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REVIEW ARTICLE

SOLUBILITY ENHANCEMENT METHODS WITH IMPORTANCE OF HYDROTROPY

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ABSTRACT

The effectiveness of formulation depends particularly on how efficiently is drug available at the site of action. Therapeutic effectiveness of a drug basically depends upon bioavailability and the solubility of drug moiety. Most of the chemical entities that are being discovered are lipophilic and have poor aqueous solubility. A more than 40% drug suffers from poor water solubility. Currently number of techniques addressed the enhancement of solubility and dissolution rate of poorly soluble drugs. Hydrotropic solubilization is one of them. Hydrotropy is a solubilization phenomenon whereby addition of large amounts of a second solute results in an increase in the aqueous solubility of another solute. A hydrotrope is a compound that solubilises hydrophobic compounds in aqueous solution. To solubilize water insoluble drugs especially in case of oral formulation, solubility remains a critical factor so for in this review various solubility enhancement techniques are highlighted and a brief review of hydrotropy and its preparation are discussed.

Keywords: Solubility, Hydrotropy, Mixed hydrotropy

INTRODUCTION

The important phenomenon in pharmaceutical formulation is "solubility" which plays very effective and significant role in the formulation of various dosage forms. Solubility of a compound in a particular solvent is defined as the concentration of a solute in a saturated solution at a certain temperature.[1]

The solubility of a drug molecule may be critical factor determining its usefulness since the solubility dictates the amount of compound that will dissolve and therefore the amount available for absorption. If a compound has low water solubility it may be subject to dissolution rate limited absorption within the gastrointestinal residence time. In biopharmaceutical terms the solubility importance has been highlighted by Biopharmaceutical Classification System (BCS) described by Amidon in 1995 which classified the drugs into the four groups as shown in Table1.[2]

The key parameters on which BCS of a drug depends upon are solubility and permeability, solubility play an important role for the absorption of drugs.[3]

Table 1: The Biopharmaceutical classification system for drugs [4]

PERMEABILITY ↑ / SOLUBILITY →	
CLASS 1 High Solubility High Permeability (Rapid Dissolution For Biowaiver) Ex. Acetoaminophen, Acyclovir, Glucose Antipyrine, Buspirone, Diazepam.	**CLASS 2** Low Solubility High Permeability Ex. Dapsone, Glipizide, Carvedilol, Amiodarone, Indinavir, Flurbiprofen.
Absorption Patttern:Well absorbed	Absorption Pattern:Variable
CLASS 3 High Solubility Low Permeability Ex. Amoxycillin, Cetrizine, Dicloxacillin, Cloxacillin, Famotidine	**CLASS 4** Low Solubility Low Permeability Ex. AmphotericinB, Colistin, Furosamide, Mebendazole, Neomycin
Absorption Patttern:Variable	Absorption Patttern: Poor
CLASS 1 High Solubility High Permeability (Rapid Dissolution For Biowaiver) Ex. Acetoaminophen, Acyclovir, Glucose Antipyrine, Buspirone, Diazepam.	**CLASS 2** Low Solubility High Permeability Ex. Dapsone, Glipizide, Carvedilol, Amiodarone, Indinavir, Flurbiprofen.

EXPRESSING SOLUBILITY AND CONCENTRATION

The Solubility is usually expressed by variety of concentration that is by Quantity per quantity, Percentage, Parts, Molarity, Molality, Mole fraction, Milliequivalents and normal solutions.[5] This is also explained in term of parts of solvent required for 1 part of solute as explained in U. S pharmacopeia which is shown in Table 2.

