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"Hydrotropy: A Promising Technique for Solubility Enhancement in Drug Delivery"

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ABSTRACT

In both formulation research and screening studies of novel chemical entities, solubilization of poorly water-soluble pharmaceuticals has shown to be a crucial problem. Hydrotropic solubilization is a technique employed to enhance the water solubility of pharmaceuticals with poor aqueous solubility. Something that solubilizes hydrophobic substances in water solution is called a hydrotrope. The issue with emulsification, which is typically. Hydrotrope solutions do not include the contaminants found in traditional surfactant solutions. This approach is the most efficient, especially at industrial levels, because it is simple to recover the dissolved solute and because hydrotrope solutions can be reused. Moreover, this method is favored over others because it offers certain benefits such as pH-independent solvent properties, high selectivity, non-flammability, and the affordability and ease of access to hydrotropes.

Introduction

Neuberg (1916) introduced the term 'hydrotropic agent' to describe anionic organic salts that significantly enhance the solubility of poorly soluble solutes in water at high concentrations. Hydrotropy refers to a solubilization phenomenon where the addition of a substantial amount of a secondary solute increases the water solubility of the primary solute. Despite this, the term has been used in literature to refer to substances that do not form micelles. These substances, which can be either liquids or solids, organic or inorganic, have the capability to dissolve insoluble molecules. The chemical structure of traditional hydrotropic salts, such as sodium benzoate, includes two key components: an anionic group and a hydrophobic aromatic ring or ring system. [1]

The best method for delivering the dose form is orally. The main issue in administering the active drug orally is the bioavailability. Solubility is defined as the highest quantity of solute that can be dissolved in a specific amount of solvent or solution at a particular temperature.

Hydrotropes are agents used to increase the the solubility of that are poorly soluble in solvents agents are hydrotropic Solubility is defined in quantitative terms as the Solute's Concentration in a saturated solution at a certain Temperature and as well as the spontaneous contact of two or more substances to generate a homogeneous molecular dispersion, to put it in qualitative words.

Solubilization is a complex process influenced by various medium effects such as salting-in or co-solvency. It involves molecular interactions balanced by different molecular-level forces. Salting-in and salting-out methods are commonly employed to enhance solubility. Salts that promote the 'salting-in' of non-electrolytes, as opposed to 'salting-out,' are termed 'hydrotropic salts,' and this process is known as "hydrotropism."[3]. The solute's solubilizing property is enhanced by hydrotropic salts through a mild interaction; nonetheless, no colloidal behavior is displayed as a result of the interaction.

Hydrotropes, which have characteristics similar to those of surface active agents, improve the solutes' aqueous solubility when they are only weakly soluble in water at ambient temperature. Hydrotropy has the potential to evolve into an industrial technique. Solubility can be quantitatively defined as the concentration of solute in a saturated solution at a specific temperature, and qualitatively as the unintentional blending of two or more substances to form a uniform molecular dispersion. A solution where the solute and solvent are in equilibrium is termed a saturated solution. Drug solubility can be measured in various ways, including volume fraction, molality, molarity, percentage, parts, and mole fraction. It is the maximum concentration of

the drug solute that can dissolve in the solvent under certain pressure, pH, and temperature conditions. While drug solubility in a saturated solution is a static property, the rate at which the drug dissolves is a dynamic characteristic that is more closely linked to bioavailability. [1].

SOLUBILITY

permeability

CLASS 1	**CLASS 2**
Examples of substances with high solubility and high permeability, which enable rapid dissolution and qualify for biowaivers, include acetaminophen, acyclovir, glucose, antipyrine, buspirone, and diazepam.	Examples of substances with low solubility and high permeability include dapsone, glipizide, carvedilol, amiodarone, indinavir, and flurbiprofen.
Absorption Pattern: Well absorbed	**Absorption Pattern**: Variable
CLASS 3	**CLASS 4**
Examples of substances with high solubility and low permeability include amoxicillin, cetirizine, dicloxacillin, cloxacillin, and famotidine.	Examples of substances with both low solubility and low permeability include amphotericin B, colistin, furosemide, mebendazole, and neomycin.
Absorption Pattern: Variable	**Absorption Pattern**: Poor

Table 1: The Biopharmaceutical classification system for drugs 4

Solubility is typically described using different concentration units such as quantity per quantity, percentage, parts, molarity, molality, mole fraction, milliequivalents, and normal solutions. This is also illustrated in terms of parts of solvent needed for 1 part of solute, as detailed in the U.S. Pharmacopeia, as shown in Table 2.

