JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

HYDROTROPIC SOLUBILITY ENHANCEMENT OF NITROFURANTOIN

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Abstract: The main aim of the present study is to increase solubility of poorly soluble drug nitrofurantoin. Orally administered drug are moderately soluble in the stomach environment and have good bioavailability if they can be entirely absorbed when taken orally. More than 40% of the NCEs (new chemical entities) introduced in the pharmaceutical industry recently are practically water insoluble. These medications have weak water solubility combined with slow drug absorption causes insufficient and unpredictable bioavailability as well as damage to the gastrointestinal mucosa. Therefore, one of the most difficult components of the drug development process, particularly for oral drug delivery system, is to improve drug solubility in order to increase its oral bio-availability. One of the key characteristics to achieve desired pharmacological response is solubility.

INTRODUCTION:

The solubility of the drug moiety determines its therapeutic effectiveness. Therapeutic effectiveness of a drug depends upon the bioavailability[1]. Orally administered drug are moderately soluble in the stomach environment and have good bioavailability if they can be entirely absorbed when taken orally. More than 40% of the NCEs (new chemical entities) introduced in the pharmaceutical industry recently are practically water insoluble.

To improve the solubility of a drug that is not very water soluble, there are many strategies that are accessible and documented in the literature. The methods are chosen based on a number of factors, including the quality of the medicine under consideration, the kind of excipients to be chosen, and the kind of dosage form intended[1]. The following are some methods for improving solubility and bioavailability:

1. By using Surfactant
2. pH Adjustment
3. Manipulation of solid state/ Polymeric Alteration
4. Self- Emulsifying Drug Delivery System
5. Micro emulsion
6. Particle Size Reduction
7. Supercritical Fluid Process (SCF)
8. Complexation
9. Kneading Method
10. Supercritical Anti solvent Technique
11. Hydrotropy

For researchers and pharmaceutical professionals, improving the solubility of various weakly soluble substances is a difficult challenge. Poor water solubility can significantly reduce pharmacological efficacy, and certain drugs can exhibit adverse effects as a result[3]. There are various methods used to increase a substance's solubility in water. Thus, the capacity to increase water solubility can be a useful tool to improve effectiveness and/or lessen negative effects for some drugs. This holds true for parenterally delivered, topically applied, and ingested solutions.

1. Methods of enhancing solubility are:

1.1 By using Surfactant-

Conventional approach to solubilize a poorly soluble substance is to reduce the interfacial tension between the surface of solute and solvent for better wetting and solvation interaction. A wide variety of surfactants like Polyglycolized glyceride, Tweens, Spans, Polyoxyethylene stearates and synthetic block copolymers like Poly (propylene oxide)-poly (ethylene oxide)- poly (propylene oxide) like Poloxamers based micelles, Poly (betabenzyl-L-aspartate)-b-poly (ethylene oxide), Poly (caprolactone)-b-poly (ethylene oxide) etc are very successful as excipient and carrier for dissolution enhancement. Improvement of drug solubility by using the amphiphilic surfactants is due to lowering surface tension between drug and solvent, improvement of wetting characteristics and micellar solubilization[2].

1.2 pH Adjustment-

Adjustment of microenvironmental pH to modify the ionization behavior is the simplest and most commonly used method to increase water solubility of ionizable compounds. As per pH-partition hypothesis and Handerson- Hesselbatch equation, ionization of a compound is dependent on the pH of media and pKa of drug.

1.3 Polymeric Alteration:

Different crystalline forms of a drug that may have different properties are known as Polymorphs. Polymorphs may differ in physicochemical properties such as physical and chemical stability, shelf-life, melting point, vapour pressure, intrinsic solubility, dissolution rate, morphology, density and biological activities as well as bioavailability. Amongst the stable, unstable and metastable crystalline polymorphs, metastable forms are associated with higher energy with increased surface area, subsequently solubility, bioavailability and efficacy. With regard to bioavailability, it is preferable to change drug from crystal forms into metastable or amorphous forms. However, the possibility of a conversion of the high energy amorphous or metastable polymorph into a low energy crystal form having low solubility cannot be ruled out during manufacture and storage A typical example for this is a high profile case involving polymorphism was withdrawal of ritonavir (Norvir®) capsules from the market in 1998 because a less soluble (and consequently less bioavailable) polymorph was identified two years after the product was approved and marketed, causing a decrease in bioavailability of the drug. This incident sensitized the pharmaceutical industry to the critical importance of polymorphism and encouraged the inclusion of polymorph screening as a routine component of preformulation studies[4].

1.4 Self- Emulsifying Drug Delivery System:

A self-emulsifying or self-micro emulsifying system is the concept of in situ formation of emulsion in the gastrointestinal tract. It is defined as the mixture of oil, surfactant, co-surfactant, one or more hydrophilic solvents and co-solvent forms a transparent isotropic solution in the absence of external phase (water) and forms fine o/w emulsions or micro-emulsions spontaneously upon dilution by the aqueous phase in the GIT and is used for improving lipophillic drug dissolution and absorption. The large quantity of surfactant in self-emulsifying formulations (30- 60%) irritates GIT5. Most self-emulsifying systems are limited to administration in lipid filled soft or hard-shelled gelatin capsules due to the liquid nature of the product. Interaction between the capsule shell and the emulsion should be considered so as to prevent the hygroscopic contents from dehydrating or migrating into the capsule shell. A Neoral® is an classical example of self microemulsfying drug delivery system (SMEDDS) [6].

1.5 A Micro emulsion:

It is an optically clear, isotropic, thermo dynamically stable translucent system which contains a mixture of oil, Hydrophilic surfactant and hydrophilic solvent in which the poorly water soluble drug dissolves. When comes in contact with water the formulation is spontaneously disperse or self emulsified to form a very clear emulsion of exceedingly small as well as uniform oil droplets containing the solubilized poorly soluble drug. These systems have been employed to increase the solubility of many temperatures which are practically insoluble in water along with incorporation of proteins for oral, parentral as well as percutaneous or transdermal use[6].

These homogeneous systems can be prepared by using a wide range of surfactant concentration and oil to water ratio of low viscosity. The surfactants like polyoxy ethylene surfactants for ex. Brij 35 or sugar esters like sorbitan monooleate (Span 80), cationic or anionic like alkyltrimethylammonium bromide and sodium dodecyl sulphate or zwitter ionic such as phospholipid lecithin because of it exhibits excellent bio-compatability[7,8].

