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Review Article

A REVIEW ON MIXED HYDROTROPY: SOLUBILITY ENHANCEMENT TECHNIQUE FOR POORLY AQUEOUS SOLUBLE DRUGS

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ABSTRACT

In case of oral administration, solubility is a key factor to demonstrate the pharmacological response in achieving the desired bioavailability of drugs. But most of the time, due to dissolution as the rate-limiting step intended for absorption of poorly aqueous soluble drugs (BCS Class-II and IV), it becomes challenging to formulate conventional dosage forms of such drugs. Different perspectives have been extensively inspected to improve the aqueous solubility and poor dissolution rate of BCS Class-II and Class-IV drugs such as micronisation, self-emulsification, pH-changing solubilization, salt formation, co-solvent, solid dispersion and hydrotropic use etc. This analysis summarizes the use of hydrotropy, which is one of the promising practice for boosting solubility in several folds by adding surplus quantity of Hydrophilic solute to improve the aqueous solubility of the primary solute without any chemical alteration of the drug compound e.g. Urea, Niacinamide , Sodium salicylate, Sodium Citrate, etc. It has several advantages like it does not need organic solvent or establishment of the emulsion system.

Keywords: Bioavailability, Hydrotropy, Hydrophilic solutes, solubility, Solubility enhancement, Mixed hydrotropy

INTRODUCTION

About 70 per cent of the drug particles are lipophilic in nature and having low aqueous solubility, which is one of the major challenging problems in the discovery and production of new drugs [1]. Solubility is a prime factor for achieving the desired pharmacological response and therapeutic efficacy[2,3]. Different organic solvents such as acetone, chloroform, methanol dimethyl formamide, PEG400 and acetonitrile have been used for the solubilization of poorly aqueous soluble drugs to perform spectrophotometric analysis with distinct flaws including high costs, instability, contamination and toxicity such as nephrotoxicity or teratogenicity [4].

Diverse formulation development techniques are currently available to enhance the solubility as well as the dissolution profile of the drug which will results in enhanced oral bioavailability[5]. Hydrotropy is one of the recognized technique available for solving problems of solvency and the best choice for preventing the use of organic solvent [6]. This review will address solubility, its need and establish various conceptual and investigative mechanisms, geometric characteristics, and its application of hydrotropic agents in the field of pharmaceutics that will help the researcher investigate hydrotropy for evolution in the modern drug delivery system.

SOLUBILITY

Any substance to be absorbed has to be existing at the absorption site in form of an aqueous solution[7-10]. Since solubility and permeability are the determining aspect for drug absorption, they can be modified or changed by solubility enhancement techniques such as micronization, chemical alteration, co-solvency, hydrotropy, micellar solubilization, etc[11]. The term "Solubility is the property of a solid, liquid or gaseous chemical substance called a solute to dissolve in a liquid , solid or gaseous solvent to form a homogeneous solution or may be explained as the greatest quantity of solute that can be dissolved in a given quantity of solvent" [12,13].

- Solubility in quantitative term express as that amount (milligram) of soluble particles required to form a saturated solution at a given temperature point.
- Solubility in qualitative term express as the simultaneous mixing of two or more phases to form a homogenous solution or molecular dispersion [14,15].

In the field of pharmaceutical sciences when quantitative data are applicable, solubility can be expressed as parts, normality, molarity, formality, volume fraction, mole fraction percent solution, and molality. The pharmacopeia lists solubility in term of the number of solvents in milliliters requires 1gm of solute to dissolve [4, 16]. The expression of solubility as per I.P and USP shown in Table 1.

BCS classification system

Drugs can also be divided into four groups within the Biopharmaceutical classification system based on solubility. In the mid-1990s, the BCS classification was introduced to categorize the drug substances in terms of their water solubility and permeability with membrane [21, 22]. Biopharmaceutic classification system is shown in Fig 1 [23, 24].

