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Hydrotrophy- Novel Concept of Drug Solublization

Ekta Sainani[1]*, D. B. Joshi[2], R. S. Bhadauria[3], M.L. Chaudhary[4]

[1]Research Scholar, Department of Pharmaceutical Chemistry, Shrinathji Institute of Pharmacy, Upali Oden, Nathdwara, Dist-Rajsamand (Raj.)-313301 India

[2]Professor, Department of Pharmaceutical Chemistry, Shrinathji Institute of Pharmacy, Upali Oden, Nathdwara, Dist-Rajsamand (Raj.)-313301 India

[3]Principal, Department of Pharmaceutical Chemistry, Shrinathji Institute of Pharmacy, Upali Oden, Nathdwara, Dist-Rajsamand (Raj.)-313301 India

[4]Assistant Professor,Department of Pharmacology, Shrinathji Institute of Pharmacy, Upali Oden, Nathdwara, Dist-Rajsamand (Raj.)-313301 India

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Corresponding author: Ekta Sainani

ABSTRACT

The present article relates to a novel mixed hydrotropic solutions used as solution mixture in Ultra violet –visible spectroscopic studies for detecting drug molecules.The novel mixed hydrotropic solutions comprising Thymol, Camphor, Sodium acetate, Niacinamide , Sodium benzoate, Urea, Trisodium citrate, Sodium salicylate, Potassium acetate, Potassium citrate, Sodium citrate, Citric acid, Metformin HCl, Caffeine and many other combination of hydrotroic blends used as solvent for detecting the drug molecule in the analysis of the drug molecules. The main advantage of this methods are it's avoid the uses of organic solvents which were already used in to the quantification of drug candidate.

Keywords: Hydrotrophy, UV- Visible spectroscopy, Solublization study

Introduction

The current main problem in the pharmaceutical industry is related to strategies that augment the aqueous solubility of drugs, as almost 70% of the newly discovered drug candidates suffer from poor aqueous solubility [1]. Solubility is one of the prime features to accomplish desired pharmacological response. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately is attributed to solubility of drug moiety [2]. Presently, numerous formulation technologies are available to enhance solubility as well as dissolution profile to enhance oral bioavailability [3]. In addition to these technologies, 'hydrotropy' is one of the recognized techniques available for resolving solubility issues. This review will elaborate various hypothetical and investigational mechanisms, geometrical features and applications of hydrotropic agents in pharmaceutical field which will aid the researchers to explore hydrotropy for progress in drug delivery.

1.1. Hydrotropy and hydrotropic agents:

In 1916, 'hydrotropy' term was coined by the scientist Carl A. Neuberg [4]. Hydrotropes with an amphiphilic molecular structure possess the ability to increase the solubility of sparingly soluble organic molecules in water [5]. It is a molecular phenomenon whereby adding a second solute (hydrotrope) helps to increase the

aqueous solubility of poorly soluble solutes [6]. Simply the presence of a large quantity of one solute enhances the solubility of another solute [7]. Hydrotropic agents are stated as ionic organic salts which help to increase or decrease the solubility of solute in a given solvent via 'salt in' or 'salt out' effects, respectively. Salts which show 'salt in' of non-electrolytes are called "hydrotropic salts" and the phenomenon is known as "hydrotropism". They do not exhibit any colloidal properties but they improve solubility by forming weak interaction with solute molecules [8]. A hydrotropic molecule interacts with a less water-soluble molecule via weak van der Waals interactions such as π–π or attractive dipole– dipole interaction [9]. Hydrotropes contain both hydrophobic and hydrophilic fractions in them. In comparison to surfactant, they contain a very small hydrophobic fraction [10]. The efficiency of hydrotropesolubilization depends on the balance between hydrophobic and hydrophilic part of hydrotrope [11]. The larger is the hydrophobic part of an additive, the better is the hydrotropic efficiency; the presence of the charge on the hydrophilic part is less significant [12]. Hydrotropic agents can be anionic, cationic or neutral, organic or inorganic and liquids or solids in nature. These are freely soluble organic compounds which enhance the aqueous solubility of organic substances by forming stack-type aggregation [13-16].