1.6 Particle Size Reduction:

Micronization or nanoization is one of the most potential approaches to improve the bioavaliblity of lipophilic drugs by any means of reduction of the particle size to its submicron level. During the Preformulation studies of any formulation particle size is an critical parameter which should be strictly controlled[9]. To enhance the solubility the reduction in the particle size as a successful way but if it is in uncontrolled or un optimized it can forms the recrystallization as well as re-aggregation of drug upon storage. Because of this a thorough study on the particle size and physical stability should be done. By using the conventional techniques size reduction to submicron range is not possible[10].

1.7 Supercritical Fluid Process (SCF):

Another novel nano-sizing and solubilization technology whose application has increased in recent years is particle size reduction via supercritical fluid (SCF) processes. Super critical fluids are fluids whose temperature and pressure are greater than its critical temperature

(Tc) and critical pressure (Tp), allowing it to assume the properties of both a liquid and a gas. It is safe, environmentally friendly, and economical. At near critical temperatures, SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power[11].

1.8 Complexation:

Cyclodextrins are a group of cyclic oligosaccharides obtained from enzyamatic degradation of starch. The three major cyclodextrins are α,β, and ʎ-CD are composed of 6,7 and 8 D-(+) glucopyranose units. These agents have a torus structure with primary and secondary hydroxyl groups oriented outwords. Importantaly cyclodextrins have a hydrophilic exterior and hydrophobic internal cavity. When the aqueous solubility of the pure drug is low then there is a greater relative solubility enhancement which is obtained through cyclodextrin[12].

1.9 Supercritical Anti solvent Technique:

In this technique supercritical carbon dioxide is suggested as a new complexation medium due to its properties of improved mass transfer and increased solvating power[13]. This method constitutes one of the most innovators methods to prepare the inclusion complex of the drug with CD in the solid state[14].

1.10 Solid Dispersion:

The concept of solid dispersion was firstly proposed by Sekiguchi and obi, who investigated the generation and dissolution performance of eutectic melts of a sulfonamide drug and a water soluble carrier in the early 1960. In this technique, a poorly soluble drug is dispersed in a highly soluble solid hydrophilic matrix, which increases the dissolution of the drug. Solid dispersion technique can yield eutectic (Non Molecular mixing) or solid solution. (Molecular Mixing) products[17].

1.11 Hydrotropy:

It is a solubilization process whereby addition of a large amount of second solute results in an increase in the aqueous solubility of another solute. It designate the increase in the solubility in water because of the presence of large amount of additives. In the Mechanism, it improves solubility more closely related to complexation involving a weak interaction between the hydrotropic agents like sodium benzoate, sodium acetate, sodium alginate, urea and the poorly soluble drugs[15]. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Additives or salts that increases the solubility in given solvent are said to be "salt in" the solute and those salts which decrease the solubility known as "salt out" of the solute. There are several salts with large anions or cations which are very soluble in water resulted in “salting in” of non electrolytes called “hydrotropic salts” a phenomenon known as “hydrotropism”. Whereas Hydrotropic solutions does not show colloidal properties and involve a weak interaction between the hydrotropic agent and solute. Specific examples may include Ethanol, aromatic alcohols like resorsinol, pyrogallol, catechol and b-napthols as well as salicylates, various alkaloids like caffeine and nicotine, ionic surfactants like diacides, SDS and dodecylated oxydibenzene[16].

I. Expressing Solubility and Concentration

Common ways to express solubility include quantity per quantity, percentage, parts, molarity, molality, mole fraction, mili equivalents, and normal solutions[3]. As seen in Table 1.1, this is also expressed in terms of the number of parts of solvent needed for every part of solute as stated in the United States Pharmacopeia.

II. Descriptive terms

The pharmacopoeia gives basic terminology to characterise a particular Relative range in the absence of precise solubilities. Table 1 contains a list of these defining terms.

Descriptive terms to dissolve 1 part of solute	Relative parts of solvents to dissolve 1 part of solute	Examples of drugs
Very soluble	Less than 1	Metoprolol, Diltiazam
Freely soluble	From 1-10	Ipratropium bromide
Soluble	From 10-30	Cyclophosphamide, carmustine, Quinidine, Procainamide, Propananolol, Timolol
Sparingly soluble	From 30-100	Fluorouracil, Sulphate, Labetolol, Ramipril
Slightly soluble	From 100-1000	Fludrabine, Atenolol, Valsartan
Very slightly soluble	From 1000-10,000	Busulphan, lomustine, Flecainide, Doxazocine
Insoluble or practically insoluble	More than 10,000	Chlorambucil, Melphlan, Lidocaine, Candesartan, Irbesartan, Nifedipine

Table 1.1 Expression for approximate solubility

02. Hydrotropy: A phenomenon called "hydrotropism" occurs when some salts with high anions or cations that are also particularly soluble in water "salt in" non-electrolytes. Both hydrophilic and hydrophobic fractions can be observed in hydrotropes[22]. They include a significantly smaller hydrophobic proportion than surfactant. The balance between the hydrophobic and hydrophilic components of

the hydrotrope determines how effectively it can be dissolved. Hydrotropic substances can be organic or inorganic, liquid or solid in form, anionic, cationic, or neutral (Fig. 1.2).

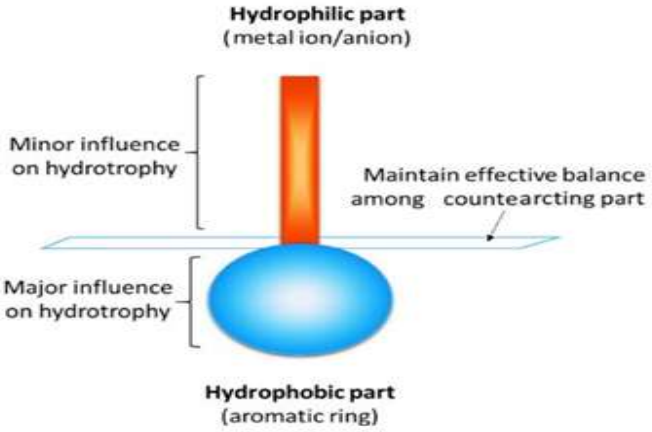

Fig 1.2 A hydrotropic agent with different structural parts

These are freely soluble organic molecules that, by aggregating into stacks, increase the solubility of organic compounds in water. Unfortunately, the mechanisms by which hydrotropes assemble are still largely undefined. Understanding the nature of hydrotrope aggregate formation in water is essential for establishing a stronger link between microscopic assembly and the related macroscopic behaviour[23]. Because hydrotropes lack the necessary hydrophobicity to produce well organized, self-associated structures like micelles even far above the MHC (minimum hydrotropic concentration), they can be distinguished from surfactants. However, it is unclear what aspect of the molecular structure or macroscopic characteristic distinguishes hydrotropes from surfactants.

