recommended, as an antidiarrhoeal mixture for children.

Formulation notes.

- Chalk is practically insoluble in water and is an indiffusible solid, which requires a suspending agent.
- Tragacanth Powder is used in this formulation.
- The concentrated cinnamon water is a flavouring agent and the syrup increases the viscosity as well as acting as a sweetener.
- Chloroform water is the preservative.

Example 34.2

Prepare 100 mL of Chalk Mixture, Paediatric BP.

	Master formula	For 100 mL
Chalk	100 mg	2 g
Tragacanth	10 mg	200 mg
Syrup	0.5 mL	10 mL
Concentrated cinnamon water	0.02 mL	0.4 mL
Double strength chloroform water	2.5 mL	50 mL
Water	to 5 mL	to 100 mL

Action and uses.

- As a cooling lotion for sunburn or skin irritation and pruritus.

Formulation notes.

- Calamine is a coloured zinc carbonate and is practically insoluble in water, as is zinc oxide. Both are indiffusible solids.
- Sodium citrate is added to control the flocculation of calamine.
- Bentonite is a thickening agent and glycerol will thicken the product and help powder adherence to the skin.
- Liquefied phenol acts as a preservative and antiseptic.

Example 34.3

Prepare 200 mL Calamine Lotion BP.

	Master formula	For 200 mL
Calamine	15 g	30 g
Zinc oxide	5 g	10 g
Bentonite	3 g	6 g
Sodium citrate	500 mg	1 g
Liquefied phenol	0.5 mL	1 mL
Glycerol	5 mL	10 mL
Water	to 100 mL	to 200 mL

Action and uses.

- A potassium-sparing diuretic used in oedema of heart failure and nephrotic syndrome.

Formulation notes.

- Spironolactone is practically insoluble in water.
- Cologel® (methylcellulose) acts as the suspending agent.
- Compound orange spirit is a flavouring agent.

Example 34.4

Prepare Spironolactone suspension 15 mg/5 mL.
Label: 5 mL three times a day. Send 100 mL. For a 4-year-old child.

	Master formula	For 100 mL
Spironolactone	q.s.[a]	300 mg
Compound orange spirit	0.2%	0.2 mL
Cologel	20%	20 mL
Water	to 100%	100 mL

[a]q.s. means sufficient.