International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 5(3): May-June 2015

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences **Review Article……!!!**

Received: 02-06-2015; Revised: 05-06-2015; Accepted: 06-06-2015

NOVEL SOLUBILITY ENHANCEMENT TECHNIQUE HYDROTROPY

Kunal Sharad Surwade[1]*, Ravindra Bhanudas Saudagar[2]

1. Department of Quality Assurance Techniques, KCT'S RGS College of Pharmacy, Anjaneri, Nashik, 422213, Maharashtra, India.
2. Department of Pharmaceutical Chemistry, KCT'S RGS College of Pharmacy, Anjaneri, Nashik, 422213. Maharashtra, India

Keywords:

Hydrotropy, Solubility, Hydrophobic drugs, Hydrotropes, Solubility enhancement

For Correspondence:

Kunal Sharad Surwade

Department of Quality Assurance Techniques, KCT'S RGS College of Pharmacy, Anjaneri, Nashik, 422213, Maharashtra, India.

E-mail:

kunalsurwade@hotmail.com

ABSTRACT

Solubility of poorly soluble drugs has been a really vital issue in screening studies of new chemical entities as well as formulation research. Drug efficacy can be restricted 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 potentiality to increase aqueous solubility can thus be a worth aid to increasing potency or reducing side effects for certain drugs. This is literal for orally, topically and parentally administered solutions. Use of the solubility attribute in bioavailability, pharmacology action and solubility enhancement of varied poorly soluble compounds is a challenging task for pharmaceutical researchers.Hydrotropy / Hydrotropic solubilization is one of the enhancement techniques which enhance solubility to many folds with use of hydrotropes like sodium citrate, sodium benzoate, urea etc; and have several blessings like; it doesn't require chemical modification of hydrophobic drugs, use of organic solvents or preparation of emulsion system etc.

INTRODUCTION

Neuberg was the first to institute the term hydrotropic agent in 1916, to designate anionic organic saltsthat, at high concentrations, significantly increase the aqueous solubility of poorly soluble solutes[1, 2]. Later Booth and Everson had shown that concentrated aqueous solutions of organic salts, such as sodium benzoate, salicylates, benzene sulfonate and cuminsulfonate can increase the solubility of many compounds. Booth and Everson were the primary to point out that the solubility increase in the hydrotropy solution does not occur in a linear fashion, but with the increase in the concentration of hydrotrope. This fact has an important bearing while understanding the mechanism of the hydrotropy[3, 4]. Hydrotropy is a solubilization phenomenon whereby addition of large amount of second solute results in an increase in the aqueous solubility of another solute. The chemical structure of the conventional Neuberg's hydrotropic salts [sodium benzoate, proto-type] consists generally of two essential parts, an anionic group and a hydrophobic aromatic ring or ring system. The type of anion or metal ion appeared to have a minor effect on the phenomenon[5]. The pharmacopoeia filed solubility in terms of number of milliliters of solvent required to dissolve 1g of solute. If exact solubilities are not known, the Pharmacopoeia provides general terms to explain a given range [6].

SOLUBILITY

The term 'Solubility' is defined as maximum amount of solute that can be dissolved in a given amount of solvent to form a homogenous system at specified temperature.

Or

Solubility is defined in quantitative terms as concentration of solute in concentrated solution at a certain temperature, and in qualitative way it can be defined as a spontaneous interaction of two or more substances to form a homogenous molecular dispersion.

The pharmacopoeia lists solubility in terms of number of milliliters of solvent required to dissolve 1g of solute. The Indian pharmacopoeia provides general terms to describe a given range [6].

Table-1 Description of solubility terms

DEFINITION	PART OF SOLVENT REQUIRED FOR 1 PART OF SOLUTE
Very Soluble	< 1
Freely Soluble	1 – 10
Soluble	10 – 30
Sparingly Soluble	30 – 100
Slightly Soluble	100- 1000
Very Slightly Soluble	1000 – 10,000
Insoluble	>10,1000

Table-2 The biopharmaceutical classification system (BCS)

CLASS	SOLUBILITY	PERMEABILITY	ABSORBTION PATTERN	RATE LIMITING STEP IN ABSORBTION
I	High	High	Well absorb	Gastric emptying
II	Low	High	Variable	Dissolution
III	High	Low	Variable	Permeability
IV	Low	Low	Poorly absorb	Case by case

HYDROTROPY

Hydrotropy is a solubilization technique 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 salicylates, sodium benzoate, sodium citrate, sodium acetate and urea have been observed to enhance the aqueous solubility of many poorly water-soluble drugs [6, 8].

ADVANTAGES OF HYDROTROPY TECHNIQUE

1. Hydrotropy is suggested to be superior to other solubilization method, such as miscibility, micellarsolubilization, co-solvency and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification.
2. It only requires mixing the drug with the hydrotrope in water.
3. It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system [9].

