

Hydrotropic Method Development for Antidiabetic Drugs

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ABSTRACT: The efficiency of medication availability on the location of action has a significant impact on formulation effectiveness. The solubility and bioavailability of a medicine's drug moiety are the two main factors that determine a drug's therapeutic effectiveness. The majority of newly developed anti-diabetic medications are lipophilic and poorly soluble in water. A medication with a greater than 40% efficacy has poor water solubility. One of the key factors in achieving the correct the level of drug concentration in the body for pharmacological response is solubility. Inadequate water solubility can significantly reduce medicinal efficacy, and certain medications also exhibit side effects as a result. One method for increasing solubility is hydrotropy, which has the advantage of not requiring hydrophobic medications that have been chemically modified the use of organic solvents, or the creation of an emulsion system. Hydrotropes include sodium benzoate, sodium citrate, urea, niacinamide, and others. So, this article discusses the creation of a hydrotropic approach for an anti-diabetic medicine

KEYWORDS: Actuator, Microprocessor, Enginehead, L293D Current Amplifier, IRF 3205 MOSFET.

I. INTRODUCTION

More than one-third of the medications listed in the Indian and US Pharmacopoeias are either poorly or completely insoluble in water. Poor biopharmaceutical qualities, particularly the insolubility of water, have been reported to be responsible for 41% of novel medication development failures (Maheshwari et al., 2010).

One of the most challenging issues with these medications is their poor solubility, which is a characteristic of the majority of newly produced pharmacological compounds (Maheshwari et al., 2011). Several organic solvents, including

acetonitrile, methanol, chloroform, and dimethylformamide, have been used to dissolve pharmaceuticals that aren't very water-soluble in order to analyse those medications Maliwal et al., 2008).

These organic solvents' shortcomings include their high price, volatility, pollution, and toxicity, including nephrotoxicity and teratogenicity. Therefore, hydrotropic agent's safe, environmentally benign, and economically advantageous solvents for spectrophotometric analysis replace these organic solvents. One of the finest options for eliminating the use of organic solvents is the hydrotropic solubilization approach (Maheshwari; 2010).

When he dissolved different chemical molecules such lipids, carbohydrates, esters, and medicines in an aqueous solution containing hydrotropes, Neuberg became the first to describe hydrotropy. A solubilization phenomena known as hydrotropy occurs when a second solute is added in significant quantities, increasing the solubility of the first solute in water. Sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate concentrated aqueous hydrotropic solutions have been seen to increase the aqueous solubility of numerous medications that aren't very water-soluble (Choudhary & Nayal, 2019; Neuberg, 1916).

The maximum amount of solute that may dissolve in a specific amount of solvent is referred to as solubility. It is described quantitatively as the solute concentration in a saturated solution at a particular temperature. The qualitative definition of solubility is the spontaneous interaction of two or more substances to create a homogeneous molecular dispersion. The analytical make-up of a saturated solution, stated as a ratio of a designated solute in a designated solvent, is referred to as solubility by the International Union of Pure and Applied Chemistry

(IUPAC). When the solute and solvent are in balance, a solution is said to be saturated. A drug's solubility can be expressed in terms of parts, percentages, molarity, molality, volume fraction, and moles (Augustijns and Brewster, 2007; Indian Pharmacopoeia, 1996).

Drugs can also be categorised into four classes of the Biopharmaceutical Classification System based on their solubility. In the middle of the 1990s, the BCS Classification was developed to categorise pharmacological compounds according to their aqueous solubility and membrane permeability (Yasir et al., 2010; Reddy and Karunakar, 2011).

Table 1: Biopharmaceutic classification system

Classification	Property
BCS-I	Highly soluble, Highly permeable,
BCS-II	Low soluble, highly permeable
BCS-III	Highly soluble, low permeable
BCS-IV	Low soluble, low permeable