Expressions	**Amount of solvent needed for each unit of solute**	**Instances of pharmaceuticals**
Very soluble	Less than 1parts	Deltiazam, Metoprolol
Freely soluble	From 1-10 parts	Ipratropium bromide
Soluble	From 10-30 parts	Timolol, cyclophosphamide, quinidine, carmustine, propranolol, procainamide
Sparingly soluble	From 30-100 parts	Ramipril, labetalol, quinidine sulfate, fluorouracil
Slightly soluble	From 100-1000 parts	Valsartan, Fludrabine, Atenolol
Very slightly soluble	From 1000-10,000 parts	Doxazocine, Busulphan, lomustine, Flecainide
Practically Insoluble	More than 10,000 parts	Irbesartan, Nifedipine, Chlorambucil, Melphlan, Lidocaine, Candesartan

Table 2: Instances of pharmaceuticals along with their solubility

The necessity of solubility (7)

The therapeutic effectiveness of a drug ultimately relies on the solubility and bioavailability of its molecules. Solubility is a key factor in attaining the desired drug concentration in the systemic circulation and eliciting a pharmacological response. Advanced research and development have introduced various new medications and their compounds to the market. However, despite their potential pharmacodynamic effects, over 40% of lipophilic drug candidates fail to reach the market due to insufficient bioavailability. The When a lipophilic medicine is introduced to the market, it takes a large dose to produce the desired pharmacological effect. Making the medication available at the appropriate site of action and at the ideal dosage is the primary goal of the further formulation and development segment. (7)

Descriptive terms

The three general factors of particle size, shape, and surface area that influence solubility medicines' physicochemical characteristics, as well as their physical shapes, solvents, the medium's pH, temperature, and surfactant usage. Solubility is recorded in the pharmacopoeia as the dissolution of 1g of solute. When exact solubility values are not available, the pharmacopoeia uses broad terms to describe specific ranges. These descriptive terms can be found in Table 1.

❖ Comprehensive Range of Solubility Enhancement Techniques

1	**Alteration of Physical Properties**
1.1	Reducing Particle Size • Micronization • Nanosuspension
1.2	Changing Crystal Structure • Polymorphs • Pseudo polymorphs
1.3	Drug Distribution in Carrier Medium • Solid solutions • Solid dispersions
1.4	Enhancing Solubility with Surfactants • Microemulsion • Self-microemulsifying drug delivery system (SMEDDS)
1.5	Complexation
2)	**Altering Chemical Structure**
2.1	Hydro trophy
2.2	Co-solvency
2.3	Nanotechnology
2.4	Salt formation
3)	**Adjusting pH Levels**
4)	**Process Involving Supercritical Fluids**
5)	**Liquisolid methods**

Drug solubility and particle size are interconnected. Decreasing particle size reduces surface area, thereby improving the drug's dissolution rate. Bioavailability of medications with low solubility often hinges on particle size. Techniques like colloid mills and jet mills are employed to achieve particle size reduction. This is not appropriate for medications with large dosage numbers since the drug's saturation solubility remains unchanged. Micronization and nanosuspension are two techniques that can be used to reduce particle size. [8]

❖ **Micronization:** This approach boosted the rate at which pharmaceuticals dissolved by increasing the surface area of the particles. However, equilibrium solubility stays constant. These medications' surface area can be increased to speed up their rate of breakdown and reduce particle size. Progesterone, fenofibrate, griseofulvin, spironolactone, and diosmin were all subjected to these procedures. enhanced the clinical effectiveness, certain drugs' bioavailability and absorption [9]

Benefits

- Produces uniform particles with minimal size variation and increased surface area.

Drawbacks

- The high-energy process disrupts the drug's crystal lattice, leading to amorphous or irregular regions in the final product.
- These areas are thermodynamically unstable and may re-crystallize under conditions of high heat and humidity.

❖ **Nanosuspension:**

Nano-suspension is a technique used to enhance the solubility of medications that are insoluble in both oil and water. It involves suspending nanoscale drug particles in a liquid medium, creating a biphasic system. Surfactants are used to stabilize these nano-sized drug particles for oral, topical, and parenteral administration. The particle size distribution in nano-suspensions typically ranges below one micron, with sizes typically falling between 200 to 600 nm. This approach has been applied to drugs such as amphotericin B, paclitaxel, buparvaquone, tarazepide, and atovaquone. There are a number of methods for creating nanosuspensions, including dissoCubes, nanopore, nano edge, and nanocrystals. (10)

Advantages

- Reducing drug particle size increases surface area, thereby enhancing:
- Bioavailability, solubility, and dissolution.
- Nanosuspension enhances drug permeability.
- Nanosuspension extends residence time for prolonged action.
- Nanosuspension improves drug bioadhesion.
- It offers the advantage of high drug loading.
- Nanosuspension avoids the use of organic solvents.

