DRUG SOLUBILITY: IMPORTANCE AND ENHANCEMENT TECHNIQUES[1]

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"Compounds with insufficient solubility carry a higher risk of failure during discovery and development since insufficient solubility may compromise other property assays, mask additional undesirable properties, influence both pharmacokinetic and pharmacodynamic properties of the compound, and finally may affect the develop ability of the compound."

1.- INTRODUCTION

The solubility of a compound depends on its structure and solution conditions. Structure determines the lipophilicity, hydrogen bonding, molecular volume, crystal energy and ionizability, which determine solubility. Solution conditions are affected by pH, cosolvents, additives, ionic strength, time and temperature. Poorly soluble compounds can dramatically reduce productivity in drug discovery and development.

Potential complications arising from low aqueous solubility:

- Compounds precipitation during serial dilution in buffer, biochemical assays, functional assays and cell-base assays
- Reduce target specifity
- Low bioavility in animal studies

A "good compound" must be able to reach its target at effective concentrations. Therefore, the lowest acceptable solubility of a compound is related to its pharmacologic potency and its permeability. Low micromolar aqueous solubility can be acceptable only for extremely potent and/or permeable compounds.

2.- IMPORTANCE OF SOLUBILITY

Oral ingestion is the most convenient and commonly employed route of drug delivery (easy administration, high patient compliance, costeffectiveness, least sterility constrains and flexibility in the design of dosage form)[2] However, the major challenge with the design of oral

[1] Savjani, K. T., Gajjar, A. K., & Savjani, J. K. (2012). Drug solubility: importance and enhancement techniques. *ISRN pharmaceutics*, *2012*.

[2] Yellela SRK. Pharmaceutical technologies for enhancing oral bioavailability of poorly soluble drugs. *Journal of Bioequivalence & Bioavailability*. 2010;2(2):28–36.

dosage forms lies within their poor bioavailability. The cause of low oral bioavailability is the poor solubility and low permeability.[3]

Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development.[4] Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. More than 40% of NCEs developed in the pharmaceutical industry are insoluble in water. For this reason, the problem of solubility is one of the major challenges for formulation chemists.

3.- TECHNIQUES FOR SOLUBILITY ENHANCEMENT

3.1.- Physical modifications

Particle size reduction[5]: The drug solubility is related to drug particle size. The larger surface area allows greater interaction with the solvent , increasing the solubility.

Methods: comminution (milling, grinding), spray drying, micronization (jet mill, totor stator colloid mills…)

Solid dispersion[6]: is refered to a group of solid products consisting of at least two different components, generally a hydrophilic matrix (PVP,PEGs…) and a hydrophobic drug.

Methods:

- *Hot-melt method* (Fusion method) (simple and economic): the physical mixture of a drug and a water-soluble carrier are heated directly until two melts. The melted mixture is cooled and solidified in ice. The final solid mass is crushed, pulverized and sieved. Important requisites are the miscibility and thermo stability of the drug and the carrier.
- *Solvent evaporation method*: the drug and the carrier are dissolved in a common solvent and then, solvent is evaporated under vacuum. The main advantage is the prevention of the thermal decomposition, but it is more expensive.

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[3] Edward KH, Li D. *Drug Like Properties: Concept, Structure, Design and Methods, from ADME to Toxicity Optimization*. Elsevier; 2008. Solubility; p. p. 56.

[4] Sharma D, Soni M, Kumar S, Gupta GD. Solubility enhancement—eminent role in poorly soluble drugs. *Research Journal of Pharmacy and Technology*. 2009;2(2):220–224.

[5] Ziegler, G. R., & Hogg, R. (2009). Particle size reduction. *Industrial Chocolate Manufacture and Use, Fourth Edition*, 142-168.

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- *Hot-melt extrusion*. Same as the fusion method except that intense mixing of components is induce by extruder. It allows the possibility of continuous production.

Nano suspension[7][8]

This technology is applied to poorly soluble drugs that are insoluble in both water and oils. A pharmaceutical nanosuspension is a biphasic system consisting of nano sized drug particles stabilized by surfactant for either oral and topical use or parentereal and pulmonar administration.

Methods:

- Precipitation technique
- Media milling
- High pressure homogenization
- Combined precipitation and homogenization.

Cryogenic techniques[9][10]

Techniques used to enhance the dissolution rate of drugs by creating nanostructured amorphous drug particles with high degree of porosity at very low temperatures. After cryogenic processing, dry powder can be obtained by several drying process (spray, atmospheric or vacuum freeze drying and liophilization)

Methods:

- *Spray Freezing onto Cryogenic Fluids*
- *Spray Freezing into Cryogenic Liquids (SFL)*
- *Spray Freezing into Vapor over Liquid (SFV/L)*
- Ultra-Rapid Freezing (URF)

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[7] Chingunpituk, J. (2011). Nanosuspension technology for drug delivery. *Walailak Journal of Science and Technology (WJST)*, *4*(2), 139-153.

