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HYDROTROPY

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Abstract
Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Drug efficacy can be severely limited by poor aqueous solubility and some drugs also show side effects due to their poor solubility. There are many techniques which are used to enhance the aqueous solubility. The ability to increase aqueous solubility can thus be a valuable aid to increasing efficiency and/or reducing side effects for certain drugs. This is true for parenterally, topically and orally administered solutions. Hydrotropy is one of the solubility enhancement techniques which enhance solubility to many folds with use of hydrotropes like sodium benzoate, sodium citrate, urea, niacinamide etc. and have many advantages like, it does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system etc.

Keywords: - Hydrotropy, Hydrotropes, Mixed Hydrotropy.

Introduction
Solubility is defined in quantitative terms as the concentration of the solute in a saturated solution at a certain temperature and in qualitative terms, it may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent. The solubility of a drug may be expressed as parts, percentage, molarity, molality, volume fraction, and mole fraction.

Drug solubility is the maximum concentration of the drug solute dissolved in the solvent under specific condition of temperature, pH and pressure. The drug solubility in saturated solution in a static property where as the drug dissolution rate is a dynamic property that relates more closely to the bioavailability rate. [1]

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Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Currently only 8% of new drug candidates have both high solubility and permeability. [2]

Hydrotropy
Hydrotropy is a solubilization phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of another solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium acetate have been observed to enhance the aqueous solubility of many poorly water-soluble drugs. [3]

Mechanism Of Hydrotrope Action [5]
A hydrotrope is a compound that solubilises hydrophobic compounds in aqueous solutions. Typically, hydrotropes consist of a hydrophilic part and a hydrophobic part (like surfactants) but the hydrophobic part is generally too small to cause spontaneous self-aggregation. Hydrotropes do not have a critical concentration above which self-aggregration 'suddenly' starts to occur (as found for micelle - and vesicle -forming surfactants, which have a not necessarily anionic, can act as hydrotropic agents. Saleh

critical micelle concentration or cmc and a critical vesicle concentration or cvc, respectively). Instead, some hydrotropes aggregate in a step-wise self-aggregation process, gradually increasing aggregation size. However, many hydrotropes do not seem to self-aggregate at all, unless a solubilisate has been added.

istory Of Hydrotropy And Basic Structure Of Hydrotrope

Hydrotropy is the term originally put forward by Neuberg [31] to describe the increase in the solubility of a solute by the addition of fairly high concentrations of alkali metal salts of various organic acids. However, the term has been used in the literature to designate non-micelle-forming substances, either liquids or solids, organic or inorganic, capable of solubilizing insoluble compounds. Hydrotropic solubilization process involves cooperative intermolecular interaction with several balancing molecular forces, rather than either a specific complexation event or a process dominated by a medium effect, such as cosolvency or salting-in.

The chemical structure of the conventional Neuberg hydrotropic salts (proto-type, sodium benzoate) consists generally of two essential parts, an anionic group and a hydrophobic aromatic ring or ring system. The anionic group is obviously involved in bringing about high aqueous solubility, which is a prerequisite for a hydrotropic substance. The type of anion or metal ion appeared to have a minor effect on the phenomenon [4].

Gaikar et al.[5], investigated whether a drug with an amphiphillic structure can exhibit hydrotropic properties. They sought to establish sodium ibuprofen as an effective hydrotrope.

On the other hand, planarity of the hydrophobic part has been emphasized as an important factor in the mechanism of hydrotropic solubilization [6,7]. This should imply that hydrotropic agents are molecules having a planar hydrophobic structure brought into solution by a polar group. Hence, it seems rational to propose that molecules with a planar hydrophobic part and a polar group, which is and El-Khordagui [8] suggested that the phenomenon of hydrotropy is not confined to the metal salts of organic acids, certain cationic salts and neutral molecules may be equally involve They used procaineHCl, PABAHCl and cinchocaineHCl as cationic salts and resorcinol and pyrogallol as neutral molecules in their studies.

Advantages of Hydrotropic Solubilization Technique [5]

Hydrotropy is suggested to be superior to other solubilization method, such as miscibility, micellar solubilization, cosolvency and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification.

It only requires mixing the drug with the hydrotrope in water.

It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.