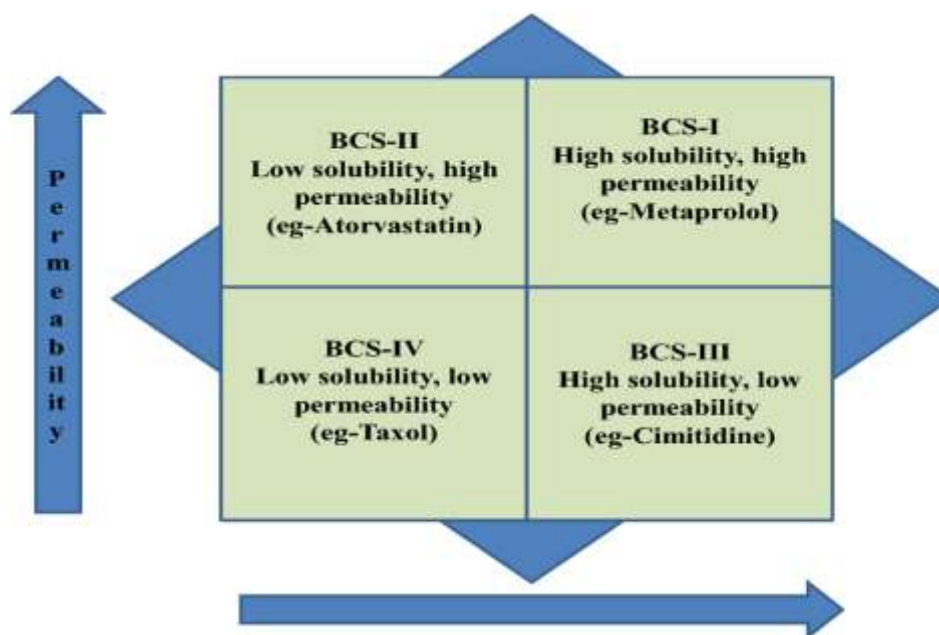


Figure: Biopharmaceutical classification system

Classification of hydrotrope

Researchers noticed that the chemical structures of the typical Neuberg hydrotrope molecules consist of two key components: an anionic, thus water soluble group, and a hydrophobic aromatic ring or ring system. While the hydrophilic ionic component aids in increasing the hydrotrope solubility in water, the planar hydrophobic moiety is thought to be crucial for causing stack type aggregation. If the goal of the ionic group is just to boost the aqueous hydrotrope solubility, then the cationic or non-ionic polar groups should be able to do this. Researchers tested

the cationics, p-aminobenzoic acid hydrochloride, procaine hydrochloride, and dibucaine hydrochloride in order to test this and discovered that they were good hydrotropes, capable of extremely successfully solubilizing the representative lipophile riboflavin. By means of all of these, they put out a new definition of hydrotropes: Hydrotropic agents are freely soluble organic compounds that are either cationic, anionic, or neutral molecules that significantly increase the solubility of organic components in water that are practically insoluble under normal circumstances (Patil et al., 2021; Bauduin et al., 2005).

Table 2: Classification of hydrotropic agents

Sr. No.	Classes of hydrotropic agent
1	Organic acids & their metal salts
2	Urea and its derivatives
3	Alkaloids
4	Phenolic derivatives
5	Surfactants
6	Aromatic cations

II. MECHANISM OF HYDROTROPY

Structure-breaker and Structure-maker

Because the donor-acceptor molecules' electrostatic force is so important in the hydrotropic solubilization process, they are also known as structure-breakers and structure-makers. Solutes that can receive and donate hydrogen contribute to increased solubility. Chaotropes are hydrotropes that break structures, whereas kosmotropes are hydrotropes that build structures (Abranches et al., 2020; Mancinelli et al., 2007).

Ability to Form Micelle-like Structures

The self-association of hydrotropes with solutes into a micellar arrangement serves as the foundation for this mechanism. When combined with a solute molecule, they create stable mixed micelles that reduce the electrostatic attraction between the head groups. Alkyl-benzene sulfonates, lower alkanoates, and alkyl sulphates are examples of hydrotropic agents that show self-association with solutes and form micelles. Through a self-association process, aromatic anionic hydrotropic agents, such as nicotinamide, increase the solubility of riboflavin. Reduced electrostatic repulsion between PMZ's head groups allows anionic hydrotropic agents like sodium salicylate to create stable mixed micelles in the presence of PMZ (Patel & Desai, 2022; Ooya et al., 2005).

Mixed hydrotropic

The process of using blends of hydrotropic agents to increase the solubility of poorly soluble drugs is known as mixed hydrotropic solubilization. This technique also reduces side effects by lowering the concentration of each individual hydrotropic agent, which may have a synergistic enhancement effect on the solubility of poorly soluble drugs (Kadam et al., 2013; Maheshwari and Jagwani, 2011).

Advantages of Hydrotropic Solubilization Technique:

1. Because the solvent feature of hydrotropy depends on pH, it has great selectivity, and it doesn't require emulsification, it is claimed to be superior to other solubilization methods including miscibility, micellar solubilization, cosolvency, and salting in.
2. It merely has to be done by combining the hydrotrope and the medication in water.
3. It doesn't call for the preparing of an emulsion system, using organic solvents, or chemically altering hydrophobic medicines (MS et al., 2023).