1.2. Mechanism:

The enhancement of water-solubility by hydrotrope is based on the molecular self-association of hydrotrope and on the association of hydrotrope molecules with the solute. Although they are widely used in various industrial applications, only sporadic information is available about the mechanisms of hydrotropism. Various hypothetical and investigational efforts are being made to clarify the mechanisms of hydrotrope. The available proposed mechanisms can be abridged according to three designs [17].

(a) Self-aggregation potential
(b) Structure-breaker and structure-maker
(c) Ability to form micelles like structure.

These unique geometrical features and different association patterns of hydrotropes assemblies distinguish them from other solubilizers [18,19].

(a) Self-aggregation potential:

Minimum hydrotropic concentration (MHC), is a critical concentration at which hydrotrope molecules start to aggregate, i.e. self-aggregation potential [6].Solubilization power of hydrotropes is governed by their self-aggregation potential [11]. This potential depends upon their amphiphilic features and the nature of the solute molecule [18, 20]. They mainly show the volume fraction dependent solubilization potential [21]. Hydrotropes strongly interact with the solute to generate the complexes and these complexes would then lead to higher aqueous solubility. These outcomes have evolved from fluorescence emissions methods [9], crystallography analysis, molecular dynamics replication and thermodynamic solubility experiments [22–24]. Apart from these, they may act as bridging agents by reducing the Gibbs energy to increase the solubility of solute [23]. Simply, the structure of hydrotrope–water mixture around the drug molecule is the true key toward understanding the origin of self-aggregation potential [25].

(b) Structure-breaker and structure-maker:

An electrostatic force of the donor–acceptor molecule plays a vital role in the hydrotropic solubilization; hence, they are also termed as a structure-breaker and a structure-maker [26, 27]. Solutes which are capable for both hydrogen donation and acceptance help to increase solubility. Solutropic agents like urea exert their solubilizing effect by changing the nature of the solvent, specifically by altering the solvent's ability to participate in structure formation or its ability of engaging in structure formation via intermolecular hydrogen bonding [28]. Structure-breaker hydrotropes are known as chaotropes while structure maker hydrotropes are known as kosmotrope [29]. Kosmotrope reduces the critical micelle concentration or CMC by increasing the hydrophobic interaction which decreases the

cloud point. Basically kosmotrope influences the cloud point by two ways i.e. (a) helps to form bigger micelles and (b) decrease of hydration. In case of amphiphilic drugs promazine hydrochloride (PMZ) and promethazine, cyclodextrin act as water structure makers and reduce the cloud point [30].

*(*c) Ability to form micelles like structure:

This mechanism is based on the self-association of hydrotropes with solutes into a micellar arrangement [31]. Basically they form stable mixed micelles with a solute molecule decreasing electrostatic repulsion between the head groups [32]. Hydrotropes like alkylbenzenesulfonates, lower alkanoates and alkyl sulfates exhibit self-association with solutes and form micelles. Aromatic anionic hydrotrope i.e. nicotinamide, improve solubility of riboflavin via self-association mechanism [33]. In case of PMZ, anionic hydrotropic agents like sodium salicylate forms stable mixed micelles by decreasing electrostatic repulsion between the head groups of PMZ [33].

1.3. Fluctuation theory of solutions:

Moreover some researchers also illustrate fluctuation theory of solutions (FTS) to determine the mechanism of hydrotropic solubilization. FTS has recognized two chief factors of hydrotrope-induced solubilization: (i) Hydrotrope–solute interaction and (ii) Water activity depression. The former is conquered by hydrotrope–solute association while the latter is improved by ionic dissociation and hindered by the selfaggregation of the hydrotropes [34]. Apart from the above-mentioned mechanism, the nature and the concentration are the drawing forces for the solubilizing potential of hydrotropes. Aromatic hydrotropic agents with planar structure interact with solute molecules via inducing stacking aggregation mechanisms [35, 36]. Caffeine exhibits parallel stacking in aqueous solutions to solubilize the riboflavin [37]. Anionic hydrotropes at low concentrations increase but at higher concentrations decrease the cloud point. Cationic and non-ionic hydrotropes show steep rise in the cloud point of amphiphilic drugs. The extent of cloud-point variation by different hydrotropes is different depending on their nature and structure [38].