Process of solubilization [13, 25, 26]

The process of Solubilization involves following three steps: -

Step 1: Inter-molecular bonds in the solute start breaking as a result molecule of solid breaks away from the bulk.

Step 2: Separation in the molecules of the solvent offer gap (hole) in the solvent for the solute.

Step 3: The feed of solid molecules is incorporated into this gap in solvent.

Strategies for overcoming low solubility [27-33]

Physical Modifications
a) Reduction in particle size
* Conventional Method
* Nano-suspension
* Micronization

b) Process of complexation
* Physical Mixtures
* Kneading Method
* Co-precipitate process

c) Alteration in crystal habit
* Polymorphs
* Pseudopolymorphism

d) Solubilization via surfactants
*Micro-emulsions
* Self Micro-emulsifying drug delivery Systems

e) Inclusion complex formulation method
* Kneading Method
* Microwave Irradiation process
* Lyophilization/ Freeze- Drying method

f) Drug dispersion within carriers
* Solid Solutions
* Solid Dispersions -Fusion Process
-Solvent Method
-Fusion Solvent Method
-Lyophilization (Spray Freeze Drying Method)
-Dropping Method
-Hot Melt Extrusion
-Spray Drying

Chemical Modifications
a) Salts Formation
b) Cocrystallization method
c) Nanotechnology
d) Co-solvency
e) Hydrotropy
f) Use of Novel Solubilizer

Polymeric Alteration
Supercritical Fluid Process
Liquisolid Technique
pH Adjustment

OVERVIEW ON HYDROTROPY

Scientist Carl A. Neuberg first coined the term 'Hydrotropic Agent' in 1916 to depute anionic organic salts which, at high concentrations, significantly enhance the aqueous solubility of poorly soluble solutes [4,34]. Hydrotropy is a peculiar and unusual solubilization phenomenon, with the addition of a significant quantity of the second solute contributing to an increase in the aqueous solubility of another solute [35]. This increase in water solubility is probably owing to the development of organized Hydrotrope molecules assemblies at critical concentrations [14]. The chemical structure of the regular Neuberg hydrotropic salts (Prototype, Sodium Benzoate) generally consists of two vital components, anionic and hydrophobic aromatic rings or rings. Evidently, the anionic group is actively engaged in the bringing of high aqueous solubility, which is a fundamental requirement for a hydrotropic substance. Apparently, the type of anion or metal ion had a slight impact on the phenomenon [36]. From the other hand, the planarity of the hydrophobic part has been acknowledged as a key determinant in the mechanism hydrotropic solubilization. Solute is composed of alkali metal salts of different organic acids. Additives or salts that increase the solubility of a particular solvent are referred to 'salt in' the solute and those salts that decrease their solubility are referred to' salt out' the solute.

Numerous salts containing large cations and anions that are themselves highly soluble in water resulting in "salting in" of non-electrolytes termed "hydrotropic salts" and this concept known as "hydrotropism". Hydrotropic solutions don't really exhibit colloidal tendencies and suggest a weak interaction between the hydrotropes and the molecule of solute 37. Hydrotropes are generally water-soluble and surface-active compounds that can significantly improve the solubility of organic solvents such as esters, acids, alcohols, aldehydes, ketones, hydrocarbons and fats [38-41].

Major advantage of the technique of hydrotropic solubilization [42]

1. It is proposed that hydrotropy is superior to other solubilization methods, such as Miscibility, Micellar Solubilization, Co-Solvency and Salting in, although the solvent character is pH independent, it is extremely selective and needs no emulsification.
2. It needs merely to mix the drug in water with the Hydrotrope.
3. It does not include chemical alterations of hydrophobic drugs, the use of organic solvents, or emulsion system preparation.

