Formulating Brick Dust

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It's almost the perfect drug. It is more potent than the current standard of care and has a better side effect profile. It can be synthesized to high purity. It is rock stable. But it is about as soluble as the sand on the beach you'd rather be lying on right now. What do you do?

Solubility is a critical concern for all dosage forms, but low solubility most frequently emerges as a challenge in the formulation of injectable and oral products. In IV products undissolved drug can kill a patient while in orals and other non-injectable dosage forms, poor solubility may severely limit bioavailability. Numerous strategies have been developed for solubilizing drugs, but most are variations on common themes. If a drug cannot be made soluble by changing its salt form or the pH of its environs, formulation options include:

Non-Aqueous and Semi-Aqueous Solutions that can be used to dissolve drug for oral administration or for slow infusion. Solvents such as propylene glycol and low molecular weight polyethylene glycols typically form the basis of these formulations. Advantages are ease of manufacture. Disadvantages are toxicity associated with the solvents, potential for precipitation in situ and difficulty of delivery. Although these formulations can theoretically be sterile filtered, this is usually slow and difficult due to the viscosity of the solvents.

Micelles and Microemulsions are visually clear, thermodynamically stable nanodispersions in which drug can be solubilized by inclusion in the micelles or microemulsion nanodroplets. They can be formulated as dispersed systems or as solutions that form dispersions upon pre-administration dilution or *in situ*. Advantages are ease of preparation and ability to sterile filter. Disadvantages are surfactant toxicity and licensing costs for some systems.

Emulsions are turbid or opaque thermodynamically unstable, but they are kinetically metastable dispersions of oil in water or water in oil. Water insoluble drugs can be incorporated into the oil phase or at the oil-water interface. These systems can be formulated with natural ingredients to yield very low vehicle toxicity but they do require specialized manufacturing equipment and must typically be heat sterilized.

Liposomes are fluid nanospheres in which nanodroplets of aqueous phase are enveloped within lipid bilayers. Although popularized for entrapping water soluble drugs, they can

also be used to carry water insoluble drugs within the bilayer itself. Advantages are low toxicity and sterile filterability. Disadvantages are stability issues, raw material costs, and need for specialized equipment and processes.

Cyclodextrins are molecules that consist of a hydrophobic pocket in which drug can reside and a hydrophilic shell that provides aqueous solubility. Because drugs complex with cyclodextrins are on a stoichiometric basis, quite high concentrations of the solubilizer are typically required. Advantages are sterile filterability, relatively low toxicity, and (usually) ease of processing. Disadvantages are high raw material and licensing costs.

Nanosuspensions are an increasingly popular means of formulating poorly soluble drugs, at least for non-intravenous applications. A non-settling colloidal dispersion of drug particles may be formed by wet milling or by controlled precipitation. The high specific surface area and curvature of these very small particles cause them to dissolve more rapidly and actually have higher thermodynamic solubility. Advantages are wide applicability and low toxicity. Disadvantages are high processing and licensing costs.

I cannot tell you what the best formulation is for your brick dust, but I can tell you that the best approach is to keep all options open. Make sure the formulator overseeing your product development has expertise in all these technologies and make sure that each is adequately investigated. If experiments are planned well, this can be done on a surprisingly low budget, and the outcome may be that you have more than one technically viable choice. In any case, an efficient exploration of options will allow you to choose a route forward that best serves your company and its investors.

Whether you are trying to develop an IV drug or improve bioavailability of an oral drug, don't get lured in by the first company who offers you an expensive, trademarked solubilizing technology. Make sure you have the right formulation expertise and make sure you don't close any doors prematurely.