1.4. Applications:

Hydrotropes have many realistic applications in both biomedical and engineering fields. The uses involve development of pharmaceutical formulations, food stuffs, detergent solutions, solute separation process, paint industry, coatings, plastic additives, selective separation and alterations in reaction kinetics. In view of these, various applications related to development of pharmaceuticals are discussed.

1.4.1. Hydrotropes as drug carrier:

Hydrotropes have unique potential to act as carriers for active pharmaceutical ingredients. They have ability to generate dynamic, non-covalent assemblies, i.e. clusters in aqueous solutions. In the presence of hydrophobic compounds, these clusters are stabilized by formation of long-lived, highly stable mesoscopic droplets due to a phenomenon known as ‘mesoscalesolubilization’. Such materials can help in processing various products ranging from pharmaceuticals, cosmetics and agrochemicals [39].

1.4.1.1. Solid dispersions:

Solid dispersions (SD) are one of the most popular approaches to improving drug release of poorly soluble drugs. It is a molecular mixture of poor water soluble drugs in hydrophilic carriers wherein the drug release profile is driven by the polymer properties. It helps to increase solubility, dissolution profile of poor water soluble drugs. Commonly used polymers in preparation of SD are povidone, cyclodextrin, starch, hydroxy propyl methylcellulose, ethyl cellulose, hydroxy propyl cellulose, polyethylene glycols and silica [40].

1.4.1.2. Transdermal formulations:

Transdermal drug administration provides the benefits of achieving a remedial effect without the risks of impending side effects that may occur after oral administration. The selection of a suitable drug carrier in transdermal formulation is very important since it can affect the percutaneous absorption [39]. 5-fluorouracil transdermal formulation was prepared using

polyglycerol fatty acid monoesters (PGMC) as hydrotrope. Mean particle size of solution consisting of PGMC was approximately 14 nm.Hydrotropic transdermal formulation enhanced skin permeation of 5-FU due its ability of hydrotrope to form aggregates [40].

1.4.1.3. Parenteral formulations:

Parenteral formulation can be administration via various routes like intravenous, intramuscular, intraarterial, subcutaneous and intra-dermal. Currently, in hospitalized patients' key element for various therapeutic aliments are parenteral products. Parenteral products provide various advantages like less dosing frequency, rapid onset of action along with good bioavailability. In addition to these conventional parenteral products, novel parenteral delivery systems like liposomes, nanoparticles, implants, patches are also available for controlled, sustained and active targeted drug delivery [40].

1.4.1.4. Miscellaneous:

2-hydroxypropyl-beta-cyclodextrin (2-HP-β-CD) was used to wrap methyl testosterone (MeT) moiety in inclusion complex of MeT-2-HP-beta-CD. The intermolecular hydrogen bonding between MeT and 2-HP-β-CD helped to enhance solubility of MeT. Also, the prepared MeT-2-HP-beta-CD complex showed 7-fold improvement in oral bioavailability of MeT [66-70]. Paclitaxel-β-cyclodextrin functionalized hyperbranchedpolyglycerol (HPG) micelles were prepared with an objective of solubility enhancement.

1.4.2. Titrimetric and spectrophotometric estimations:

The analysis of poorly aqueous soluble drugs is commonly carried out by spectrophotometric method. It involved using various organic solvents like acetone, acetonitrile, benzene, carbon tetrachloride, diethyl ether, ethanol, methanol and toluene. A major drawback related to these organic solvents was their volatile nature, toxicity, flammability and cost. To overcome such difficulties, hydrotropic solutions were used.

1.4.3. Green chemistry:

1.4.3.1. Separation of mixture:

Hydrotropic solutions possess high industrial demand due to their easy availability, good recovery, absence of fire hazards and higher separation factors without any solutes emulsification problem [41]. It helps to enhance the solubility of various organic solutes such as acids, alcohols, aldehydes, esters, fats, hydrocarbons and ketones [42]. The concentration and hydrophobic parameters (surface area, molar volume of the hydrophobic parts) of hydrotropes appear to be important in solute separations. The influence of a chain length of a hydrotropic agent helps to improve solute recovery. The addition of the short chain cationic hydrotropes to sodium dodecyl sulfate (SDS) phase helped to enhance oil recovery.