Type	Examples
Aromatic anionics	Sodium benzoate, nicotinamide (fig.1.3)
Aromatic cationics	Para-aminobenzoic acid hydrochloride (fig.1.3)
Aliphatics and linear compounds	Sodium alkanoate, urea and N, N-dimethyl urea (fig.1.3)

Table 1.3 Examples of hydrotropic agents

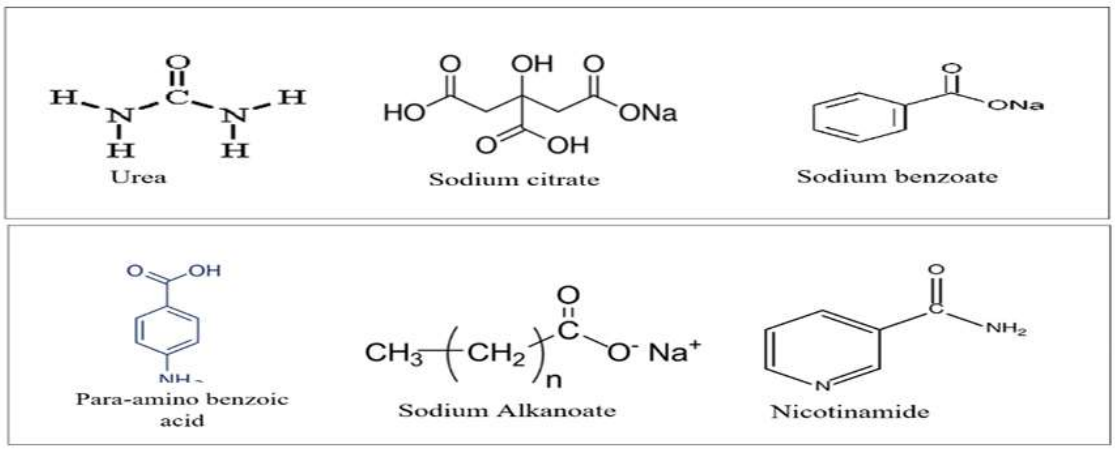

Fig 1.3 Structure of Hydrotropic agents

These chemicals have the ability to lower surface tension to extremely low levels, and at a fairly specific concentration, they self-assemble. In high concentration they behave like surfactants[24]. The short alkylbenzene sulfonates, such as xylenesulfonate and cumenesulfonate,that are sodium salts are the compounds that are most frequently associated to the term "hydrotrope." They can be "simple" co-solvents, hydrotropes, or actual surfactants, depending on the length of the alkyl chain.

2.1 Hydrotrops and Surfactants

Amphiphilic organic molecules with a close structural similarity to conventional surfactants have been found as hydrotropes. A surfactant is a solubilizer. In the surfactant micelle, a substance that is insoluble in solvents is solubilized. Solubilization is typically increased by factors that enhance the micelle's diameter or aggregation number. The solubilizers fatty soaps, polyethoxylated non-ionics, and quaternary ammonium surfactants are some examples of frequently used solubilizers. Once the CMC is attained, solubilization significantly rises. Only at extremely high doses are hydrotropes effective [25,26].

2.2 Mechanism of Hydrotropes:

Each hydrotrope has the ability to be selective toward a single component in the solution. Hydrotrope self-aggregation in the bulk phase has been considered to be the cause of hydrotropy. Minimum hydrotropic concentration is the concentration below which solubilization does not take place. self-aggregation and micelle formation drive the solubilization of the hydrophobic drugs. MHC is the solute-induced evidence for the micelle-like behavior of the hydrotropes. MHC is caused by increase of solvent−solvent (especially hydrotrope−hydrotrope) interactions from the bulk, and not by the hydrotrope self-aggregation in the bulk solution. MHC denotes the concentration at which self association begins and is often indicated by changes in solution properties such as viscosity, conductivity, surface tension, or solubility[27].

The available proposed mechanisms can be abridged according to three designs.

(a) Self-aggregation potential

(b) Structure-breaker and structure-maker

(c) Ability to form micelles like structure.

(a) Self-aggregation potential

The minimum hydrotropic concentration (MHC), also known as the self aggregation potential of hydrotrope molecules, is a critical concentration at which they begin to assemble. The ability of hydrotropes to self-assemble is what determines how soluble they are. Their amphiphilic characteristics and the make-up of the solute molecule determine this potential. They primarily display the solubilization potential[28] that is volume fraction dependent. Strong interactions between hydrotropes and the solute result in complexes, which increase the solute's solubility in water.

(b) Structure-breaker and structure-maker

Because the donor-acceptor molecules' electrostatic force is so important to hydrotropic solubilization, they are also known as structure-breakers and structure-makers. The solubility of a substance is aided by its capacity for both hydrogen donation and uptake. The way that solubilizing agents, such as urea, work is by modifying the character of the solvent. More specifically, they do this by preventing the solvent from participating in the development of new structures or from doing so by way of intermolecular hydrogen bonds. Structure creating hydrotropes are called kosmotropes, whilst structure-breaking hydrotropes are referred to as chaotropes. Kosmotrope lowers the cloud point by enhancing the hydrophobic interaction, which lowers the critical micelle concentration, or CMC. Basically, kosmotrope affects the cloud point in two ways:

(a) Aids to form larger micelles

(b) Reduction in hydration. Cyclodextrin functions as a water structure builder and lowers the cloud point in the cases of the amphiphilic medicines promazine hydrochloride and promethazine[29].

(c) Ability to form micelles like structure

The self-association of hydrotropes with solutes into a micellar arrangement serves as the foundation for this mechanism. Essentially, they create stable mixed micelles by mixing in a solute molecule to lessen the electrostatic attraction between the head groups. Alkylbenzene sulfonates, lower alkanoates, and alkyl sulphates are examples of hydrotropes that form micelles and self-associate with solutes. Nicotinamide, an aromatic anionic hydrotrope, increases the solubility of riboflavin by a self-association process. By reducing electrostatic repulsion between the head groups of PMZ [29, 30], anionic hydrotropic agents like sodium salicylate generate stable mixed micelles in the case of PMZ.

2.3 Preparation of hydrotropes:

By sulfonating an aromatic hydrocarbon solvent, hydrotropes are created (i.e., toluene, xylene or cumene). The hydrotropes are 'pure' substances, but they are generated and transported either as granular solids, which normally have an activity level of 90–95%, or as aqueous solutions, which typically have an activity level of 30–60%. Sodium sulphate and water are also included in granular solids. Spray drying, which involves source control and dust collection, is used to create granular hydrotropes products.