Mechanism of hydrotropical action

The hydrotropic enhancement of water-solubility is based on the hydrotropic molecular self-interaction and the interaction of hydrotropic molecules with the solute. Although extensively used in various industrial applications, only limited knowledge about the Hydrotropism Mechanisms is available. There are several hypothetical and investigative efforts being made to clarify the Hydrotrope Mechanisms. The mechanisms offered can be shortened according to three designs [43]:

- Self-aggregation potential
- Structure-breaker and structure-maker
- Tendency to develop micelles like structure

These unique geometrical features and different association patterns of hydrotropes assemblies distinguish them from other solubilizers [44,45].

Self-Aggregation Potential

Minimum hydrotropic concentration (MHC), is a critical concentration at which hydrotrope molecules start to aggregate, i.e. self-aggregation potential. The ability of hydrotropes to solubilize is regulated by their capacity for self-aggregation [46]. The capacity relies on its amphiphilic properties and the structure of the solvent molecule [44,47]. They mainly show the volume fraction dependent solubilization potential. Hydrotropes dynamically combine with the solute to create the complexes and these complexes would then attend to higher aqueous solubility. These findings have evolved from fluorescence emissions methods [48], crystallography analysis, molecular dynamics replication and thermodynamic solubility experiments [49,50]. Besides these, they can serve as bridging agents by lowering the Gibbs energy to increase solubility. Simply, the structure of hydrotropical aqueous mixture around the drug molecule is the true explanation toward understanding the origin of self-aggregation potential[51.]

Structure-breaker and structure-maker

An electrostatic force of the donor–acceptor molecule acts a fundamental role in the hydrotropic solubilization; hence they are also called as a structure-breaker and a structure-maker [52, 53]. Solutes which are capable for both hydrogen donation and acceptance help to increase solubility. Solutropic agents like urea exert solubilizing impact by altering the nature of the solvent, in particular by altering the capacity of the solvent to make a significant contribution for structure formation or its capacity to participate in structure formation by intermolecular bonding of hydrogen [54]. Structure-breaker hydrotropes are referred to as chaotropes, while kosmotropes are referred to as structure-maker Hydrotropes [55]. Kosmotrope decreases the critical micelle concentration by increasing the hydrophobic interaction which decreases the cloud point. Basically, kosmotrope influences the cloud point by two ways i.e. (a) helps shape bigger micelles like structure and (b) hydration reduction. Cyclodextrin serves as water structure makers in the case of amphiphilic drugs promazine hydrochloride (PMZ) and promethazine and lowers the cloud point [56].

Tendency to develop micelles like structure

This principle is associated with self-association of hydrotropes with solutes in a micellar system [57]. They generate stable mixed micelles with a solute molecule that reduces electrostatic repulsion among the head groups. [58]. Hydrotropic agents like alkyl- benzene sulfonates, lower alkanoates and alkyl sulfates demonstrate self-association with solutes and form micelles. Aromatic anionic hydrotrope i.e. Nicotinamide, improving riboflavin's solubility by self-association mechanism [59]. In case of PMZ, anionic hydrotropes like sodium salicylate forms stable mixed micelles by lowering electrostatic repulsion between the head groups of PMZ.

MIXED HYDROTROPY

Mixed hydrotropic solubilization method is the phenomenon to increase the solubility of poorly water-soluble drugs by using a mix of hydrotropic carrier, which may give incredible synergistic enhancement result on solubility of poorly water-soluble drugs. Use of hydrotropic agents in blend have advantage over the use of single hydrotope to reduce in concentration of individual carrier as to minimize the side effect during formulation of water insoluble drugs dosage forms. In place of using a huge concentration of one hydrotrope, a blend of 5 hydrotropic agents can be utilized in 1/5th concentrations reducing their individual toxicities [60].

Advantages of mixed hydrotropic solubilization

- The large total concentration of hydrotropic agents needed to achieve a small increase in solubility can be decreased by using a combination of lower concentrations of agents.
- It is a modern, quick, cost-effective, safe, reliable, precise and eco sustainable method for the titrimetric and spectrophotometric analysis of drugs that are poorly water-soluble and discourage the use of organic solvents.
- It precludes the use of organic solvents, thus preventing the issue of residual toxicity, volatility defect, emissions, cost etc [36].