Mixed hydrotropy

Mixed hydrotropic solubilization technique is the phenomenon to increase the solubility of poorly water-soluble drugs in the blends of hydrotropic agents, which may give miraculous synergistic enhancement effect on solubility of poorly water soluble drugs, utilization of it in the formulation of dosage forms of water insoluble drugs and to reduce concentration of individual hydrotropic agent to minimize the side effects (in place of using a large concentration of one hydrotrope a blend of, say, 5 hydrotropes can be employed in $1/5^{th}$ concentrations reducing their individual toxicities. [14]

Advantages Of Mixed Hydrotropic Solubilization [5]

1.It may reduce the large total concentration of hydrotropic agents necessary to produce modest increase in solubility by employing combination of agents in lower concentration.

2.It is new, simple, cost-effective, safe, accurate, precise and environmental friendly method for the analysis (titrimetric and spectrophotometric) of poorly water-soluble drugs titrimetric and spectrophotometric precluding the use of organic solvents.

3.It precludes the use of organic solvents and thus avoids the problem of residual toxicity, error due to volatility, pollution, cost etc.

A list of drugs studied by hydrotropic solubilization and its solubility enhancement ratio is presented in Table I.

Table I: Hydrotropic solubilization study of various poorly water-soluble drugs

S. No.	Drug	Hydrotrope	Solubility Enhancement Ratio	Reference
1.	Ketoprofen	2 M Potassium Acetate	210	9
		1 M Aspirin Sodium	50	10
		2 M Sodium Salicylate	90	10
		2 M Sodium Benzoate	250	10
		2 M Sodium Acetate	80	10
		30% Urea + 11.8% Sod. Citrate +		11
		13.6% Sod. Acetate	560	12
		30% Urea + 30% Sod. Citrate	700	13
		Sod. o-hydroxybenzoate		14
		Nicotinamide		14
		Sod. m-hydroxybenzoate		14
		Sodium Ascorbate,		14
		Sod.2,5-Dihydroxybenzoate		14
2.	Hydrochlorthiazide	8 M Urea	55	15
		2 M Sod Acetate	70	15
		2 M Nicotinamide	43	16
		1 M Ligocaine HCl	50	17
		20% Chlorpheniramine Maleate	40	18
		2 M Sod. Acetate + 8 M Urea	74	19
		8% Nicotinamide + 8% Sod. Acetate + 8% Sod. Benzoate + 8% Sod. Citrate + 8% Urea	25	20
3.	Olenzepine	1 M Sod. Benzoate	6	21
		1 M Sod. Acetate	19	21
		1 M Sod. Bicarbonate	22	21
		1 M Sod. Chloride	74	21
		1 M Sod. Gluconate	12	21
		1 M Thiourea	89	21
		1 M Trisodium Citrate	59	21
		1 M Urea	98	21
4.	Aceclofenac	40 % Urea	15	22
		40% Sod. Citrate	12	22
		0.5 M Ibuprofen Sodium	120	23
		2 M Sod. Benzoate	1000	24
		22.5% Urea + 22.5 % Sod. Citrate	700	25
		20 % Urea + 10 % Sod. Citrate	280	22
		20 % N,N- Dimethylurea + 20 % Sod. Citrate	1155	26
5.	Paracetamol	40% Sod. Gentisate	3.3	27
		40% Sod. Salicylate	6	27
		40% Sod. Glycinate	7.5	27
		40% Nicotinamide	15	27
		1 M Urea	50	28

		30% Urea+ 20% Sod. Citrate	2	29
		Sod. Benzoate		30
		Sod. Acetate		30
6.	Nimesulide	2 M Nicotinamide	12	31
		2 M Sod. Ascorbate	156	31
		2 M Piperazine	3248	31
		2 M Sod. Benzoate	58	31
		2 M Sod. Salicylate	67	31
7.	Naproxen	2 M Nicotinamide	210	32
		2 M Sod. Benzoate	120	33
		0.5 M Ibuprofen Sod.	350	34
8.	Ibuprofen	1 M Sod. Acetate	2	35
		1 M Sod. Salicylate	5.3	35
		1 M Sod. Toluate	3	35
		1 M Sod. Toluene Sulfonate	2.3	35
		1 M Sod. Ibuprofen	480	36
		2 M Sod. Benzoate	81	33
		Nicotinamide	62	37
9.	Flurbiprofen	2 M Sod. Benzoate	110	33
		0.5 M Sod. Ibuprofen	105	38
10.	Nalidixic Acid	2 M Sod. Benzoate	98	39
		2 M Nicotinamide	21	39
11.	Norfloxacin	2 M Sod. Benzoate	40	39
		2 M Nicotinamide	5	39
		8 M Urea	9	40
		Ascorbic Acid		41
12.	Tinidazole	2 M Sod. Benzoate	6	39
		2 M Nicotinamide	7	39
		1 M Lignocaine HCl	6	42
		1.25 M Sod. Citrate	60	43
		4 M Sod. Acetate	70	43
		8 M Urea	105	43
13.	Metronidazole	2 M Sod. Benzoate	5	39
		2 M Nicotinamide	10	39
		8 M Urea	6	40
14.	Cefixime	8 M Potassium. Acetate	120	44
		6 M Ammonium Acetate	240	44
		0.5 M Metformin HCl	18	45
		0.5 M Potassium Citrate		46
		1.25 M Sod. Citrate		46
		8 M Urea		46
15.	Salicylic Acid	0.5 M Ibuprofen Sodium	12	47
		2 M Sod. Salicylate	6	47
		2 M Sod. Saccharin	15	48
		1 M Calcium Disodium Edentate	45	49
		2 M Sod. Benzoate	12	11