2.4 Characteristics of hydrotropes[31]:

1. Hydrotropes are completely soluble in water.
2. Hydrotropes are surface active and aggregate in aqueous solution because of their amphiphilic structure.
3. Cheap and easy availability.
4. Nontoxic and non-reactive.
5. The solvent character being independent of pH, high selectivity, and the absence of emulsification are the other unique advantages of hydrotropes.

2.5 Features of hydrotropes[31]:

1. Unprecedented solubilization increase.
2. Easy recovery of solute from solution.
3. Economical and cost effective.
4. Absence of emulsion.
5. Absence of hazards present in other solvents used in extractive separation.

2.6 Functions of Hydrotropes in Solution:

Effectiveness Factor:

Applying the Setschenow model yields the efficacy factor for each hydrotrope. The solubility of poorly soluble pharmaceuticals is influenced by temperature and the ionic strength of the solvent. A hydrotropic compound significantly improves the solubility of drug molecules. This phenomenon is known as the salting-out effect. Making use of the empirical formula created by Setschenow, i.e.

$\log f = \log (S0) - \log (S) = KsC$ (1)

Where,

f is the activity co-efficient

(=S0/S) and S0 and S represent the solubilities in mol/m3 of the drugs in water and in the hydrotropic agent solution of concentration c, respectively.

Setschenow constant is represented by the symbol Ks and the values can be obtained from the slope of the plot between log f vs c. A positive or a negative value for Ks indicates salting-out and salting-in respectively[33].

The Setschenow constant Ks can be considered as a measure of the effectiveness of a hydrotrope under any given conditions of hydrotrope concentration and system temperature. In general, with an increase in temperature, the Setschenow constant increases.

2.7 MIXED HYDROTROPY:

The process of combining mixtures of hydrotropic agents to increase the solubility of medications that are not very water-soluble is known as mixed hydrotropic solubilization. This method may have an additive or synergistic effect on improving the solubility of medicines with low water solubility. It has also been shown how to formulate several medications that are not very water soluble using the hydrotropic solubilization technique[34].

Instead of using a high concentration of just one hydrotrope, a mixture of, say, five hydrotropes can be used in 1/5th concentrations, reducing their individual toxicities, which may have a miraculous synergistic enhancement effect on the solubility of poorly water soluble drugs, utilisation of it in the formulation of dosage forms of water insoluble drugs, and to reduce concentration of individual hydrotropic agent to minimise side effects.

2.8 ADVANTAGES OF MIXED HYDROTROPIC SOLUBILIZATION[35]

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 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.

03. URINARY TRACT INFECTIONS:

Urinary tract infections (UTIs) are among the most common bacterial infections, affecting approximately 150 million people worldwide each year[41]. The most typical bacterial infection that adult patients suffer occurs are Urinary tract infection. As much as 1% of all clinical visits 21 in the United States are thought to be related to managing UTIs, which has a yearly cost of more than $3.5 billion, there is a significant medical burden associated with UTIs [42,43]. Around 50% of women will experience a UTI at some point in their lives, which is disproportionately dangerous for them. Numerous bacteria and fungi can cause UTIs, but uropathogenic Escherichia coli (UPEC), Klebsiella pneumoniae, Enterococcus faecalis, and Proteus mirabilis are the most prevalent pathogens. The general public's impression of UTI treatment presumes that it might be as easy as using antibiotic medication to eradicate the infection.

Urinary tract infection (UTI) is a serious bacterial infection that affects both men and women and occurs infrequently. Uncomplicated UTIs, also known as lower UTIs (cystitis) and upper UTIs(pyelonephritis), often affect people who are otherwise healthy and have no structural or neurological abnormalities of the urinary tract. There are a number of risk factors for cystitis, including female gender, a history of a UTI, sexual activity, vaginal infection, diabetes, obesity, and genetic predisposition. Urine blockage, urinary retention brought on by neurological conditions, immunosuppression, renal failure, renal transplantation, pregnancy, and the presence of foreign materials like calculi, indwelling catheters, or other drainage devices are all considered to be complicated UTIs. Both Gram-negative and Gram-positive bacteria, as well as some fungi, are responsible for UTIs.

04. NITROFURANTOIN

Nitrofurantoin possesses bacteriostatic antiseptic properties that are active against urinary tract bacteria. The most acceptable route for drug delivery that offers a high benefit and patient compliance is the oral route. Prior to the introduction of trimethoprim-sulfamethoxazole and newer beta-lactam antibiotics in the 1970s, nitrofurantoin was a common treatment for lower urinary tract infections. For the treatment of uncomplicated lower urinary tract infections, nitrofurantoin has lately been designated as the first-line medication by a number of important guidelines [43]. The use of nitrofurantoin has increased once again as a result of rising antibiotic resistance as well as an increase in the prevalence of bacteria that produce extended-spectrum beta- lactamases (ESBLs).

Urinary tract infections continue to be the predominant condition for which nitrofurantoin is used, both therapeutically and preventatively. Because it concentrates in the lower urinary tract and has a low serum concentration while serving this purpose, nitrofurantoin is favourable[44]. It also has no impact on gut flora. A faucal reservoir-derived bacteria that colonizes the per urethral space and later ascends the urinary system is the main cause of urinary tract infections. Due in part to its negligible impact on intestinal flora, researchers believe that nitrofurantoin's sustained efficacy and low levels of resistance are due to this drug.

05. Experimentation:

5.1 Organoleptic properties:

The colour, odour, and appearance of the drug sample were evaluated.

5.2 Determination of Melting Point:

The melting point of Nitrofurantoin was determined using capillary method and checked, whether it complies with the reported Melting point in IP.

5.3 Solubility of Nitrofurantoin:

Solubility of Nitrofurantoin was determined in distilled water, methanol, ethanol and dimethylformamide. Solubility studies were performed by taking excess amount of API in different beaker containing the solvents. The mixture was shaken at regular intervals. The solutions were filtered and analyzed spectrophotometrically at 370mm.

5.4. Preparation of Reagents:

The reagents were prepared as per Indian Pharmacopoeia.

5.5 Preparation of dilution media (pH 6.8 phosphate buffer):

About 28.80 g of disodium hydrogen phosphate was weighed and placed in a 1000 ml volumetric flask. To this, about 11.45 g of potassium dihydrogen phosphate was added and then volume was adjusted to 1000 ml with distilled water. The prepared solution was tested using pH meter. The pH of solution was adjusted to 6.8 (0.5).The solution was freshly prepared for all the experimental procedures.

5.6 UV-Visible Spectrophotometric Analysis:

The calibration curve of the Nitrofurantoin was plotted in between concentration and absorbance in phosphate buffer pH 6.8.