Drawbacks

The primary issue with nanosuspension is instability brought on by agglomeration, crystal formation, and Ostwald ripening.(10)

1.2 CHANGING CRYSTAL STRUCTURE

a) Polymorphs

b) Pseudo polymorphs

Polymorphism refers to the ability of a solid material to exist in multiple distinct crystalline forms, known as polymorphs. These forms share the same chemical composition but exhibit varying physicochemical properties such as stability, solubility, texture, melting point, and density.

Amorphous drugs are favored over crystalline forms due to their higher surface area and greater energy content. (11).

The order of different solid forms of drugs is generally ranked as follows: Amorphous > Metastable polymorphs > Stable polymorphs.

Dispersion of drugs within a carrier

It was initially discovered in 1961 that solid dispersion may be used to enhance drug absorption and dissolution. This phrase generally describes the addition of active substances to a dispersion within an idle carrier , which is achieved either by the solvent method, the fusion method, or the fusion solvent technique. In 1961, it was discovered that using solid dispersion could enhance medication absorption and dissolution. Typically, this term describes incorporating active substances into an inert carrier through methods such as fusion, solvent, or fusion-solvent techniques.

Solid solution: In solid dispersion, two crystalline solids are blended to form a new crystalline solid. This process involves crystallizing two components together in a homogeneous, single-phase system to create a mixed crystal. Compared to conventional enteric systems, solid dispersion typically results in significantly higher dissolution rates.

Solid dispersion: originally proposed by Sekiguchi and Obi, is a valuable pharmaceutical method to improve the dissolution rate, absorption, and therapeutic effectiveness of drugs. It involves solid products typically comprising a hydrophilic matrix and a hydrophobic drug. Commonly used hydrophilic carriers include polyethylene glycols, polyvinyl pyrrolidone, and Plasdone-S630. Surfactants are often employed in the formation of solid dispersion to facilitate the process.

Benefits

- Prevention of thermal decomposition of drugs and carriers

Drawbacks

- High cost
- Challenges in complete solvent removal
- Difficulty in identifying a suitable common solvent

SOLUBILISATION BY SURFACTANTS

A microemulsion is a clear, stable, and isotropic system that enhances the solubility of poorly water-soluble drugs by combining oil, surfactant, and hydrophilic solvent. Surfactant selection is based on criteria such as HLB value and non-toxicity. When these components interact with water, they spontaneously form tiny, uniform oil droplets in a highly transparent emulsion, effectively solubilizing the poorly soluble drug. Microemulsions are utilized to deliver proteins orally, parenterally, and intravenously, and they improve the solubility of drugs that are nearly insoluble in water. An oil-in-water (o/w) microemulsion is particularly effective, as it enhances solubility by incorporating poorly soluble molecules into the oil phase. (13)

Benefits

The release of drugs from well-established microemulsion pre-concentrates typically occurs independently of digestion. This characteristic allows for consistent bioavailability and effectiveness without requiring co-administration with meals. (14)

Complexation:

The utilisation of cyclodextrins in medication complexation has been observed to augment drug stability and water solubility. Pharmaceutically significant cyclodextrins consist of six, seven, or eight dextrose molecules (α, β, γ-cyclodextrin) bonded in a 1,4- arrangement to create rings with different diameters. With its lipophilic center and hydrophilic perimeter, the ring allows for the formation of noncovalent inclusion complexes by suitably sized organic molecules, which increases its chemical stability and aqueous solubility. (15)

There are drawbacks to complexation despite all of its alluring benefits. The molecule must, first and foremost, be able to form complexes with particular ligands. Solubility increase may be quite limited for substances whose solubility is very low to begin with. The second restriction is the Ap type complexes; precipitation may still occur even if the system is diluted. This also holds true for solubilization by combination methods, such complexation and pH modification. Finally, the possible toxicity concern, which is connected to regulatory and quality control issues The development process may become more complex and expensive in the presence of ligand (16)

❖ **Chemical Modification :**

A) Co-Solvency :

Adding co-solvents can enhance the solubility of drugs that are poorly soluble in water. The presence of organic co-solvents alters the solubility characteristics of pharmaceuticals in aqueous solutions. These co-solvents typically include hydrogen bond donor or acceptor groups with small hydrocarbon regions. While the hydrophilic groups facilitate solubility in water through hydrogen bonding, the hydrophobic hydrocarbon regions can disrupt the water's hydrogen bonding network, thereby reducing intermolecular attractions among water molecules. (17)

B) Hydrotropy

Hydrotropy refers to a phenomenon where the solubility of a solute in water increases significantly when a large amount of another solute is added. Various poorly water-soluble drugs have demonstrated increased solubility in concentrated aqueous solutions containing hydrotropes like sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate. (18)

