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| | Sprowel's American Pharmacy. |
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**محتوى المحاضرة**

## General suspension considerations

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The choice of developing a solution or a suspension formulation is ultimately made on the basis of the aqueous solubility of the drug. The dose of the drug required will be decided by the clinical profile of the drug and therefore cannot be varied. Similarly, the dosing volume is largely fixed: an oral product would have a dosing volume of 5 mL and an eye-drop formulation a dosing volume of 10 µL. Once the equilibrium solubility of the drug in water is known, a simple calculation will establish whether a solution is likely to be possible or not.

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If the drug has some aqueous solubility, but not sufficient for a straightforward solution to be developed, then the solubility of the drug may need to be suppressed, so as to maintain the suspended nature of the drug. Solubility suppression may be achieved by:

- the addition of an antisolvent: Antisolvents act in the opposite manner to cosolvents in that they reduce the aqueous solubility of the drug rather than enhance it.

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If the drug has some aqueous solubility, but not sufficient for a straightforward solution to be developed, then the solubility of the drug may need to be suppressed, so as to maintain the suspended nature of the drug. Solubility suppression may be achieved by:

- Variation of the pH of the medium may be appropriate if the drug is ionizable. Generally, pH manipulation is used to increase the solubility of drugs by causing the ionic species to form and allowing greater interaction with water, but the opposite intention can be used to find the pH of minimum solubility and use that for suspension formulation, assuming of course that the pH is acceptable for the intended route of administration. A weak acid will show low solubility in low-pH conditions, whereas a weak base will show low solubility in high-pH conditions.

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If the drug has some aqueous solubility, but not sufficient for a straightforward solution to be developed, then the solubility of the drug may need to be suppressed, so as to maintain the suspended nature of the drug. Solubility suppression may be achieved by:

- A prodrug such as an ester is also likely to show lower aqueous solubility than its counterpart ‘real’ drug, so is a potential formulation option.

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Flavours, sweeteners and colours

Products intended for oral dosing to children will generally require a colourant, sweetener and flavour to make them palatable. Although the intensity of the taste of a drug molecule will be less in a suspension formulation than in a solution formulation.

The effects of flavours and colours on the physical behaviour of the suspension are likely to be limited, because of the low concentrations used,

especially for colours. Traditionally, sugar (sucrose) has been used to sweeten oral formulations, but the use of sugar is now severely restricted because of concerns over dental caries and potential interference with diabetic glucose control.

Several sweeteners are available, all of which are much sweeter than sugar, and hence are used in much lower concentrations. All of the common sweeteners are ionizable: saccharin is commonly used as the sodium salt and acesulfame is provided as the potassium salt; hence the effect of the mobile ions on the electrical double layer needs to be considered.

Another consideration applies to aspartame: its degradation products include phenylalanine, so it should not be ingested by patients with phenylketonuria, and hence it may be reasonable to avoid its use, depending on the patient population to be treated.

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Antimicrobial preservatives

Any time water is present in a multidose or nonsterile suspension formulation, an antimicrobial preservative is required to prevent microbial contamination. A range of potential preservatives are available, including sorbic acid, benzoic acid, parabens, sucrose and benzalkonium chloride.

- Sucrose has a preservative action at concentrations ≥ 67% w/v. It is unlikely to be used in commercial products because of its cariogenic potential but may be encountered in extemporaneous products, albeit more likely in solution formulations. Sucrose will not interfere with the DLVO behaviour of the system as it does not ionize, so will not be localized in the diffuse layer, and will not adsorb onto the particle surface. It will, however, affect the density and viscosity of the system, and so will have an effect on the sedimentation profile of the suspension.
- Benzalkonium chloride is typically used in aqueous eye-drop formulations at concentrations of ~0.01% w/w. It is a cationic surfactant and will dissociate in aqueous solutions to produce $Cl^-$ ions and a long-chain ionized surfactant moiety. Hence it is likely to affect both the surface potential of the solid drug by deposition of the benzalkonium

part of the molecule and the diffuse layer surrounding the solid particle by production of mobile $Cl^-$ anions.

- Sorbic acid and benzoic acid are both weak acids used in oral formulations at ~0.2% w/v. They are most effective as preservatives in the un-ionized state, in which state they will not interfere with the flocculation behaviour of the drug. However, sorbic acid is commonly used as the potassium salt and benzoic acid as the sodium salt; both show mid-range pKa values (4.8 for sorbic acid and 4.2 for benzoic acid), so will be partially ionized in oral formulation pH conditions. Some effect of charged moieties arising from this ionization is likely in the diffuse layer, and hence this will directly affect the flocculation behaviour of the suspension.
- Parabens are a family of molecules based on p-hydroxybenzoic acid, with alkyl group esterification at the acid group. These are commonly used at a preservative concentration of ~0.2% w/v. Parabens will not ionize at the pH conditions to be expected in a pharmaceutical product, so they are unlikely to interfere with the flocculation behaviour of the particles.

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Buffers

A buffer is defined as a mixture of a weak acid or base and one of its salts and is designed to maintain the pH of an aqueous system within very narrow limits.

Buffers may be used in suspension formulations if a particular pH is required because of the route of administration, or if the solubility of the drug is suppressed by it being formulated at a particular pH, as discussed earlier.

Because of their ionic nature, buffer systems will contribute charges to the formulation, which will affect the flocculation behaviour of the suspension by virtue of being associated with the diffuse layer surrounding the particle. The use of a buffer may also affect the ionization state of other components, such as preservatives, with subsequent effects on their efficacy and the concentration required.

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Chemical stabilizers

A range of chemical stabilizers may be used to increase the chemical stability of the drug. These include antioxidants, such as ascorbic acid (≈0.2% w/v), sodium metabisulfite (≈0.1% w/v), and chelators such as ethylenediaminetetraacetic acid (EDTA).

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Density and viscosity modifiers / suspending agents

Increasing the density of the suspension formulation may help to reduce the sedimentation rate of the dispersed particles. This may be achieved by the addition of a sugar such as dextrose or sucrose, which would not be expected to change the flocculation behaviour other than by retarding sedimentation.

Viscosity modifiers (suspending agents) will reduce the sedimentation of the particles and keep them suspended for longer. The viscosity of the system can be adjusted by the addition of polymeric materials or inorganic materials such as clays.

Five cellulosic polymers are commonly used:

- methylcellulose
- hydroxypropyl cellulose
- hydroxypropyl methylcellulose
- carboxymethylcellulose
- sodium carboxymethylcellulose

These are water soluble and available in a range of molecular weights and degrees of substitution, allowing a range of viscosities.

Also clays and gums can be used as viscosity modifiers.

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Physical stability considerations

In addition to chemical and temperature stability, physical stability is equally important for suspension formulations. Sedimentation should ideally be kept to a minimum, and where sedimentation is permitted or unavoidable, easy redispersion of the sediment is necessary.

The patient or carer should be able to redisperse the sediment by inversion and gentle shaking of the bottle only; the bottle should carry an appropriate instruction.

An approach for assessment involves particle size distribution and drug content of representative samples taken from the top, middle and bottom of the container. Ideally, these should be consistent across depth and over time, meeting preset product specifications.