5.7 Standard calibration curve of Nitrofurantoin in distilled water:

In a volumetric flask containing 50 ml of distilled water 5 mg of pure drug was transferred. From it 5 ml of solution was withdrawn and diluted to 50 ml to make stock solution (100µg/ml). Solution of concentration varying from 2ug/ml, 4 ug/ml, 6 ug/ml, 8 ug/ml, 10ug/ml were made from stock solution. JASCO UV/visible Spectrophotometer was used to measure absorbance for each solution at λmax of 370nm, graph was plotted for absorbance versus concentration of nitrofurantoin.

5.8 Infrared Spectrophotometric Analysis:

Nitrofurantoin drug was placed in the scanning slot of Fourier Transform InfraRed (FT-IR) Spectrophotometer and scanned at the range from 4000 to 400 cm-1 to obtain the IR of Nitrofurantoin. FTIR Spectrum of Nitrofurantion was then spectrum compared with reference.

5.9 Determination of Setschenow constant:

The effectiveness factor of each hydrotrope was determined by applying the model suggested by Setschenow, later modified58 by Pathak and Gaikar, and is given by the following equation:

$\log f = (\log S0) - \log (S) = KsC$

where,

f is the activity co-efficient (=S0/S) and S0 and S represent the solubilities in mol/m3 of the drugs in water and in the hydrotropic agent (urea) solution of concentration c, respectively. A positive or a negative value for Ks indicates salting-out and salting-in respectively.

The Setschenow constant Ks can be considered as a measure of the effectiveness of a hydrotrope under any given conditions of hydrotrope concentration and system temperature. In general, with an increase in temperature, the Setschenow constant increases[45]. Analogous to the increase in solubility and mass transfer coefficient, the enhancement factor (which is defined as the ratio in absence and presence of a hydrotrope, reported in the literature for both solubility and mass transfer coefficient) also increases.

5.10 Selection of Ratios of Drug and Carrier in Physical Mixture:

Urea and Sodium citrate are used individually in the ratio of 1:2, 1:4, 1:6 and in another blend of urea and sodium citrate are used as mixed hydrotropy in ratio of 2:2, 2:4, 2:6, 4:2, 4:4, 4:6, 6:2, 6:4, 6:6, 1:1. Therefore, optimized combination of hydrotropes was selected for the preparation of hydrotropic solid dispersion (HSD).

5.11 Preparation of HSDs of Nitrofurantoin:

For preparation of 3g HSD containing Nitrofurantoin and hydrotropic blend in 1:2 ratio, Nitrofurantoin (1 g), urea (2 g) were accurately weighed. Minimum quantity of distilled water at 68℃–70℃ contained in a 200 ml beaker was used to dissolve the urea and Sodium citrate. Then, Nitrofurantoin was added to this beaker (at 35℃–40℃) and a Teflon-coated magnetic bead was dropped in it.

Magnetic bead was stirring in a beaker using a magnetic stirrer, maintaining the temperature at 35℃–40℃ until Nitrofurantoin got completely solubilized. Stirring was continued till the semisolid mass remained in beaker. Semisolid mass was spread on watch glasses in thin layers for quick drying. All the watch glasses were kept in oven, maintained the temperature at 40℃ for drying. When the mass became dry, it was transferred in pestle mortar and triturated, again kept in oven for drying. After drying, the powder of solid dispersion was passed through sieve number 100. After this, the HSD powder was stored in air-tight glass bottles[60]. Same procedure was repeated to prepare HSDs containing Nitrofurantoin and hydrotropic blend of (NF: urea) in ratios of 1:2, 1:4, 1:6. (NF: urea) in ratios of 1:2, 1:4, 1:6 and (Urea: sodium citrate) in ratios of 2:2, 2:4, 2:6, 4:2, 4:4, 4:6, 6:2, 6:4, 6:6, 1:1.

5.12 Determination of Drug Content in Hydrotropic solid dispersion[45]:

3 g of Hydrotropic Solid dispersion containing about 1 gm of nitrofurantoin was accurately weighed and transferred to a 100 ml volumetric flask. About 50 ml of distilled water was added, and flask was shaken to dissolve the formulation completely. Then, volume was made up to the mark with distilled water, and the absorbance of this solution was measured at 370 nm against reagent blank. In each case, analysis was performed in triplicate. The drug content was determined using regression equation:

$Y = 0.1211\ X - 0.0740.$ (2)

5.13 Selection of HSD ratio:

Carrier ratio 2:2 was used for preparation of Nitrofurantoin (1g), urea (2g), and sodium citrate (2g) were selected for the preparation of Fast Disintegrating tablets.

5.14 Enhancement ratio[45]:

Solubilities were determined by following formula:

$$\text{Enhancement ratio} = \frac{\text{Solubility of drug in hydrotropic solution}}{\text{Solubility of drug in distilled water}}$$

5.15 Differential Scanning Calorimetry

The thermograms of nitrofurantoin were obtained using a DSC- 3 Thermal advantage DSC differential scanning calorimeter. Solid samples were analysed. 10 mg samples were placed in aluminium pans and heated from 30 °C to 350 ℃ at a scanning rate of 10 °C/min under nitrogen flow rate of 10 ml/min.

5.16 Powder X-ray Diffraction (XRD) Studies

The powder XRD spectra of the prepared HSDs were obtained using Rigaku Ultima IV.

06. RESULTS AND DISCUSSION

6.1 DRUG CHARACTERIZATION

NITROFURANTOIN

6.1.1. Organoleptic Properties:

It was lemon yellow, odourless, crystalline powder.

6.1.2. Melting Point

The melting point of the nitrofurantoin was found to be 265 to 270℃, which complies with melting point reported in United States Pharmacopoeia.

6.1.3. Solubility

Sr. No.	Media	Solubility	Relative parts of solvents to dissolve 1 part of solute
1	Water	Very slightly soluble	From 100-1000
2	Ethanol	Very slightly soluble	From 100-1000
3	Methanol	Very slightly soluble	From 100-1000
4	Ether	Insoluble	More than 10,000
5	Dimethylformamide	soluble	From 10-30

Table 6.1.3: Solubility of Nitrofurantoin

6.1.4. Fourier Transform Infrared Spectrophotometer Analysis (FTIR)

All the prominent and primary peaks were observed in FTIR spectrum of Nitrofurantoin and compared with the reference spectrum as per United State Pharmacopoeia.