Benefits of the Hydrotropic Solubilization Technique

- Hydrotropy is considered superior to other methods of solubilization, such as miscibility, micellar solubilization, cosolvency, and salting in, due to its pH-independent solvent nature, high selectivity, and avoidance of emulsification.
- It involves simply mixing the drug with the hydrotrope in water.
- Hydrotropy eliminates the need for chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion systems. (19)

Mechanism of Hydrotropy

The exact mechanism of action of hydrotropes is still up for debate and far from established. Numerous scholars offered their own theories regarding the potential hydrotrope mechanism. Three hypotheses proposed to explain hydrotropic activity include:

(a) Formation of complexes between solute and hydrotrope,

(b) Disruption or breaking of tetrahedral water molecule complexes,

(c) Self-association of hydrotropes.

However, these hypotheses have not fully elucidated the mechanism of hydrotropes.

C) Nanotechnology:

Nano Suspension:

Nanosuspension technology is a critical method for enhancing the solubility of poorly soluble drugs. It involves finely dispersed solid drug particles in an aqueous vehicle, suitable for oral and topical use, as well as parenteral and pulmonary administration. The particle size distribution typically ranges from 200 to 600 nm in nanosuspensions. Reducing the particle size of the drug in nanosuspensions increases its surface area, thereby enhancing dissolution rate and solubility, which ultimately improves bioavailability. (21)

❖ **LIQUISOLID METHOD:**

Liquid can be converted into a dry, free-flowing, and easily compressible powder using the liquisolid technique, achieved by blending with a suitable carrier and coating material. This method transforms liquid medications, suspensions, or solutions into powders that exhibit good flow and compression properties when mixed with specific excipients. Liquisolid compacts are effective powder forms of liquid medications that are easy to handle and compress. This technique is cost-effective and practical for industry use due to its straightforward manufacturing process and the efficient formulation of liquisolid powders. The absorption and adsorption of the drug dissolved in the liquid vehicle occur when it interacts with carrier materials like cellulose, where the liquid is absorbed into particles and subsequently adsorbed onto their surfaces. The coating material, with its large surface area and high adsorptive capacity, enhances the desired flow characteristics of the liquisolid system. (22)

Benefits

- Various poorly soluble medications can be formulated using this system.
- Production costs are significantly lower compared to soft gelatin capsule manufacturing.
- Enables liquid drugs to be pulverized into a flowable and compressible form.
- Particularly beneficial for manufacturing oily and liquid drugs.
- Enhances solubility and bioavailability when orally administered to water-insoluble drugs.
- Specifically applicable to powdered liquid pharmaceuticals.

❖ **Supercritical fluid technique:**

Non-volatile solutes can dissolve in supercritical fluids (SCFs) close to the critical point of carbon dioxide. SCFs are single-phase substances above their critical temperature and pressure, offering economic, safe, and environmentally friendly properties. The low operating conditions (temperature and pressure) of SCFs make them appealing for pharmaceutical research applications. Existing between liquid and gas phases, SCFs possess advantageous properties for product processing. Variations in temperature, pressure, or both near critical points affect density, transport properties (such as viscosity and diffusivity), and other physical characteristics (such as polarity and dielectric constant). Common supercritical solvents include carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water. (23,24)

❖ **Salt Formation :**

By using salt production techniques, drug solubility and dissolution can be improved. This technique is employed to watch how different medications or chemical interactions affect the body. Salt is generated when a drug ionizes. It is equally effective when administered parenterally and in various liquid and solid dosage forms. Of the more than 300 new chemical entities that the FDA cleared for marketing between 1995 and 2006, 120 of them were salt forms. Moreover, 54 of the 101 authorized salts of basic medications were made using hydrochloric acid, indicating that the hydrochloride salt form was the most widely utilized. Depending on the pH, the solubility of an acidic or basic medication in water dictates whether the chemical will form appropriate salts. .. Physiochemical characteristics are one of the techniques it employs to modify the drug's stability, bioavailability, purity, and manufacturability. To increase solubility, low soluble drug candidates have long been processed with salt. (25) Examples include theophylline, barbiturates, and aspirin. The water-insoluble steroid progesterone is soluble in One readily available commercial example of this technique is peanut oil.(26)

Conclusion

This article leads us to the conclusion that solubility is a crucial factor in determining a drug's oral bioavailability that is poorly soluble. Drug solubility is essential for formulating various dosage forms of different medications and plays a crucial role in the oral absorption rate of drugs with low water solubility. Many medications have solubility problems that impact their bioavailability and necessitate improving their solubility. The nature and characteristics of the drug, including its pharmacokinetic behavior, chemical makeup, and physical nature, influence the choice of any technique for enhancing solubility. Numerous techniques, including those previously discussed, are available for enhancing the solubility of poorly soluble drugs.

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