FREQUENTLY USED HYDROTROPES

The Hydrotropes are recognized to self-assemble in solution. The categorization of Hydrotropes on the basis of molecular structure is complicated since a broad variety of compounds have been reported to show hydrotropic behavior. Specific examples may comprise ethanol, aromatic alcohols like Resorcinol, Pyrogallol, Catechol, a- and b-Naphthols and Salicylates, Alkaloids like Caffeine and Nicotine, Ionic surfactants like Diacids, SDS (Sodium Dodecyl Sulfate) and Dodecylated Oxidibenzene. The aromatic Hydrotropes with anionic head groups are frequently studied compounds. They are large in number because of isomerism and their efficient Hydrotropical action may be due to the availability of interactive pi-orbitals. Hydrotropes with the cationic hydrophilic group are rare, e.g. salts of aromatic amines, such as procaine hydrochloride [42]. List of hydrotropic agents are shown in Table 2.

Features of the hydrotropic agents [63]

- Completely water-soluble and virtually insoluble in system.
- Because of its amphiphilic structure, the hydrotropes are surface active and aggregate in aqueous solution.
- The availability is easy and cheap.
- Non hazardous and non-reactive.
- Temperature insensitive, when dissolved in water.
- The other main advantages of hydrotropes are independent of pH, high selectivity and absence of emulsification.

Importance of Hydrotropes [63]

- Use of hydrotropes to solubilize organic compounds, dyes, drugs and biochemicals.
- Aqueous hydrotrope solutions establish safe and efficient medium for the extraction of natural products and organic synthetic reactions.
- Hydrotropes have been tested in the expansion of extractive separation processes in protein separation and distillation as an extractive solvent for the separation of phenolic mixtures at close boiling points
- They are used as fragrance extraction agents.
- Hydrotropes have wide-ranging applications in the formulation of detergents, health care and household use.
- They are used as an extraction agent for active components from crude drug.
- As fillers and extenders, in chemical formulations.
- Hydrotropical nanotechnology solubilization (by controlled precipitation). They were used to boost heterogeneous reaction rates.
- Hydrotropy to allow rapid release from the suppositories of poorly water-soluble drugs.

- Used to separate water-oil emulsions.
- It can be used in the oil industry, in tertiary petroleum recovery and in other processes. This process may be used to recover the solute in crystalline form as an improved purity, and the remaining mother liquor could be used to concentrate the hydrotrope for recycling.
- Hydrotropes increase the stability of concentrated liquid detergents by optimizing surfactant solubility and by influencing the gelling tendency that liquid detergents can exhibit when water is diluted.
- Aqueous hydrotropic solutions provide safe and efficient media for natural product extraction and for organic synthetic reactions.
- Liquid detergents can be regulated by the addition of hydrotropic agents at the viscosity and cloud point (the temperature at which a clear substance starts to become hazy when cooling).
- Hydrotropes have been used as additives to glues used in the leather industry in shampoos, degreasing agents and printing pastes.
- The use of hydrotropic, sodium xylene sulfonate in paper pulp factory yields excellent results.

TABLE 1: INTERPRETATION OF SOLUBILITY AS PER I.P AND USP [17, 18,19,20]

Descriptive terms to dissolve one part of	Relative amounts of solvents to dissolve one part of solute	Examples of drugs
Very soluble	Solubility < 1	Diltiazem, Metoprolol
Freely soluble	1 < solubility < 10	Ipratropium Bromide
Soluble	10 < solubility < 30	Cyclophosphamide, Propranolol, Carmustine, Procainamide, Timolol, Quinidine
Lightly soluble	30 < solubility < 100	Labetalol, Fluorouracil, Quinidine Sulphate, Ramipril
Moderately soluble	100 < solubility < 1000	Atenolol, Fludarabine, Valsartan
Very moderately soluble	From 1000-10,000	Busulfan, Doxazocine, Flecainide, lomustine
Insoluble or practically insoluble	>10,000	Lidocaine, Melphalan, Nifedipine, Candesartan, Irbesartan, Chlorambucil