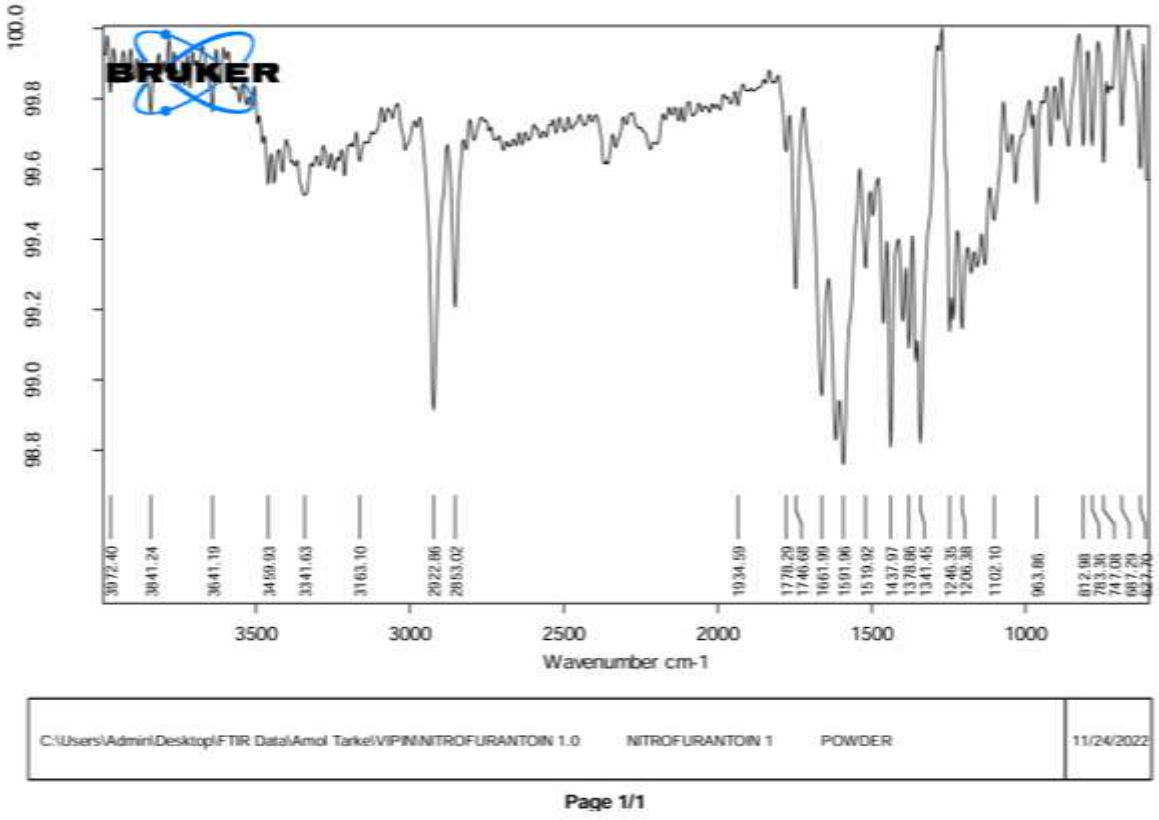

Fig. 6.1.4 Graph of Fourier Transform Infrared Spectrophotometer Analysis (FTIR)

Bond Stretching	Reported frequency cm-1	Observed Frequency cm-1	Assignment
N- H	3300-3350	3341.63	1º amine
C=O	1750-1700	1746.68 1661.99	carbonyls
N-O	1550-1475 1360-1290	1519.92 1341.45	Nitro compound
C-O	1500-1400 1320-1000	1437.97 1246.35	Ethers
C=N	1690-1640	1661.99 1663.52	Imine
N-N	1575-1630	1590.05	Nitro compound
C-N	1225-1020	1204.41 1204.11	Vinyl ether
C=C	980-960	963.36	Alkene

Table 6.1.4 Frequencies occurred in FTIR Spectrum

The Reported frequencies were found to be concurrent with a reference spectrum of Nitrofurantoin. The IR spectrum of Nitrofurantoin exhibits main bands near or wave number (cm) 3341.63, 1746.68, 1519.92, 1437.97, 1246.35, 1661.99 which was concurrent to reported frequencies.

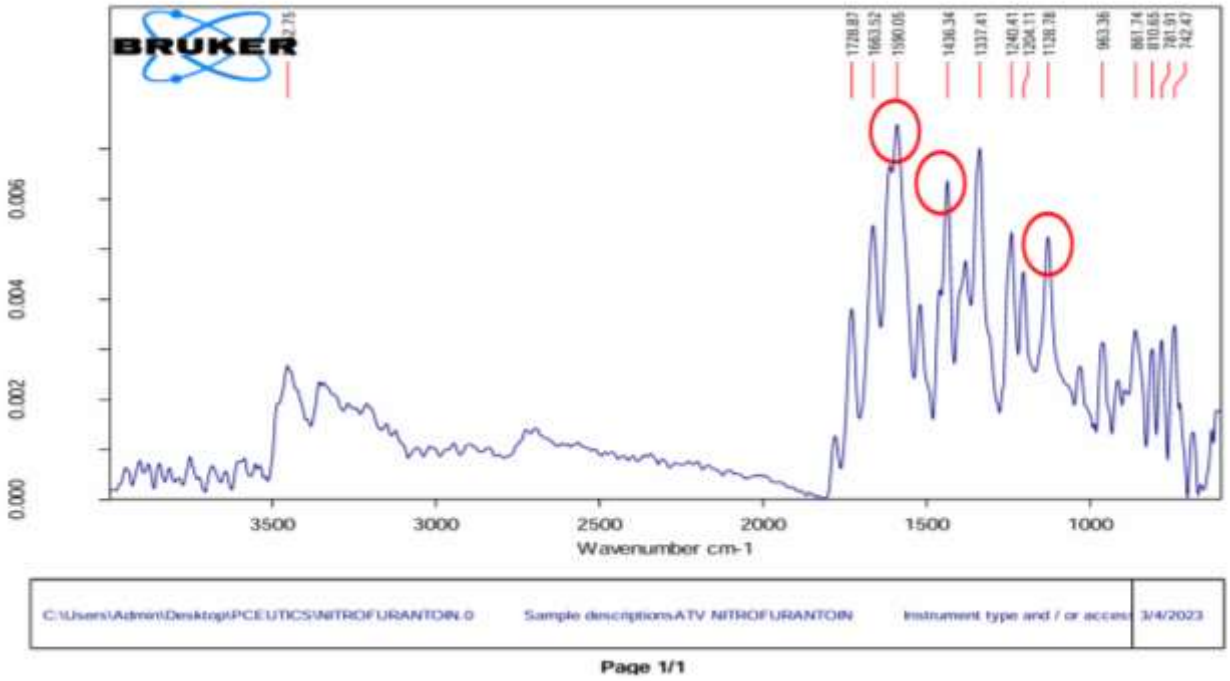

Fig 6.1.5. Fourier transform Infrared Spectrophotometer analysis of hydrotropic solid dispersion.