		8 M Urea	8	11
		1.25 M Sod. Citrate	85	11
16.	Cefadroxil	6 M Urea	10	50
17.	Theophylline	2 M Sod. Salicylate	18	51
		Sodium Benzoate		52
		Sodium o-hydroxybenzoate		52
		Sodium m-hydroxybenzoate		52
		Sodium p-hydroxybenzoate		52
		Sodium 2,4-Dihydroxy Benzoate		52
		Sodium 2,5-Dihydroxybenzoate		52
		Sodium 2,6-Dihydroxybenzoate		52
		Sodium 3,4-Dihydroxybenzoate		52
		Sodium 3,5-Dihydroxybenzoate		52
		Sodium 3,4,5 –Trihydroxybenzoate		52
18.	Methotrexate	4 % Gallic Acid	31	53
		9 % Dihydroxy Benzoic Acid	70	53
19.	Furosemide	2 M Sod. Salicylate	30	54
		0.5 M Ibuprofen Sod.	105	55
		Urea		56
		Sod. Acetate		56
		Sod. Benzoate		56
		Sod. Citrate		56
		5 M Urea + 1 M Sod. Acetate + 0.4 M Sod. Citrate	15	56
20.	Clotrimazole	Urea		57
		Nicotinamide		57
21.	Nifedipine	1 M Urea	2.4	58
		1 M Mannitol	2	58
		1 M Citric Acid	19	58
		1 M Sod. Citrate	5	58
		1 M Sod. Acetate	1.4	58
		1 M Sod. Lauryl Sulphate	9.5	58
		1 M Sod. Benzoate	22.4	58
22.	Fenofibrate	10 % Urea	5.86	59
		10 % Sod. Citrate	3.16	59
		15 % Urea + 15 % Sod. Citrate	74	59
		20 % Urea + 10 % Sod. Citrate	233	59
23.	Lauric Acid	3 M Sod. Cumene Sulfonate	9.5	60
		3 M Sod. p- xylene Sulfonate	7.3	60
		3 M Sod. p- toluene Sulfonate	6	60
24.	Budesonide	45% Urea + 5% Sod. Citrate	20	61
25.	Ornidazole	0.5 M Ibuprofen Sodium	8	62
		10 M Urea	10	63
		45% Urea + 5 % Sod. Benzoate	12	64
26.	Aspirin	10 M Urea	6	65
		1 M Sod. Salicylate		66