TABLE 2: EXAMPLES OF HYDROTROPES [23, 47, 61, 62]

Type	Examples
Aromatic Cationics	Procaine hydrochloride, caffeine, and Para amino benzoic acid hydrochloride
Aromatic Anionics	Sodium benzoate, Sodium salicylate, Sodium benzene di-sulfonate, Sodium 3-hydroxy-2-naphthoateNicotinamide, Sodium cinnamate, N , N -diethylnicotinamide and N , N -dimethyl benzamide, Sodium para toluene sulfonate, Sodium benzene sulphonate, Sodium cumene sulfonate
Aliphatics and Linear Compounds	Sodium alkanoate, Urea and N, N -dimethyl urea

TABLE 3: EXAMPLES OF TITRIMETRIC AND SPECTROPHOTOMETRIC ESTIMATIONS FOR WHICH HYDROTROPICAL AGENTS ARE INVOLVED [2]

Drugs	Formulation dosage	Hydrotropes	Improvement in solubility (times)
Titrimetric Analysis			
Aceclofenac	Bulk drugs and tablets	0.5 M Ibuprofen Sodium	120
		0.5 M Sodium Salicylate	400
Famotidine	Bulk Drug	2.0 M Sodium Salicylate	25
Theophylline	Bulk Drug	2.0 M Sodium	18
Salbutamol Sulphate	Bulk Drug	2.0M Nicotinamide	17
Naproxen	Tablets	0.5M Ibuprofen Sodium	350
Spectrophotometric Analysis			
Amlodipine Besylate	Bulk drug and tablets	2.0M Sodium Acetate	75
Aceclofenac	Bulk drug and tablets	2.5M Sodium Salicylate	400
Atorvastatin	Tablets	2.0M Urea	07
Cefadroxil		6.0M Urea	10
Diclofenac Sodium	Tablets	7.5M N,n Dimethyl Urea	11
Hydro-cholorothiazide	Tablets	2.0M Nicotinamide	43
Ketoprofen	Tablets	2.0M Potassium Acetate	210
Lovastatin	Tablets	4.0M Sodium Acetate	06
Naproxen	Tablets	0.5M Ibuprofen Sodium	350
Nalidixic Acid	Tablets	Sodium Benzoate	98
Simvastatin	Bulk drug and tablets	Sodium Chloride	90
Tenofovir Disoproxil fumarate	Tablets	Sodium Benzoate	121

NOVEL PHARMACEUTICAL USES OF HYDROTROPIC SOLUBILIZATION IN DIVERSE FIELDS OF PHARMACY [64]

- Quantitative assessment of poorly water-soluble drugs by spectrophotometric and titrimetric analysis prohibiting the use of organic solvents shown in Table 3.
- Preparation of hydrotropic solid dispersion of poorly water-soluble drugs preventing the utilization of organic solvents. Such as felodipine using PEG6000 and polyvinyl alcohol [37].
- Formulation of dry syrups of poorly water-soluble drugs.
- Development of topical solutions of poorly water-soluble drugs, preventing the utilization of organic solvents. Such as tinidazole, metronidazole and salicylic acid via sodium benzoate and sodium citrate.
- Preparation poorly water-soluble drugs I.V dosages forms.

- Application of hydrotropical solubilizers as enhancers for permeation.
- The use of hydrotropy to rapidly release from the suppositories of poorly water-soluble drugs.
- Application of hydrotropic solubilization in nanotechnology by controlled precipitation process.
- In the field of pharmacognosy it is used in extraction of active constituents from crude drugs.
- Hydrotropic solutions can also be tried to establish the dissolution fluid to find out the analysis of dosage form of poorly water-soluble drug shown in Table 4.