By comparing the peaks of drug observed in drug spectrum, it was observed that there was some significant change in peaks of Drug and hydrotropic agent. 1590.05, 1204.41, 1204.11, 963.36 are the new peaks generated between the hydrotropic solid dispersion.

7. UV Spectroscopy:

The maximum absorption value of pure drug, Nitrofurantoin was found at 370 nm wavelength in phosphate buffer pH 6.8. Therefore 370 nm was recorded as λmax of the pure drug Nitrofurantoin. The observed λmax value of drug was found to complied with the specification of Indian pharmacopoeia. Hence the drug was considered to be pure. The UV spectrum of Nitrofurantoin is shown in Figure 7.1.

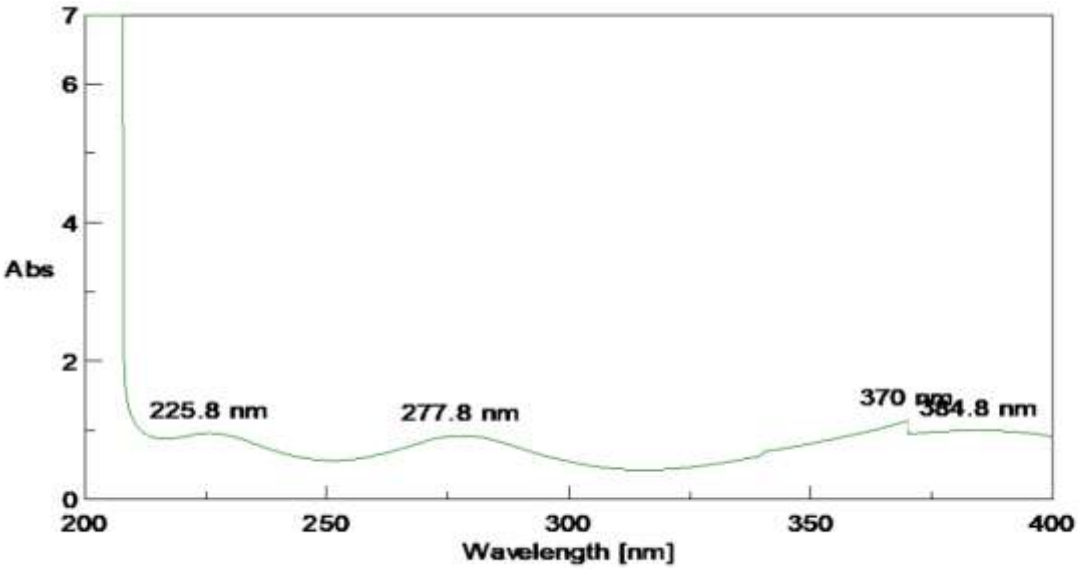

Fig 7.1 UV Spectrum of Nitrofurantoin in Phosphate buffer pH 6.8

8. Calibration curve of Nitrofurantoin in Distilled water

A solution of 100 µg/ml of Nitrofurantoin was scanned in 400 to 200 nm. The drug exhibited the λ max at 370nm and range showed reproducibility. From the standard curve of Nitrofurantoin in Distilled water it was observed that the Nitrofurantoin obeys Beer-Lambert's law in the range of 2-10ug/ml in the medium.

Conc. (µg/ml)	Absorbance
0	0.0020
2	0.0932
4	0.1971
6	0.3127
8	0.4303
10	0.5374

Table 8.1 Calibration of Nitrofurantoin in Distilled water

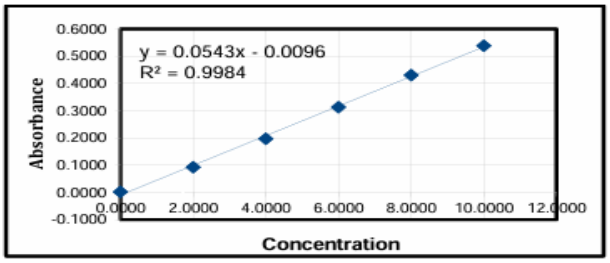

Table 8.2 Calibration curve of Nitrofurantoin in Distilled water

7. Differential scanning calorimetry

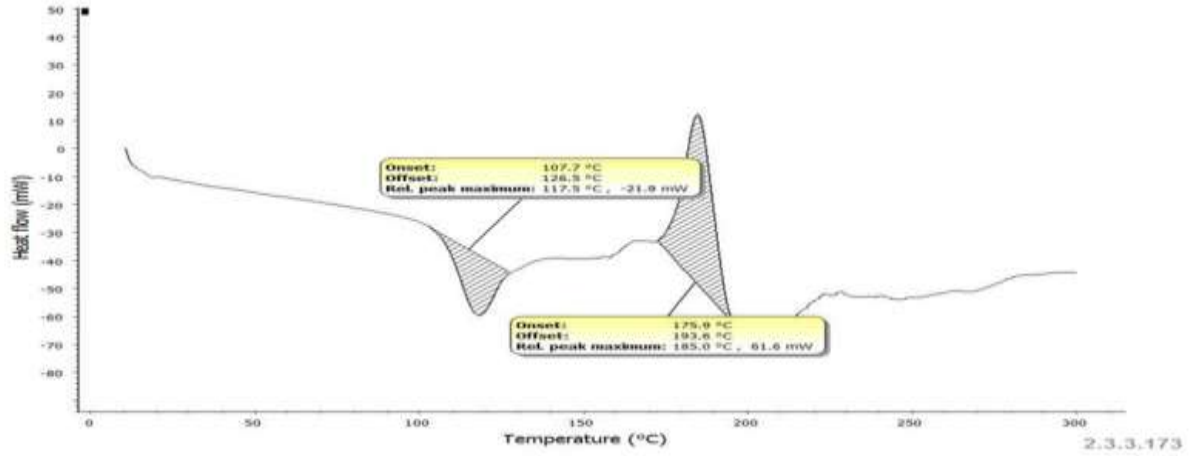

Fig 7.1. DSC of Hydrotropic solid dispersion

Differential scanning calorimetry is among the well-established method used for the thermal analysis of materials Enthalpy changes appearance/disappearance of peaks, and changes to a peak(s) onset time, shape, relative area, as a function of temperature are exhibited in DSC thermograms. Information regarding drug-excipient interactions and formation of new entities is often obtained from DSC analysis of a formulation.

The DSC thermogram obtained from the analysis of Hydrotropic solid dispersion is shown in Fig 7.1, Hydrotropic solid dispersion in solid state exhibits 2 peaks. First peak shows an endothermic peak, melting peak range from 107.7℃ to 126.5℃. Second peak also shows an endothermic peak, Melting peak range from 175.9℃ to 193.6℃. These observations, and the reports supports the formation of a stable hydrotropic solid dispersion which is of semi-crystalline nature.