MECHANISM OF HYDROTROPE

A hydrotropy is a compound that solubilized hydrophobic compounds in aqueous solutions. Typically, hydrotropes consist of a hydrophilic part and a hydrophobic part (surfactants), but the hydrophobic part is generally too small to cause spontaneous self-aggregation. Hydrotropes do not have a critical concentration above which self-aggregation 'suddenly' starts to occur (as found for micelle – and vesicle – forming surfactants, which have a not necessarily anionic, can act as hydrotropic agent, 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 [8].

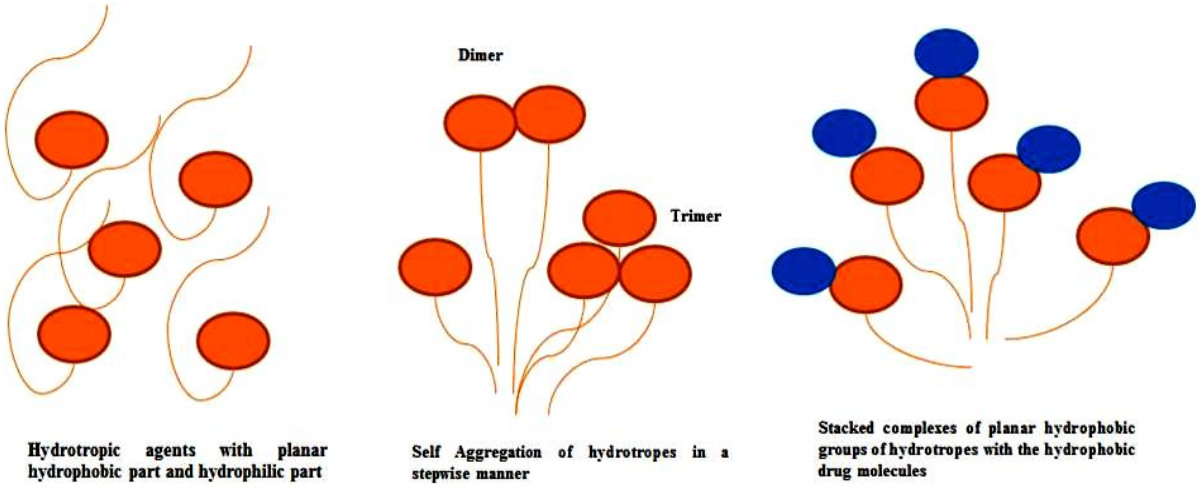

FIG. 1 Mechanism of Hydrotrope

CUSTOMARILY USED HYDROTROPES

The hydrotropes are known to self-assemble in solution [9]. The classification of hydrotropes on the basic of molecular structure is difficult, since a wide variety of compound have been reported to exhibit hydrotropic behavior. Distinct examples may include ethanol [9], aromatic alcohols like resorcinol, a- and b- naphthols and salicylates, alkaloids like caffeine and nicotine[10], ionic surfactants like di-acids [11], sodium dodecyl sulphate [12]and dodecylatedoxidibenzene[13]. Hydrotropes with cationic hydrophilic group are rare, e.g. salts of aromatic amines, such as procaine hydrochloride [14].

CHARACTERISTIC OF HYDROTROPES

- Hydrotropes are surface active and aggregate in aqueous solution because of their amphiphilic structure.
- Completely soluble in water and practically insoluble in system.
- Should not produce any temperature when dissolved in water.
- .Non toxic and non reactive.
- Cheap and easy availability
- Insensitive to temperature effects, when dissolved in water.
- The solvent character being independent of pH, high selectivity, and the absence of emulsification are the other unique advantages of hydrotropes[15].

Table-3 Hydrotropic solubilization study of various poorly water soluble Drugs

SR NO.	DRUG	HYDROTROPE	REFERENCE
1	Ibuprofen	Sodium acetate, Sodium benzoate, Sodium toluene sulfonate, Sodium salicylate and Sodium toluate	21
2	Ketoprofen	Potassium acetate	22
3	Naproxen	Niacinamide	23
4	Piroxicam	Ibuprofen sodium	24
5	Olanzepine .	Sodium benzoate, sodium acetate, sodium bicarbonate, sodium chloride,sodium gluconate, thiourea, trisodiumcitrate and urea	25
6	Lornoxicam and Paracetamol	Urea	26
7	Aceclofenac	Urea and sodium citrate	27
8	Theophylline	Urea and sodium citrate	28
9	Glipizide	PEG (Polyethylene glycol) 4000, mannitoland urea	29
10	Escitalopram	Niacinamide	30
11	Chlorobenzene	Citric acid, sodium benzoate and urea	31
12	1,1/1,2-diphenylethane	Diethylnicotinamide, sodium pseudocumenesulfonate and sodium thiocyanate	32
13	L-Tyrosine	Caffeine, Nicotinamide, Sodium salicylateand SodiumBenzoate	33
14	m/p– amino nitrobenzene	Sodium benzoate, sodium saccharin, dimethyl benzamide	34
15	Methyl benzoate	Citric acid, urea and nicotinamide	35
16	Furfural	Urea, tri-sodium citrate, sodium toluate and sodium benzoate	36
17	Acetylsalicylic acid	Sodium salicylate, sodium benzoate, nicotinamide and urea	37
18	m/paminoacetophenone	Diethyl nicotinamide, sodium pseudocumenesulfonate	38