Table 2: Examples of drugs with their solubility [6, 7, 8, 9]

Terms	Parts of solvent required for 1 part of solute	Examples of drugs
Very soluble	Less than 1parts	Metoprolol, Deltiazam
Freely soluble	From 1-10 parts	Ipratropium bromide
Soluble	From 10-30 parts	Cyclophosphamide, carmustine, Quinidine, Procainamide, Propananolol, Timolol
Sparingly soluble	From 30-100 parts	Fluorouracil, Quinidine Sulphate, Labetolol, Ramipril
Slightly soluble	From 100-1000 parts	Fludrabine, Atenolol, Valsartan
Very slightly soluble	From 1000-10,000 parts	Busulphan, lomustine, Flecainide, Doxazocine
Practically Insoluble	More than 10,000 parts	Chlorambucil, Melphlan, Lidocaine, Candesartan, Irbesartan, Nifedipine

SOLUBILITY ENHANCEMENT TECHNIQUES

NANONIZATION[10]

It is a technique where a drug particle is converted into nanocrystals having size range of 200-600nm. Pearl milling, homogenization in water, homogenization in non aqueous media is currently used technologies for preparing nanocrystals.

SUPERCRITICAL FLUID RECRYSTALLIZATION (SCF) [10]

Those fluids are referred to as supercritical fluids which are having temperature and pressure greater than its critical temperature and critical pressure so as they are acquire properties of both gas and liquid. The best example of this is carbon dioxide. SCF are highly compressible at critical temperatures and allows alteration in density and mass transport characteristics which determines its solvent power due to moderate changes in pressure. As the drug gets solubilized within SCF they can be recrystallized with reduced particle size of drug.

USE OF SURFACTANTS[11]

To enhance both permeability of drug and dissolution, the surfactants are used as absorption enhancers which fulfills the above criteria. The proposed mechanism is that the wetting is first primarily promoted and further there is penetration of dissolution fluid into solid drug particles. Solubility enhancement of poorly water soluble antimicrobial drug, enrofloxacin has been studied using a series of surfactants and co-solvents. Among the surfactants, ionic surfactants were preferred over the non ionic surfactants as they were better solubilizing agents. In case of anionic surfactants they possess highest solubility rates, considering example of sodium dodecyl sulphate which is an anionic surfactant was a better solubilizing agent than cetyltrimethyl ammonium bromide which is a cationic surfactant.

EVAPORATIVE PRECIPITATION[12]

In this technique there is a rapid phase separation for nucleation and growth of microparticles and nanoparticles of water insoluble drugs. In this low boiling solvent is selected and a suitable amount of drug is added to it and the resultant solution is passed and pumped through a inert tube which is heated to a temperature under pressure above the selected organic solvent boiling point and sprayed into the heated aqueous solution through a fine atomizing nozzle. Further the surfactants are added so as to optimize the particle size.

MICRONIZATION[13]

This process typically emphasize on the reduction of drug particle size so as to increase in surface area which directly enhances dissolution characteristics and bioavailability of drug. The size range of drug particles after this process is 1-10 microns. The commonly used methods are spray drying and fluid energy or jet mill (by attrition methods).

SONOCRYSTALLISATION[13]

This technique is successfully employed to reduce particle size by using ultrasound, is sonocrystallisation which is a novel approach by use of anti-solvents and liquid solvents. By adding these anti-solvents and liquid solvents, recrystalllization of poorly water soluble drugs occurs.

HIGH PRESSURE HOMOGENIZATION[13]

It is basically involves the use of high pressure with very high velocity by passing the crystalline drug aqueous dispersion through a narrow gap. The proposed mechanism for this process is by shear forces and cavitations due to which particles get disintegrated. In this homogenization process drug particle which are obtained is dependent on directly pressure, nature of drug substance and number of homogenization cycles undergone. It can be performed in two ways: either in water (that is in disso cubes) or in water reduced media (nanopure).

NANOMORPH TECHNOLOGY (NT) [13]

By use of NT low water soluble drug substances are converted into amorphous nanomorph from crystalline state. In this suspension of drug substance is prepared in a solvent which is mixed with other solvent in a chamber, due to this a conversion of drug suspension into a true molecular solution occur. Precipitation of drug substance is induced by the aqueous solution of polymer. These polymers play an important role in preventing of aggregation or growth and maintain their nanoparticulate state. The example is CAP, Calcium-phosphate based nanoparticles which improve the oral bioavailability of hormones and proteins.