8. Powder X-ray Diffraction (XRD) Studies

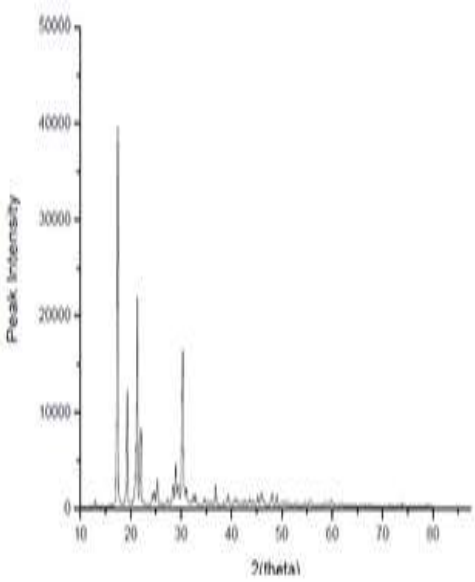

Fig 8.1 Powder X-ray Diffraction (XRD) Study of Nitrofurantoin

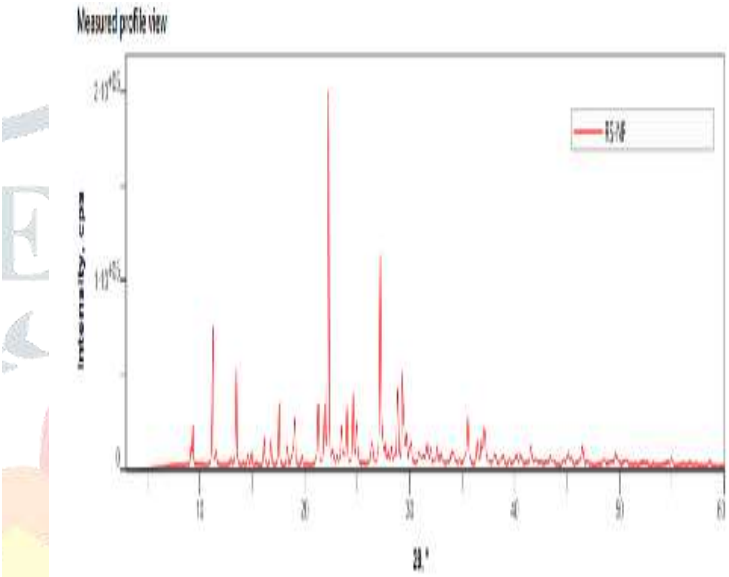

Fig 8.2 Powder X-ray Diffraction (XRD) Study of Hydrotropic solid dispersion

XRD diffraction patterns of Hydrotropic solid dispersion exhibited sharp peaks which indicates that the Hydrotropic solid dispersion is of semi crystalline nature. This study confirmed that HSDs were not present in amorphous form; rather they were of semi crystalline nature. As hydrotropic solid dispersion, exhibited sharp peaks at 2θ of 22.2281(18), 11.2624(19), 13.472(2), 27.167(4).

9. Setshenow constant

$\text{Log } f = \text{Log } (S^{o}) - \text{Log } (S) = KsC$ (3)

Where, f = activity co-efficient

S0 and S = the solubilities in mol/m3 of the drugs in water and in the hydrotropic agent solution of concentration C.

Ks= Setschenow constant

A positive or a negative value for Ks indicates salting-out and salting-in respectively

Preparation of Solid Dispersion with different Hydrotrope:

- **Urea**

NF	Urea	Ratio	Ks
1 mg	2mg	1:2	-0.5447
1 mg	4 mg	1:4	-0.1843
1 mg	6 mg	1:6	0.4149

Table 9.1 Setchenow constant of Urea

- **Sodium Citrate**

NF	Sodium Citrate	Ratio	Ks
1 mg	2mg	1:2	-0.2206
1 mg	4 mg	1:4	0.1046
1 mg	6 mg	1:6	0.4102

Table 9.2 Setchenow constant of Sodium Citrate

10. Enhancement ratios in solubility:

Enhancement ratios in solubility were determined by following formula:

$$\text{Enhancement ratio} = \frac{\text{Solubility of drug in hydrotropic solution}}{\text{Solubility of drug in distilled water}}$$

Urea	2mg	2mg	2mg	4mg	4mg	4mg	6mg	6mg	6mg	1mg
SC	2mg	4mg	6mg	2mg	4mg	6mg	2mg	4mg	6mg	2mg
Ratio	2:2	2:4	2:6	4:2	4:4	4:6	6:2	6:4	6:6	**1:2**
ER	3.45	2.51	2.43	0.13	2.13	1.74	1.62	0.72	0.08	**3.91**

Table 10.1 Enhancement ratio of urea and sodium citrate hydrotropic mixture

- **Urea**

NF	Urea	Ratio	ER
1 mg	2mg	1:2	**3.50**
1 mg	4 mg	1:4	1.52
1 mg	6 mg	1:6	0.38

Table 10.2 Enhancement ratio of urea as Hydrotropic agent

- **Sodium Citrate**

NF	Sodium Citrate	Ratio	ER
1 mg	2mg	1:2	**2.81**
1 mg	4 mg	1:4	0.78
1 mg	6 mg	1:6	0.38

Table 10.3 Enhancement ratio of sodium citrate as Hydrotropic agent

11. Summary:

About 45% of new chemical entities coming from the discovery are poorly soluble. Hydrotropy is a solubilization process where addition of a large amount of second solute exerts an increase in the aqueous solubility of another solute. The other solute can be a poorly soluble drug. Hydrotropes may be cationic, anionic or a neutral molecule, and possesses a hydrophobic as well as a hydrophilic group. Finding the right hydrotropic agent for a poorly soluble drug requires screening of a large number of hydrotropic agents. However, significant solubility enhancement of drug can be easily achieved by selecting correct hydrotropic agent. Hydrotropic solubilization technique is a promising approach with great potential for poorly soluble drugs. Nitrofurantoin is an antibacterial agent specially used in the treatments of Urinary tract infection. It has low solubility and high permeability.

12. CONCLUSION:

1. The Hydrotropic technique is used to increase the solubility of poorly soluble drug Nitrofurantoin.
2. Solubility of the poorly soluble drug Nitrofurantoin has been increased by Mixed Hydrotropy.
3. Urea and Sodium Citrate is used. The solubility of the ratio 1:1 i.e. Nitrofurantoin and urea has been increased by 3.91 folds.

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