[8] Ghosh, I., Bose, S., Vippagunta, R., & Harmon, F. (2011). Nanosuspension for improving the bioavailability of a poorly soluble drug and screening of stabilizing agents to inhibit crystal growth. *International journal of pharmaceutics*, *409*(1), 260-268.

[9] Leuenberger H. Spray freeze-drying—the process of choice for low water soluble drugs? *Journal of Nanoparticle Research*. 2002;4(1-2):111–119.

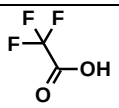
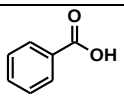
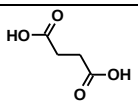
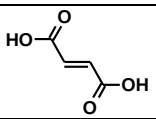
[10] Mumenthaler M, Leuenberger H. Atmospheric spray-freeze drying: a suitable alternative in freeze-drying technology. *International Journal of Pharmaceutics*. 1991;72(2):97–110.

Crystal engineering[111213]

The comminution techniques can produce particles which are highly heterogeneous, charged, and cohesive, with the potential to cause problems in downstream processing and product performance. Hence, crystal engineering techniques are developed for the controlled crystallization of drugs to produce high purity powders with well-defined particle size distribution, crystal habit, crystal form (crystalline or amorphous), surface nature, and surface energy . By manipulating the crystallization conditions (use of different solvents or change in the stirring or adding other components to crystallizing drug solution), it is possible to prepare crystals with different packing arrangement; such crystals are called polymorphs. As a result, polymorphs of the same drug may differ in their physicochemical properties such as solubility, dissolution rate, melting point, and stability. Most drugs exhibit structural polymorphism and it is preferable to develop the most thermodynamically stable polymorph of the drug to assure reproducible bioavailability of the product over its shelf-life under a variety of real-world storage conditions.

3.2.- Chemical modifications

Change of pH, use of buffer, derivatization, complexation and Salt formation. The salts formation was the approach used in 3D-NET projects to increase the solubility of the target molecules. As a example, the molecule 11B and their salts were evaluated and a different activity was observed related only to their different solubility.

11B					
HBr					
PVA-178-E	**PVA-178-F**	**PVA-178-G**	**PVA-187-A**	**PVA-187-B**	**PVA-187-D**

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[12] Moulton, B., & Zaworotko, M. J. (2001). From molecules to crystal engineering: supramolecular isomerism and polymorphism in network solids. *Chemical Reviews*, *101*(6), 1629-1658.

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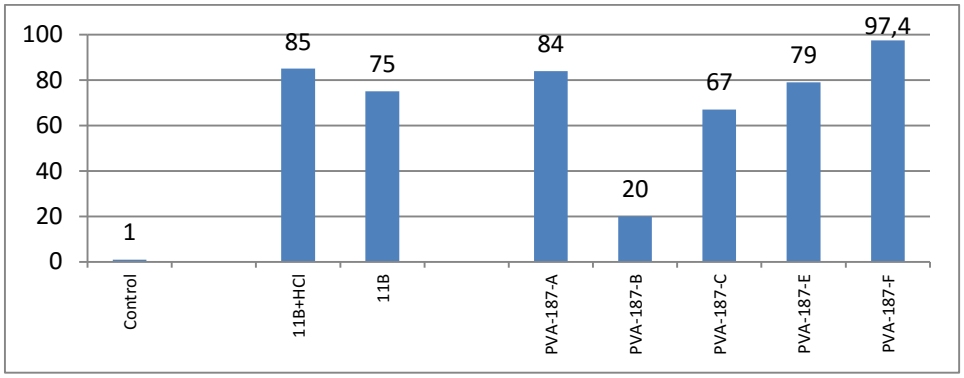

3.3.- Miscellaneous Methods.

Supercritical Fluid (SCF) Fluids[14][15]

Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp), allowing it to assume the properties of both a liquid and a gas. At near-critical temperatures, SCFs, are highly compressible allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of the fluid that largely determine its solvent power. Once the drug particles are solubilised within the SCF (usually carbon dioxide), they may be recrystallised at greatly reduced particle sizes. The flexibility and precision offered by SCF processes allows micronisation of drug particles within narrow ranges of particle size, often to submicron levels

Inclusion complex-formation techniques[16]

Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The most commonly used host molecules are cyclodextrins. The enzymatic degradation of starch by cyclodextrin-glycosyltransferase (CGT) produces cyclic oligomers, Cyclodextrins (CDs).

Methods:

- Kneading Method
- Lyophilization/Freeze-Drying Technique

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- Microwave Irradiation Method

Micellar solubilization

The use of surfactants to improve the dissolution performance of poorly soluble drug products is probably the basic, primary, and the oldest method. Surfactants reduce surface tension and improve the dissolution of lipophilic drugs in aqueous medium. They are also used to stabilise drug suspensions.

Hydrotropy

Hydrotrophy is a solubilisation process, whereby addition of a large amount of second solute, the hydrotropic agent results in an increase in the aqueous solubility of first solute. Hydrotropic agents are ionic organic salts, which consist on of alkali metal salts of various organic acids. Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotrophic agents like sodium benzoate, sodium acetate, sodium alginate, urea, and the poorly soluble drugs.