DRUG DISPERSION IN CARRIERS[14, 15, 16, 17, 18]

It was first recognized in 1961 that by use of solid dispersion, enhanced dissolution and absorption of drug. This term typically refers to dispersion in an inert carrier by addition of active ingredients, which is prepared by either solvent method or fusion method or by fusion solvent method. The carriers for preparation of solid dispersions are hydrophilic in nature and generally used Poly Vinyl Pyrrolidine, Poloxamer 188, Polyethylene Glycol, Plasdone–S630 and sugar carriers such as lactose,

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sucrose and mannitol. Sometimes surfactants are also used such as Tween-80, Docusate sodium etc. The solubility of etoricoxib, allopurinol, meloxicam, olanzapine, Carbamazepine can be improved by solid dispersion using suitable hydrophilic carriers like etoricoxib with different sugar carriers, allopurinol with polyvinylpyrrolidone (PVP) K30, PVP K90 and polyethylene glycol (PEG) 4000 and PEG 6000, meloxicam with Poloxamer 188, carbamazepine with crospovidone and hydroxypropylmethylcellulose, olanzapine with pregelatinised starch and sodium starch glycollate.

BY USE OF CO-SOLVENTS[19]

By addition of co-solvents, solubility of poorly water soluble drugs can be improved. There is a dramatic change in the solubility of drugs by addition of organic co-solvent into the water. The co-solvents are having hydrogen acceptor or donor groups with a small hydrocarbon region. The hydrophobic hydrocarbon region usually interferes with the hydrogen bonding network of water which consequently reduces the intermolecular attraction of water while the hydrophilic hydrogen bonds ensures water solubility.

CHEMICAL MODIFICATIONS[20]

For increasing the aqueous solubility of poorly water soluble drugs, change in pH of a system is the simplest and most effective method. There is an exponential increase in the solubility of ionizable drug by changing the pH of solution. The drug which is to be efficiently solubilised should be a weak base with a high pKa value or weak acid with a low pKa value. The use of salt forms is a well known technique to enhanced dissolution profiles. Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs.

CRYSTAL HABIT MODIFICATION[20]

The property of a compound to exhibit in more than crystalline form is referred to as polymorphism. It is observed that they exhibit different physiochemical property such as stability, melting point, density etc. but are identical chemically.

MOLECULAR ENCAPSULATION WITH CYCLODEXTRINS[21]

The unique property of cyclodextrins and their derivative is their ability to form molecular inclusion complexes with poorly water soluble drugs. These are usually having a hydrophobic cavity having enough space to accommodate "guest" molecules which are lipophilic in nature and oligosaccharide shaped bucket to hold this cavity. Thus the drugs get encapsulated in the cavity and results in improved aqueous solubility and enhance dissolution rates. Barbiturates and NSAIDS are examples with enhanced bioavailability.

HYDROTROPIC SOLUBILISATION

It is a technique firstly introduced by Neuberg (1916).[20, 22] It is a process where large amount of secondary solute added and as a results increased aqueous solubility of water insoluble drugs.

MECHANISM OF ACTION OF HYDROTROPE

Neubergs conventional hydrotropic salts generally consist of two parts, a hydrophobic aromatic ring or ring system and anionic group. The prerequisite for a hydrotropic substance is anionic group which is responsible for bringing high aqueous solubility. There is a minor effect on the type of anion or metal ion. On the flip side planarity of hydrophobic part also plays a crucial role in hydrotropic solubilisation mechanism.[23] Those salts or additives which increases solubility in a given solvent are referred to as "salt in" and which decreases solubility are referred to as "salt out". Hydrotropism refers to as salting in of non electrolytes which are highly soluble in water. The mechanism involved in hydrotropy is related to complexation which involves interaction between lipophilic drugs and the hydrotropic agents such as urea, nicotinamide, sodium alginate, sodium benzoate etc.[22]