TABLE 4: SOLUBILITY ENHANCEMENT OF POORLY WATER-SOLUBLE DRUGS BY USING HYDROTROPES [23].

Drugs	Category of drugs	Hydrotropic agents Used	Enhancement in solubility
Amlodipine Besylate	Antihypertensive	Urea	7 times
Aceclofenac	NSAIDS	Urea, Sodium citrate	250 times
Benzoic acid	Antifungal, Antibacterial	Sodium benzoate, Sodium salicylate	14-fold enhancement with sodium benzoate and 28 fold with sodium salicylate
Curcuminoid	Natural compound (Phenolic)	Sodium Salicylate, Sodium Benzoate, Resorcinol.	144 times
Cefadroxil	Antibiotic (Cephalosporin)	Urea	10 times
Chartreusin	Cytotoxic agent	Sodium Benzoate, Sodium trihydroxy Benzoate.	Solubility enhanced.
Fenofibrate	Lipid lowering drug	Urea, Sodium citrate	233 times
Glipizide	Antidiabetic	Sodium Benzoate, Sodium acetate, Sodium salicylate.	55 times
Indomethacin	NSAIDS	Sodium p-hydroxy benzoate	117.5 times
Ketoprofen	NSAIDS	Urea, Sodium Acetate, Sodium Citrate	570 times
Losarton	Antihypertensive	Sodium chloride	63 times
Metronidazole	Antiprotozoal	Sodium Benzoate	5 times
Nalidixic acid	Antibiotic	Sodium Benzoate	98
Norfloxacin	Antibiotic	Sodium Benzoate	40 times
Pramipexole Dihydrochloride	Antiparkinson	Urea, Sodium acetate	46 times
Pacilitaxel	Anticancer	N N Diethyl Nicotinamide, N N Dimethyl Benzamide	Solubility enhanced.
Simvastatin	Antihyperlipidemic	Sodium chloride	90
Tinidazole	Antiparasitic	Sodium Benzoate	6 times
Tenofovir Disoproxil fumarate	Antiretroviral	Sodium Benzoate	112-121 times