Environmental considerations

Given that the octanol-water partition coefficient of hydrotropes is 1, they have a poor potential for bioaccumulation. According to research, hydrotropes have very low vapour pressures (2.0×10^{-5} Pa), making them barely volatile. They can degrade aerobically. More than 94% of the activated sludge is removed during the secondary wastewater treatment process. Studies on fish's acute toxicity have revealed an LC50 > 400 mg active ingredient (a.i.)/L. The EC50 for *Daphnia* is >318 mg a.i./L. Green algae are the most vulnerable species, with EC50 values between 230 and 236 mg a.i./L and No Observed Effect Concentrations (NOEC) between 31 and 75 mg a.i./L. It was determined that the aquatic Predicted No Effect Concentration (PNEC) was 0.23 mg a.i./L. Hydrotropes are not considered to constitute an environmental threat because the ratio of Predicted Environmental Concentration (PEC) to Predicted Natural Environmental Concentration (PNEC) is less than 1 (Namdev et al., 2022; Hopkins et al., 2011).

Commonly used Hydrotropes:

It is known that the hydrotropes self-assemble in solution. Since a wide range of substances have been reported to display hydrotropic behaviour, it is challenging to classify hydrotropes based on molecular structure. Ethanol, aromatic alcohols such as resorcinol, pyrogallol,

catechol, a- and b-naphthols, and salicylates, alkaloids such as caffeine and nicotine, and ionic surfactants such as acids, SDS (sodium dodecyl sulphate), and dodecylated oxidibenzene are a few such examples. The majority of investigated compounds are aromatic hydrotropes with anionic head groups. Due to isomerism, they are numerous, and the presence of interacting pi-orbitals may be the source of their effective hydrotrope action. Rare hydrotropes include salts of aromatic amines like procaine hydrochloride, which have cationic hydrophilic groups. They are known to influence surfactant aggregation leading to micelle formation, phase manifestation of multi-component systems with reference to nano dispersions and conductance percolation, clouding of surfactants and polymers, etc. in addition to improving the solubilization of

compounds in water (Kunz et al., 2016; Dhapte and Mehta,2015).

Characteristics of hydrotropes

- Hydrotropes are surface dynamic and total in watery arrangement because of their amphiphilic nature, and they are virtually insoluble in the framework.
- When broken down in water, it shouldn't generate any heat.
- Easy and affordable accessibility
- Nonreceptive and nonlethal.
- When broken down in water, insensitive to temperature effects.
- The dissolvable character being free of pH, high selectivity, and the nonappearance of emulsification are the other one of kind points of interest of hydrotropes (Hodgdon and kaler,2007; Jain et al., 2010).

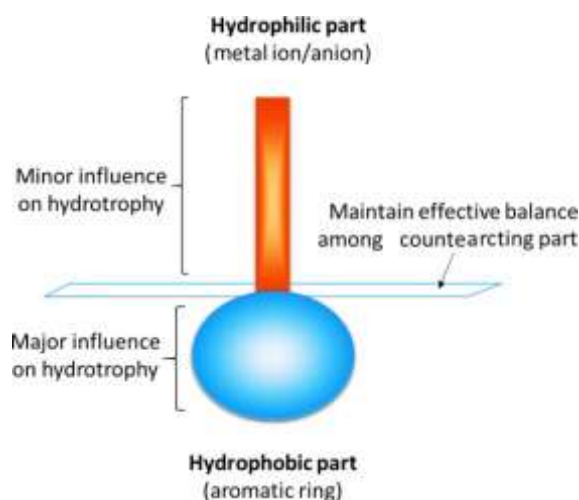


Figure: Structure of hydrotrope

Pharmaceutical applications of hydrotropic solubilization in various fields of pharmacy

- Making injections of medications with weak water solubility.
- Using hydrotropic solubilizers to improve permeability.
- Using hydrotropy to quickly release medications that are poorly water-soluble from suppositories.
- Using mixed hydrotropy to create injection dosage forms for medicines with weak water solubility.
- The use of hydrotropic solubilization (by controlled precipitation) in nanotechnology. In the discipline of pharmacognosy, hydrotropic solubilization is used to recover the active ingredients from crude pharmaceuticals.