ADVANTAGES OF HYDROTROPIC SOLUBILISATION

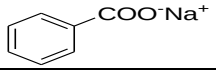
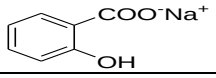
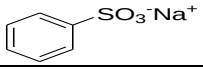
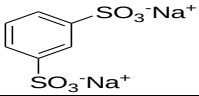
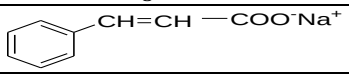
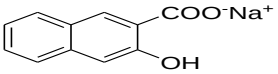
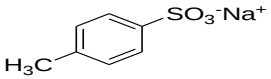
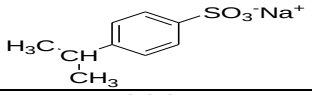
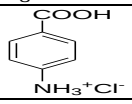
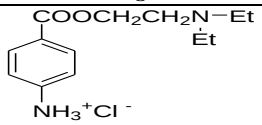
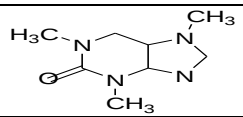
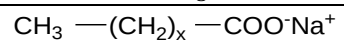
- This process doesn't require emulsification, highly selective and solvent character is independent of pH so it is preferred over other solubilisation methods such as cosolvency, micellar solubilisation.
- It primarily involves the mixing of hydrotrope and drug directly into solvent which is water.
- It precludes the chemical modification of hydrophobic drugs or preparation of emulsion system.

Hydrotropes are having the ability to increase the solubility of poorly water soluble drug and this tendency is greatest when concentration of hydrotropes is sufficiently enough to form the associated structures. Minimum hydrotrope concentration is referred to concentration of hydrotrope at which self association occurs. Hydrotrope can be categorized according to their structure as shown in Table 3.

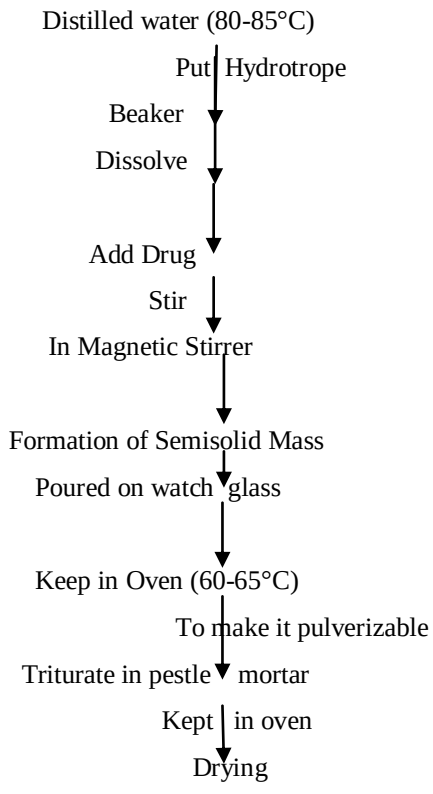
METHOD OF PREPARATION OF HYDROTROPIC SOLID DISPERSION

It is a relatively new technique in which the drug and selected hydrotropes are taken in different ratio in beaker, distilled water is added at a temperature ranging between 80-85°C. Then the selected hydrotrope is taken and added to water. Then slowly add drug to the beaker and teflon coated magnetic bead is dropped in beaker, temperature is to be maintained for optimum stirring and stirring is continued until semisolid mass is obtained. This semisolid mass is spread on several watch glasses and is placed in oven maintaining a temperature of 60-65°C. Then the trituration is done with pestle and mortar and after drying passes it through sieve no.100 and kept in desiccators for 6 days. Flow chart 1.[25, 26]

Table 3: Classification of Hydrotropes[24]