		1.5 M Metformine HCl	15	67
27.	Glipizide	2 M Sod. Salicylate	55	68
		2 M Sod. Benzoate	33	68
		2 M Sod. Acetate	14.5	68
28.	Ezetimibe	3 M Urea	25	69
29.	Simvastatin	3 M Urea	55	70
30.	Curcuminoids	4 M Sod. Salicylate	133	71
		3 M Sod. Benzoate	49	71
		3 M Resorcinol	8.5	71
31.	p- Nitrobenzoic Acid	3 M Sod. Benzoate	14.2	72
		3 M Sod. Salicylate	9.6	72
		3 M Nicotinamide	5	72
32.	Furfural	3 M Urea	7.1	73
		3 M Tri Sod. Citrate	5.7	73
		3 M Sod. Toluate	4	73
		3 M Sod. Benzoate	3	73
33.	Desloratidine	8 M Urea	20	74
34.	Levofloxacin	4 M Urea	10	75
35.	Ethyl Acetate	3 M Tri. Sod. Citrate	12.5	76
		3 M Sod. Salicylate	3.8	76
		3 M Sod. Benzoate	13	76
		3 M Urea	8.8	76
36.	Acetaminophen	8 M Urea	18	77
		Pheniramine Maleate	5	78
		Chlorpheniramine Maleate	5	78
		Brompheniramine Maleate	5	78
37.	Torsemide	2 M Sod. Acetate + 8 M Urea	86	79
38.	Saquinavir	1.2 M Ascorbic Acid	473	80
		1.2 M Nicotinamide	462	80
		1.2 M Resorcinol	449	80
		1.2 M Dimethyl Urea	52	80
39.	Salicylamide	Pheniramine Maleate		78
		Chlorpheniramine Maleate		78
		Brompheniramine Maleate		78
40.	Ranitidine .HCl	10 M Urea	1500	81
41.	Styrene - Ethylbenzene	Urea		82
		Nicotinamide		82
		Sod. Benzoate		82
42.	Atorvastatin Calcium	2 M Urea	7	83
		1 M Sod. Acetate	13	84
		1 M Sod. Salicylate	12	84
		1 M Nicotinamide	4.6	84
		1 M Sod. Ascorbate	9.3	84
43.	Diclofenac Sodium	7.5 M N,N-Dimethylurea	11	85
		1 M Urea	10	28
44.	Gatifloxacin	1.5 M Metformin HCl	18	86

		2 M Sod. Benzoate	230	86
		7.5 M N,N-Dimethylurea	15	87
		20% N,N-Dimethylurea + 20 % Sod. Citrate	15	88
45.	Medazepam	Sod. Salicylate		7
46.	Oxazepam	Sod. Salicylate		7
47.	Methyl Benzoate	3 M Citric Acid	16	89
		3 M Urea	15.4	89
		3 M Nicotinamide	11.3	89
48.	Eprosartan Mesylate	2 M Sod. Acetate + 8 M Urea	56	19
49.	Valsartan	0.01 M Sod. Citrate	10	90
50.	Ofloxacin	45 % Urea + 5 % Sod. Benzoate	12	91
51.	Alizarin	3 M Potassium p-toluene Sulfonate		92
		3 M Citric Acid		92
		3 M Nicotinamide		92
52.	Toluene	Urea		93
		p-toluene Sulfonic Acid		93
53.	Olmesartan Medoxamil	2 M Sod. Acetate + 8 M Urea	44	94
54.	Esomeprazole	0.5 M Metformine HCl	35	95
55.	Nitazoxanide	1 M Sod. Benzoate	10	96
		1 M Sod. Salicylate	12	96
		1 M Sod. Benzoate + 1 M Sod. Salicylate	17	96
56.	Benzyl Acetate	3 M Sod. Salicylate		97
		3 M Sod. Benzoate		97
		3 M Urea		97
		3 M Citric Acid		97
57.	Itopride	0.5 M Metformine HCl	48	95
58.	Nitrazepam	Sod. Salicylate		7
59.	Glimeperide	Benzoic Acid		98
		Ascorbic Acid		98
		Citric Acid		98
60.	Cephalexin	8 M Urea	6	99
61.	Etodolac	35 % Sod. Benzoate	144	100
		35 % Sod. Salicylate		100
62.	Indomethacin	2 M Urea	9	101
		2 M Nicotinamide	69	101
		2 M Sod. Benzoate	80	101
		2 M Sod. p-hydroxyl Benzoate	117	101
		Resorcinol	30	101
63.	Benzodiazepines	Sod. Salicylate		7
64.	Amoxicillin	10 M Urea	11	102
		5 M Potassium Acetate	12	102
65.	Atenolol	1 M Metformin HCl	3	103

66.	Femotidine	1.5 M Metformin HCl	7	104
67.	Clonazepam	Sod. Salicylate		7
68.	Albendazole	2 M Sod. Salicylate	2	105
		2 M Sod. Benzoate	11	105
		2 M Nicotinamide	17	105
		2 M Sod. Ascorbate	1	105
		2 M Sod. Acetate	2.5	105
69.	Carbamazepine	Sod. Salicylate	112	14
		Sod. Benzoate	99	14
70.	Rapamycin	Benzyl Alcohol	>400	106
		Benzoate Buffer		106

(Solubility enhancement ratio is kept blank if not mentioned in litreture)

Conclusion

By this article we conclude that, Solubility is a most important parameter for the oral bioavailability of poorly soluble drugs. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs and solubility is also the basic requirement for the formulation and development of different dosage form of different drugs. Solubility can be enhanced by hydrotropic solublization techniques and number of folds increase in solubility is reported too.

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