Green synthesis:

Hydrotropes provide a simple, efficient and green platform for various industrial organic transformations. Moreover, being economic, non-toxic, non-flammable and eco-friendly, hydrotropic solutions possess surplus physico-chemical features required as alternate green solvents for organic reactions. Within the outline of green chemistry, aqueous hydrotropic method offers several advantages such as trouble-free handling, cleaner reaction profile, high conversions rate and short reaction time making it useful option for the rapid synthesis.

The perspectives for Hydrotropy:

The progress in hydrotropy has boosted their use in various operational fields. Specifically, the utilization of hydrotropic compounds has been increasingly recognized in formulation development. Various experimental studies have confirmed their solubility potential along with a non-toxic, non-flammable and eco-friendly nature. However, many challenges remain with respect to their structure based mechanism and toxicity profiling since their crucial side effects on normal cells during active targeting are yet to be assessed [43].

1.6 Mixed Solvency:

Maheshwari proposed the concept of mixed solvency. He is of the opinion that all

substances have solubilizing power and all soluble substances whether liquids, solids or gases may enhance the solubility of poorly water soluble drugs. He has carried out solubility studies on poorly water soluble drug, salicylic acid (as model drug). Solubility studies were carried in the solutions containing hydrotropic agents (urea and sodium citrate), cosolvents (glycerin, propylene glycol, PEG300 and PEG400) and water soluble solids (PEG4000 and PEG6000) [43].

Advantages of Mixed-Solvency:

- It precludes the use of organic solvents and thus avoids the problem of residual solvent toxicity, pollution, costetc.
- It may reduce the individual concentration of solubilizers and so reduce their toxicity associated to their highconcentration.
- It may reduce the total concentration of solubilizers, necessary to produce modest increase in solubility by employing combination of agents in lower concentrations, provided synergistic solubility enhancement is achieved due to employment ofblends.

Spectrophotometric Methods

Qualitative analysis through spectrophotometric methods achieves fast and accurate results using only small sample quantities. This fast and effect instrumentation has become an essential tool in the pharmaceutical industry thanks to its adaptability and economic value. Qualitative analysis has proven highly useful in many major forms of organic compounds and helps to ensure patient health and safety. Qualitative analysis of organic compounds can be achieved through the simple process of UV spectrophotometry. UV spectrophotometers measure the visible regions of ultraviolet light and can provide valuable information about the levels of active ingredients present in pharmaceutical compounds, as well as detect any impurities. By measuring the absorption of UV radiation of light, spectrophotometric analysis can quantify these levels at a highly accurate rate [44].

Many drugs, particularly poorly water-soluble or water-insoluble compounds such as ivermectin, abamectin and griseofulvin, exhibit poor, incomplete, and/or irregular absorption when administered to humans or animals because of their irregular dissolution rate. To increase dissolution rate, prior formulation systems utilized reduction in particle size by milling, by coprecipitation with a water-soluble carrier, by formation of a solid solution in a water-soluble carrier, by formation of a suitable more soluble salt, by formulation with a buffer salt, by the addition of small amounts of surfactant to improve wettability, and by adsorption onto a high-surface- area silica [45-46].

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 hencesolubility 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. Meera C S, Sayyad A B, Sawant S D. Review on various technique of solubility enhancement of poorly soluble drugs with special emphasis on solid dispersion. Journal of Pharmacy Research. 2010;3(10):2494-2501.
2. Solubility, From Wikipedia, the free encyclopedia, http.://en.wikipedia. encyclopedia, http.://en.wikipedia.org/wiki/Solubility.
3. Osol, A. (Eds.) In: “Remington’s

Pharmaceutical sciences," Eastern Pensylvania, Mack Publishing Company, 1990, 18: 203.

4. Martin A, Bustamanate P, Chun AHC. Physical Pharmacy, New Delhi, B.I. Wavely Pvt. Ltd, 1994, 4,223.

5. NeubergC.Hydrotrophy. Biochem J. Pharm. 1989; 75(7): 577.

6. Indian Pharmacopoeia, Govermentof India ministry of health and family Welfare, 4th ed., The Controller of Publication, Delhi, 1996,332.