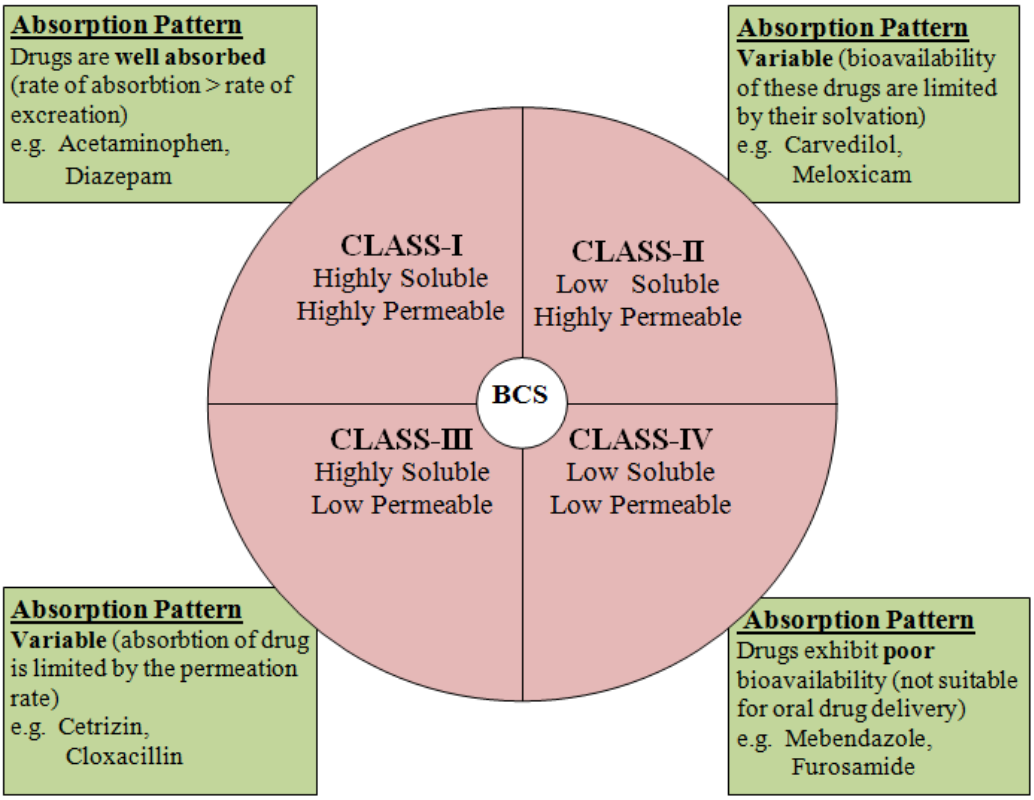

Fig.1: BCS classification

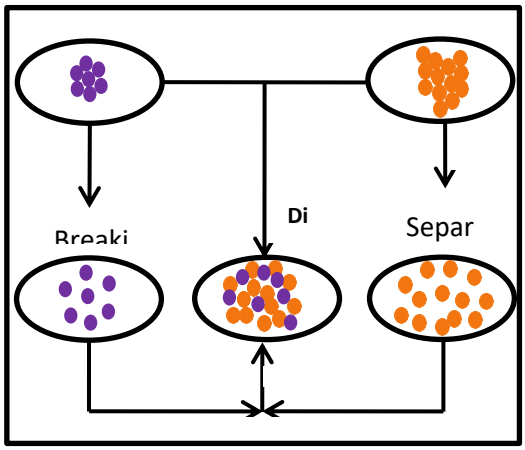

Fig. 2: Process of solubilization

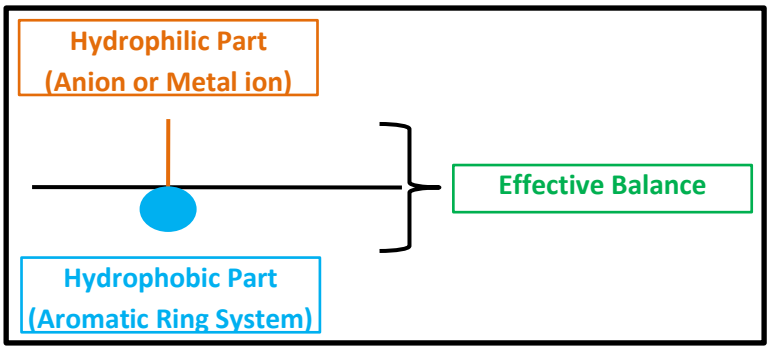

Fig. 3: The internal effective structure of a hydrotropic agent

CONCLUSION

By this article we reach the conclusion that the drug's solubility is the most significant factor influencing the drug's formulation as well as the drug's therapeutic effectiveness, thus the most crucial factor in the production of the formulations. Drug dissolution is the rate-determining stage for oral absorption of poorly water-soluble drugs and solubility is also the essential prerequisite for the formulation and production of various dosage forms of various drugs. Most of the drugs mentioned in pharmacopeia are poorly soluble in water. Solubility is one of the essential criteria for choosing correct solvent to evaluate poorly water-soluble drugs that can also use harmful, costly and record-keeping organic solvents. There are many techniques in which hydrotropy is of great importance to increase aqueous solubility of poorly water-soluble drugs. Hydrotropy is characterized as a process of solubilization whereby the addition of large quantities of second solute results in an increase in the aqueous solubility of another solute and the chemicals used in hydrotropy are called hydrotropes. For example Sodium Benzoate, Urea, Nicotinamide, Sodium Salicylate etc.this method is safe, simple, and eco-friendly. This approach is gaining a lot of values in the current scenario and may prove to be the best method in the future.

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