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Practical aspects of improving drug solubility of poorly soluble drugs in formulations

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Drugs are classified based on the BCS drug classification system. Thus there are drugs that have high and low solubility and those that have high and low bioavailability. The bioavailability of Class II drugs is limited by their solubility. Thus there is a wastage of the drug that is not bioavailable. This can be minimized by improving the drug solubility which would also result in a reduction in the dose. Over the years a lot of research has been done on improving solubility of drugs and various methods (conventional and novel) have been developed. While there are theoretical aspects of improving solubility, one must also consider the practical aspect of using it and then also think of the regulatory approval process. While some strategies may appear very promising, it may not be feasible to scale them up or register such a product due to safety constraints.

Some of the commonly used strategies to improve aqueous solubility are as follows:
A. Physical methods: In these methods physical force or energy is used to achieve the required objective.

1. Particle size reduction: This is a time tested method and very reliable too. Also does not require any particular regulatory clearance. Decreasing the particle size increases the surface area available for contact with solvent and thereby improves the water solubility or the rate of dissolution. In some cases particle size needs to be reduced to a level of 1 micron or less (in the nanometer range). This does provide significant increases in solubility but the active ingredient becomes statically charged and very difficult to handle. Thus material handling at large scale becomes very challenging for the production personnel.

2. High energy mixing: Most directly compressible formulations are made by dry mixing process. The dry mixing process is most commonly carried out in a tumble mixer. The energy provided to the powder during this process is low. As a result, loose aggregates of drugs do not disperse well in the dry mix and show low solubility. If the same process were to be done in a high shear mixer the energy provided would be significantly high. Thus, during the high shear mixing process the aggregates of drug particles would normally break up and distribute evenly over the (hydrophilic) excipients thus providing a dry mix which would be uniform and provide an improved dissolution.

B. Formulation approaches:
3. Use of "solid" solvents (solid dispersions): Drugs that have low water solubility do have significant solubility in solvents such as polyethylene glycols or poloxamers. Thus, the active ingredient needs to be dispersed in the molten solvent and allowed to dissolve. Use of excessive amounts of PEGs in tablets causes sticking during compression. Also, PEGs are waxy in nature and show up on tablet surface as shiny grey spots.

4. pH modifiers: Most of the drugs are either acidic or basic in nature. Acidic excipients can be used for improving solubility of basic drugs or basic excipients can be used for improving solubility of acidic drugs. There are restrictions on the amount of such acidic or basic excipients that one can use in a formulation.

5. Use of surfactants / wetting agents: Some of the drugs are hydrophobic in nature and do not wet easily. As a result they exhibit low water solubility. The solubility of such drugs can be easily improved by adding a suitable surfactant such as Polysorbates or sodium dodecyl sulfate (SDS). Surfactant can be added either during granulation in the granulating solution or in the dry mix itself prior to wet granulation. Polysorbates are generally liquids hence they cannot be added in the dry mix, so they have to be included in the granulating solution. On a bulk scale, the dissolution of a surfactant in water can result in formation of a considerable amount of stable foam. Also, in some cases, Polysorbates can cause changes in colour of tablets on storage, leading to a mottled appearance.

6. Use of hydrophilic excipients: Simple excipients such as Povidone can be used to improve the water solubility and rate of dissolution. Adding the required amount of excipient such as Povidone can help in obtaining modest improvement in solubility. In the presentation these examples would be explained in detail and examples from actual case studies would be provided.

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