MIXED HYDROTROPY

Mixed hydrotropic solubilization technique is used to increase the solubility of poorly water-soluble drugs in the blends of hydrotropic agents, which may give enhancement effect on solubility of poor water-soluble drugs. [Using a large concentration of 1 hydrotrope, a blend of 5 hydrotropes can be employed in 1 / 5th concentrations reducing their toxicities [16].

Advantages of Mixed Hydrotropic Solubilization

- 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.
- It is new, simple, cost-effective, safe, accurate, precise and environmental friendly method for the analysis (trimetric and spectrophotometric) of poorly water-soluble drugs trimetric and spectrophotometric precluding the use of organic solvents [17, 18].

- It precludes the use of organic solvents and thus avoids the problem of residual toxicity, error due to volatility, pollution, cost etc[19]. A list of drugs studied by hydrotropic solubilization and its solubility enhancement ratio is presented in table -4

Table-4 Hydrotropicsolubilization study of various poorly water-soluble drugs

SR. NO.	DRUG	HYDROTROPE	SOLUBILITY ENHANCEMENT RATIO
1	Nimesulide	2M Nicotinamide	150
2	Aceclofenac	40% Urea	25
3	Ketoprofen	2M Potassium acetate	210
4	Hydrochlorothiazide	8M Urea	70

CONCLUSION

By this article we conclude that, solubility of the drug is the most important factor that controls the formulation of the drug as well as therapeutic efficacy of the drug, hence the most critical factor in the formulation development. 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. The hydrotropic solubilization techniques described above alone or in Combination can be used to enhance the solubility of the drug. Solubility can be enhanced by many techniques and number of folds increase in solubility. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. It is now possible that to increase the solubility of poorly soluble drugs with the help of various techniques as mentioned above.

REFERENCES

1. Neuberg C. Hydrotropy. Biochem. Z .1916; 76: 107-109.
2. K. S. Rathore, Y. S. Tanwar, R. K. Nema, G. D. Gupta; The Pharma Review,2008.
3. H. S. Booth, H. E. Everson; Hydrotropic solubilities in aqueous sodium o-, m- and p-xylene sulfonate solutions.Ind.Eng.Chem.1950; 42: 1536-1537.
4. H. S. Booth, H. E. Everson; Hydrotropessolubilities in 40% sodium xylene sulfonate Solution.Ind.Eng.Chem.1948;40: 1491-1493.
5. A. J. Shinde, K. C. Garala, N. R. Jadhav, H. M. More; Pharmainfo.Net, 2007: 4(2): 5-8
6. R. K. Maheshwari; ThePharma Review, 2006; 4(2): 148-154.
7. V. G. Gaikar, et al.; Drug Dev.Ind.Pharm, 1997; 23(2):309-312.
8. G. K. Poochikian, et al, Journal of Pharmaceutical Sciences, 1979; 68:728-729.
9. R. K. Maheshwari, M. Singh; Asian Journal of Chemistry, 2008; 2(6): 4922-4924.
10. R. K. Maheshwari; Asian Journal of Chemistry, 2008; 18(1): 393-396.
11. D. Singh, A. K. Sharma, O. P. Pandey, M. S. Rajput; International Journal of Pharma And Bio Sciences, 2010; Oct-Dec: 711-714.
12. R. K. Maheshwari, S. Sharma, N. Rai, M. S. Rajput; Journal of Pharmacy Research, 2010;3(3): 442-443.
13. Indurkhya, M.Pharm Thesis, Shri S.G. Institute of Technology and Science, Indore, India, 2009.