7. Shiv M. Solubility Enhancement. Need.Pharmainfo.net.2009.

8. Shinde AJ. etal. Solubilization of poorly soluble drugs: A Review". Pharmainfo.net. 2007; 5:6.

9. SarSantosh K, RathodNutan.Micellar properties of alkyltrimethylammmonium bromide in aquo-organic solvent media. Res. J. Chem. Sci.2011;4:22-29.

10. Thenesh-Kumar S,Gnana-Prakash D. Nagendra-Gandhi N. Effect of hydrotropes on the solubility and mass transfer coefficient of 2-nitrobenzoic acid, Pol. J. Chem. Technol., 11,54–58(2009).

11. Ramesh N, Jayakumar C, Nagendra Gandhi N. Effective separation of Petro products through Hydrotropy. Chem. Eng. Technol.2009;32(1):129–133.

12. Rodriguez A, GraciniM,Moya ML. Effects of addition of polar organic solvents on micellization, Langmuir.2008; 24: 12785- 12790.

13. Jain P, Goel A, Sharma S, Parmar M.SolubilityEnhancement Techniques with Special Emphasis OnHydrotrophy.International Journal of Pharma Professional's Research. July 2010; 1(1): 34-45.

14. Evstigneev MP, EvstigneevVP, Hernandez Santiago AA, Davies, David B.Effectof a mixture of caffeine and nicotinamide on the solubility of vitamin (B2) in aqueous solution.Eur. J. Pharm. Sci.. 2006; 28(1-2):59-66.

15. Suzuki H, Sunada, H. Mechanistic studies on hydrotropic solubilization of nifedipine in nicotinamidesolution.Chemand Pharm Bulletin.1998; 46 (1):125-130.

16. Da Silva RC, Spitzer M, Da Silva LHM, Loh, W.Investigations on the mechanism of aqueous solubility increase caused by some hydrotropes, ThermochimicaActa. 1999; 328:161-167.

17. Sanghvi R, Evans D, Yalkowsky SH. Stacking complexa-tion by nicotinamide: A useful way of enhancing drug solubility. Int J Pharm. 2007;336:35–41.

18. Bauduin P, Renoncourt A, Kopf A, TouraudD, Kunz W. Unified concept of solubilization in water by hydrotropesand cosolvents. Langmuir. 2005;21:6769–6775.

19. Rasool AA, Hussain AA, DittertLW. Solubilityenhance-mentof some water-insoluble drugs in the presence of nicotina- mide and related compounds. J Pharm Sci. 80:387–393.

20. Coffman RE, Kildsig DO. 1996. Self-association of nicotinamidein aqueous solution: Light-scattering and vapor pressure osmometry studies. J Pharm Sci. 1991; 85:848– 853.

21. Maheshwari RK. Analytical techniques using hydrotropic solubilization [Thesis]. Department of Pharmacy, Shri G.S. Institute of Technology and Science, Indore, 2008,61-62.

22. Maheshwari RK. Mixed hydrotropyin spectrophotometric analysis of poorly water-soluble drug. Indian Pharmacist. 2007;6:66-67.

23. Patel SK, AmolDK, WaghmodeP, Dhabale AS. Solubility enhancement of ibuprofen using hydrotropic agents. Int. J. of Pharm. and Life Sci. 2011; 2(2):542-545.

24. Pandey S, MaheshwariRK. A novel spectrophotometric method for the estimation of ketoprofenin tablet dosageform using hydrotropic solubilization phenomenon. Journal of Scientific Research. 2010; 6(3):209-212.

25. MaheshwariRK, Lakkadwala S, Vyas R, Ghode, P. Spectrophotometric determination of naproxen tablets using niacinamide as hydrotropic solubilizing additive. Journal of Current Pharmaceutical Research. 2010;04:11-14

26. Maheshwari RK, Prasad S, PandeyP, WanareG. Novel Spectrophotometric analysis of Piroxicam Tablets Using Ibuprofen Sodium as Hydrotropic Solubilizing Agents.Int. J. Pharma. Sci. Drug Res.. 2010; 2(3):210-212.