- Quantitative assessments of pharmaceuticals that are poorly soluble in water using UV-visible spectrophotometric analysis without the use of organic solvents.
- Titrimetric analysis for quantitative assessments of medications with poor water solubility. utilising sodium benzoate, such as ibuprofen, flurbiprofen, and naproxen (Patil et al., 2021; Darwish et al., 1989).

III. METHOD DEVELOPMENT USING HYDROTROPY

Preparation of Standard Stock Solution:

In order to prepare the standard drug solution, 10 mg of the drug were dissolved in 0.1 N of solvent (1000 g/ml) in a volumetric flask holding 10 ml. It was sonicated for ten minutes after being

vortexed for two minutes. One millilitre of the aforementioned solution was spiked out and diluted to the proper strength with 0.1N solvent (100 g/ml). For 5 minutes, the solution was sonicated.

Determination of Absorption maxima:

For the analysis of drug absorption maxima, standard stock solution (100 g/ml) is scanned between 200 and 800 nm. The final outcome provides the maximum wavelength.

Procedure for determination of Calibration curve:

By dilution of aliquots of (1, 2, 3, 4, 5, 6) ml in 0.1N HCl and volume was produced up to the mark with 0.1N HCl, it is possible to prepare from stock solution (10, 20, 30, 40, 50, 60) g/ml solutions.

Assay of drug:

10mg of the medication, which had been precisely measured, was dissolved in enough 0.1N solvent to make up a volume of 10ml (1000 g/ml). It was vortexed for 2 minutes to mix the solution, and then sonicated for 10 minutes. A spiked 1ml solution was taken from the drug stock and diluted with 0.1N solvent (100g/ml) to make 10ml. The aforesaid solution was further diluted by pipetting off 1 ml of it and adding 10 g/ml of methanol to make it equal to 10 ml. The findings demonstrate whether the parameters are accurate and valid (Tegeli et al., 2021)

IV. VALIDATION OF UV - SPECTROPHOTOMETRIC METHOD

The accuracy, precision, linearity, detection limit, quantitation limit, robustness, and other criteria used in the UV spectrophotometric method validation are all taken into consideration (ICH,2003).

Linearity

To obtain final concentrations of 2, 4, 6, or 10 g/ml, appropriate aliquots of drug working standard solutions can be taken in various 10 ml volumetric sizes and diluted up to the mark with distilled water. After plotting absorbance vs concentration, calibration curves are created, and

regression equations for both medicines can be computed.

Range

By drawing the calibration curve, it was possible to determine the analytical method's range by measuring the distance between the higher and lower levels.

Precision

The medications were examined at concentrations of 4 g/mL, and each concentration was examined three times on the same day to assess the intraday precision. Similar measurements of inter-day precision were made, however the analysis was done every day for two days in a row. Analysing six samples of the same drug concentrations (4 g/mL) allowed researchers to establish the repeatability (intraday) of the approach. To determine the variation, the absorbance of each was measured and reported in terms of relative standard deviation.

Accuracy

By calculating saxagliptin recoveries using the standard adds approach at three distinct levels—60, 100, and 140%—the accuracy of the procedure was evaluated. The average recovery percentage was calculated.

Detection Limit

The lowest amount of analyte in a sample that can be detected but not always quantitated as an accurate number is the Detection Limit of a specific analytical method. You can express the detection limit (LOD) as follows. $LOD = 3.3\sigma/S$ Where is the response's relative standard deviation. S is the calibration curve's slope (of the analyte).

Quantitation limit

The lowest amount of analyte in a sample that can be quantitatively quantified with enough precision and accuracy is the quantitation limit of an analytical process.

One way to state the Quantitation Limit (LOQ) is as follows: $LOQ = 10/S$ Where is the response's relative standard deviation. S is the slope of the analytes calibration curve. (Konari et al., 2015; ICH,2005).