Category	Examples	Structure
Aromatic anionics	Sodium benzoate	
	Sodium salicylate	
	Sodium benzene sulphonate	
	Sodium benzene disulphonate	
	Sodium cinnamate	
	Sodium3-hydroxy-2-naphthoate	
	Sodium para toluene sulphonate.	
	Sodium cumene sulphonate	
Aromatic cationics	Para amino benzoic acid hydrochloride	
	Procaine hydrochloride	
	Caffeine	
Aliphatics and linear anionics	Sodium alkanoate	

Flow Chart1. Preparation of hydrotropic solid dispersion



MIXED HYDROTROPY

It is a solubilization technique to increase the water solubility of poorly water soluble drugs by using different ratio of blends of hydrotropic agents which gives synergistic enhancement effect. The main advantage of this technique is that it reduces the concentration of individual hydrotropic agents which directly reduces the side effects of individual hydrotropic agent. A novel, safe and sensitive method of spectrophotometric determination of Hydrochlorothiazide in tablets was developed using mixed hydrotropic solubilisation technique and concluded that there is enhancement of solubility up to 25 folds by mixed hydrotropy. Hydrotropic solid dispersion of aceclofenac was formulated and evaluated by using six blends of hydrotropes (urea and sodium citrate) and concluded that solubility of aceclofenac increases synergistically by mixed hydrotropic solublization technique.[27]

A further study was analyzed by using mixed hydrotropy on nitazoxanide, using sodium benzoate and sodium salicylate as hydrotropic agents and accomplished that there is enhancement of solubility up to 12 folds.[28]

Various drugs have been enlisted here whose solubility has been enhanced by use of hydrotropes which is presented in Table 4.

Table 4: Solubility enhancement of poorly water soluble drugs by using hydrotrope

Drugs Name	Category	Hydrotropes Used	Solubility Enhancement
Curcuminoids[29]	Natural compound(Phenolic)	Sodium Salicylate, Sodium Benzoate, Resorcinol.	144 times
Chartreusin[30]	Cytotoxic agent	Sodium Benzoate, Sodium trihydroxy Benzoate.	Solubility enhanced.
Cefadroxil[32]	Antibiotic (Cephalosporin)	Urea	10 times
Glipizide[32]	Antidiabetic	SodiumBenzoate, Sodium acetate, Sodium salicylate.	55 times
Fenofibrate[33]	Lipid lowering drug	Urea, Sodium citrate	233 times
Aceclofenac[34]	NSAIDS	Urea, Sodium citrate	250 times
Pramipexole Dihydrochloride[35]	Antiparkinson	Urea, Sodium acetate	46 times
Pacilitaxel[36]	Anticancer	N N Diethyl Nicotinamide, N N Dimethyl Benzamide	Solubility enhanced.
Losarton[37]	Antihypertensive	Sodium chloride	63 times
Simvastatin[37]	Antihyperlipidemic	Sodium chloride	90
Tenfovir Disoproxil Fumerate[38]	Antiretroviral	Sodium Benzoate	112-121 times
Metronidazole[39]	Antiprotozoal	Sodium Benzoate	5 times
Tinidazole[39]	Antiparasitic	Sodium Benzoate	6 times
Norfloxacin[39]	Antibiotic	Sodium Benzoate	40 times
Nalidixic acid[39]	Antibiotic	Sodium Benzoate	98
Ketoprofen[40]	NSAIDS	Urea, Sodium Acetate, Sodium Citrate	570 times
Indomethacin[41]	NSAIDS	Sodium p-hydroxy benzoate	117.5 times
Amlodipine Besylate[42]	Antihypertensive	Urea	7 times
Benzoic acid[43]	Antifungal, Antibacterial	Sodium benzoate, Sodium salicylate	14 fold enhancement with sodium benzoate and 28 fold with sodium salicylate
Pacilitaxel[44]	Anticancer	Hydrotropic polymer and hydrogel	Solubility enhanced

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