27. Sable PN, Chaulang GM, Bhosale AV, Chaudhari PD. Novel Spectrophotometric Estimation of Olanzepine Using Hydrotropic Solubilizing Agent. Research J. Pharm. and Tech. 2009;2(2):297-300.

28. Banerjee T, Banerjee B, Jain P. Spectrophotometric Estimation of Lornoxicam and Paracetamol Tablet dosage form using Hydrotropic Solubilizing Agent.International Journal of ChemTech Research. 2012;4(1):232-239.

29. Tiwari BK, Gupta V, Jain A, Pandey A. Enhancement of solubility of aceclofenac by using different solubilization technique. Int. J. of Pharm. and Life Sci. March 2011;2(3): 620-624.

30. JayakumarC, bertiemorais A, Arunodhaya N, Gandhi .N. Solubility enhancement of theophylline drug using different solubilization techniques. International Journal of Pharmaceutical and Clinical Science. 2012; 2(1):7-10.

31. Shukla M, Rathore P, Jain A, Nayak S. Enhanced solubility study of glipizideusingdifferentsolubilization techniques. Int J Pharm Pharm Sci.2010;2(2):46-48.

32. Choudhary NH, kumbhar MS, digheDA, Mujgond P.S, Singh M.C.. Solubility Enhancement of Escitalopram Oxalate Using Hydrotrope.Int J Pharm PharmSci, 5(1),121-125.

33. NatarajanA, ChinnakannuJ.Nagarajan N. Effect of Hydrotropes on Solubility and Mass Transfer Coefficient of Chlorobenzene.Res.J.Chem.Sci. 2012; 2(8):9-13.

34. M. Dhinakaran, Antony B M,Gandhi N. Reflection of hydrotropy technique in the segregation of 1, 1/1,2-diphenylethane.Afr J. Basic and Appl. Sci.2012; 4 (2):55-59.

35. Rakesh K., JayakumarC,Nagendra Gandhi.Extraction studies through hydrotropy–l-tyrosine.Int J ChemSci Tech. 2012; 2(2):13-19.

36. 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.

37. SenthilN,JayakumarC,GandhiN.Eeffectof hydrotropes on solubility and mass transfer coefficient of methyl benzoate. Mod Appl Sci.2009;3(3):101-104.

38. JayaKumarC, Gandhi N.Hhydrotropic study on furfural - comprehensive design-expert plot. Mod Appl Sci. 2009; 3(4):117-130.

39. Thenesh SK, Gandhi N. Aassociation model of hydrotropy for the effect of hydrotropeson solubility and mass transfer coefficient of acetylsalicylic acid. Int J Pharm Pharma Sci.2012;4(3):600-605.

40. Dhinakaran M, Bertie AM, Gandhi N. Separation of m/p- aminoacetophenone using hydrotropy. E J Chem. 2012;9(4):2006-2014.

41. Maheshwari RK. Analytical techniques using hydrotropic solubilization [Thesis]. Department of Pharmacy, Shri G.S. Institute of Technology and Science, Indore, 2008,73-87.

42. MaheshwariRK, Govil N, Rai M, Rajput MS.New titrimetric estimation of naproxen bulk drug sample using ibuprofen sodium as hydrotropic solubilizing agent. Int J Pharm Bio Sci.2010;1(1):1-3.

43. Maheshwari RK. Analytical techniques using hydrotropic solubilization [Thesis]. Department of Pharmacy, Shri G.S. Institute of Technology and Science, Indore, 2008,107.

44. BoylanJC, In; The Theory and Practice of Industrial Pharmacy, Lachman L, Lieberman HA,Kanig JL. 3 rd Edition, Varghese Publishing House Mumbai. 1987.p.457.

45. Agashe, H.B., Jain, N.K., In; Pharmaceutical Product Development, Jain, N.K., Editor, 1st Edition, CBS Publishers and Distributors, New Delhi,

2006,38.

46. Ansel, H.C., Allen, Jr., L.V., Popovich, N.G., Editors, Pharmaceutical Dosage Forms and Drug Delivery Systems, 7th Edition. Philadelphia: Lippincott Williams and Wilkins; 2000.