14. N. Jain, R. Jain, N. Thakur, B.P. Gupta, J. Banweer, S. Jain. International Journal of Applied Pharmaceutics, 2010; 2(3): 11-14.
15. M. H. Hatzopoulos, J. Eastoe, P. J. Dowding, I. Grillo, B. Demé, S. E. Rogers, R. Heenan and R. Dyer. Effects of Structure Variation on Solution Properties of Hydrotropes: Phenyl versus Cyclohexyl Chain Tips. Langmuir. 2012; 28: 9332−9340.
16. R.K. Maheshwari, R.S. Shukla. Asian Journal of Pharmaceutics, 2008; Jan: 68-69
17. R.K. Maheshwari, S. Deswal, D. Tiwari, N. Ali, S. Jain. Asian Journal of Chemistry, 2009; 21(2): 1642-1644.
18. R.K. Maheshwari, S.R. Bishnoi, D. Kumar. Asian Journal of Chemistry, 2008; 20(8): 6594-6596.
19. R. Jain, V. Sahu, N. Jain, S. Jain. PharmaceuticaAnalyticaActa, 2011; 2(7): 1000-1035.
20. PriyankaArjaria, Manoj goyal, International Journal of Pharmaceutical andPhytopharmacological Research (eIJPPR), Res. 2013; 3 (1): 17-23
21. Patel SK, Amol DK, WaghmodeP, Dhabale AS. Solubilityenhancement of ibuprofen using hydrotropic agents. Int. J.of Pharm. and Life Sci. 2011; 2(2): 542-545.
22. Pandey S, MaheshwariRK. A novel Spectrophotometric method for the estimation of ketoprofen in tablet dosage formusing hydrotropic solubilization phenomenon. Journal of Research. 2010; 6(3):209-212.
23. Maheshwari RK, Lakkadwala S, Spectrophotometric determination of naproxen tablets usingniacinamide as hydrotropic solubilizing additive. Journal ofCurrent Pharmaceutical Research. 2010; 04:11-14
24. Maheshwari RK, WanareG. NovelSpectrophotometric analysis of Piroxicam Tablets UsingIbuprofen Sodium as Hydrotropic Solubilizing Agents. Int. J.Pharma. Sci. Drug Res.. 2010; 2(3): 210-212.
25. Sable PN, Chaulang GM, Bhosale AV, Chaudhari PD. NovelSpectrophotometric Estimation of Olanzepine UsingHydrotropic Solubilizing Agent. Research J. Pharm. AndTech. 2009; 2(2):297-300.
26. Banerjee T, Banerjee B, Jain P. SpectrophotometricEstimation of Lornoxicam and Paracetamol Tablet dosageform using Hydrotropic Solubilizing Agent.InternationalJournal of ChemTech Research. 2012; 4(1):232-239.
27. Tiwari BK, Gupta V, Jain A, Pandey A. Enhancement ofsolubility of aceclofenac by using different solubilizationtechnique. Int. J. of Pharm. and Life Sci. March 2011;2(3):620-624.
28. Jayakumar C, bertiemorais A, Arunodhaya N, Gandhi .N.Solubility enhancement of theophylline drug using differentsolubilization techniques. International Journal ofPharmaceutical and Clinical Science. 2012; 2(1): 7-10.
29. Shukla M, Rathore P, Jain A, Nayak S. Enhanced solubilitystudy of glipizideusingdifferentsolubilization techniques. IntJ Pharm Pharm Sci.2010; 2(2):46-48.
30. Choudhary NH, kumbhar MS, dighe DA, Mujgond P.S, SinghM.C.. Solubility Enhancement of Escitalopram Oxalate UsingHydrotrope.Int J Pharm PharmSci, 5(1), 121-125.
31. NatarajanA, ChinnakannuJ.Nagarajan N. Effect ofHydrotropes on Solubility and Mass Transfer Coefficient ofChlorobenzene.Res.J.Chem.Sci. 2012; 2(8) :9-13.
32. M. Dhinakaran, Antony B M,Gandhi N. Reflection ofhydrotropy technique in the segregation of 1, 1/1,2-diphenylethane.Afr J. Basic and Appl. Sci.2012; 4 (2): 55-59.
33. Rakesh K., JayakumarC,NagendraGandhi.Extraction studiesthrough hydrotropy–l-tyrosine.Int J ChemSci Tech. 2012;2(2): 13-19.
34. Dhinakaran M, Bertie AM, Gandhi N. Enhanced solubility and reflection of hydrotropy technique in the segregation of ofm/p-aminonitrobenze. ChemSci Trans. 2012; 1(2):261-268.
35. SenthilN,JayakumarC,GandhiN. Eeffect of hydrotropes on solubility and mass transfer coefficient of methyl benzoate.Mod Appl Sci.2009; 3(3):101-104.
36. JayaKumarC, Gandhi N.Hhydrotropic study on furfural -comprehensive design-expert plot. Mod Appl Sci. 2009;3(4):117-130.
37. Thenesh SK, Gandhi N. Aassociation model of hydrotropy forthe effect of hydrotropes on solubility and mass transfercoefficient of acetylsalicylic acid. Int J Pharm PharmaSci.2012;4(3):600-605.
38. Dhinakaran M, Bertie AM, Gandhi N. Separation of m/paminoacetophenoneusing hydrotropy. E J Chem.2012;9(4):2006-2014.