PREVIOUS WORK DONE ON SOLUBILITY ENHANCEMENT OF VARIOUS ANTIDIABETIC DRUGS USING HYDROTROPY

Drug used	Work performed	References
Gliclazide	Developed a simple, precise, innovative, environmentally friendly, and exact method for estimating the dosage of the medication Gliclazide, which is weakly water soluble. For quantitative analysis in the current study, a mixed hydrotropic mixture of 2M urea and 6M trisodium citrate was used. Beer's law was observed for gliclazide in the concentration range of 4 g/ml to 12 g/ml, and the mean recovery ranged from 95.33% to 96.35%. The devised method was approved in accordance with ICH principles.	(Kumar et al., 2019).
Pioglitazone	Developed two straightforward, economical spectrophotometric techniques to measure pioglitazone hydrochloride. In the first method (method A), a hydrotropic solution of citric acid (0.1M) was used as a solubilizing agent to solubilize the fine powder and tablet dosage form of pioglitazone hydrochloride (a poorly water soluble medication) for spectrophotometric measurement in the UV region. By using a hydrotropic approach, it was discovered that pioglitazone hydrochloride had a maximum absorbance at 269 nm in a solution of 0.1M citric acid. The second technique (method B) relies on an oxidative-coupling reaction between 3-methylbenzothiazolin-2-one hydrazone (MBTH) and pioglitazone hydrochloride when ferric chloride is present. Hydrotropic agents and frequently used tablet additives did not significantly interfere with the assay method.	(Ramakrishna et al., 2013).
Atorvastatin Calcium and Pioglitazone	8.0 M sodium benzoate aqueous solution was used as a hydrotropic agent in the development of a method for the simultaneous estimation of atorvastatin calcium (ATV) and pioglitazone (PIO) in tablet dosage form. In 8.0M sodium benzoate solution, atorvastatin calcium (ATV) and pioglitazone (PIO) significantly increased their aqueous solubility by 55 and 71 fold, respectively.	(Sharma and Sharma, 2010)
Atorvastatin	Developed a method to estimate the dosage of atorvastatin (ATV) in tablet form utilising a hydrotropic agent in a 0.5 M sodium benzoate aqueous solution. With 0.5M sodium benzoate solution, this model drug's aqueous solubility was increased 22 times without interfering with the analysis procedure. Atorvastatin (ATV) exhibited its highest absorbance at 268 nm, and Beer's law was observed for concentrations between 0.1 and 0.6 g/ml.	(Rani et al., 2015).
Gabapentin and Methylcobalamin	Developed and approved a combined dose form of methylcobalamin (MC) and gabapentin (GBP). For	(Sharma et al., 2011)

	<p>the simultaneous measurement of bapentin (GBP) and methylcobalamin (MC) in combination dose form, spectrophotometric techniques have been devised. For the simultaneous estimation of the Simultaneous Equation Method, the Absorbance Ratio Method, and the Derivative Spectrophotometry Method, spectrophotometric methods have been devised. Utilising 5.0M 5.0M sodium benzoate as a hydrotropic agent in tablet dose form. Simultaneous equation method is the foundation of the suggested approach. Methylcobalamin (MC) and gabapentin (GBP) both have absorption maxima (max) at 313 nm and 334 nm, respectively.</p>	
Gliclazide	<p>Developed an environmentally friendly and accurate method for measuring the dosage of the medication Gliclazide, which is weakly water soluble. For the quantitative analysis, a mixed hydrotropic mixture of 2M urea and 6M trisodium citrate was utilised. Beer's law was observed for gliclazide in the concentration range of 4 g/ml to 12 g/ml, and the mean recovery ranged from 95.33% to 96.35%.</p>	(Satheesh Kumar et al., 2018)
Empagliflozin	<p>Hydrotrophy-based eco-friendly method developed for empagliflozin estimation. For EMPA, the increase in solubility in mixed hydrotropic solution was greater than 50 and 70 percent, respectively. By dissolving EMPA in a sodium acetate:urea (2M:8M) solution employed as a solvent, the stability of medications was examined. The wavelength at which EMPA's highest absorbance was recorded was 256.0 nm.</p>	(Bhati et al., 2022)
Glipizide	<p>Cosolvency and hydrotrophy procedures were used in an attempt to increase the solubility of glipizide. In the cosolvency method, polyethylene glycol, propylene glycol, glycine, and ethanol were four cosolvents that were taken into consideration. In the hydrotrophy method, sodium benzoate, sodium citrate, and sodium salicylate were three different hydrotropes that were utilised in concentrations of % (5,10,15,20,25,30,35, & 40). PEG was discovered to be the most suitable cosolvency approach when compared to the other three. With an increase in PEG concentration, glipizide's solubility increased.</p>	(Swarupanjali,2021)
Rosiglitazone	<p>For spectrophotometric analysis of the poorly water-soluble medication rosiglitazone maleate, the hydrotropic solution of urea was used as a solubilizing agent. In a study to determine solubility, it was discovered that rosiglitazone maleate was more soluble in a 6M solution of urea by a factor of more than 14.</p>	

V. CONCLUSION

Drug's solubility is its most important physical characteristic for its oral bioavailability, definition, development of different measurements of different drugs, and for quantitative analysis. Hydrotrophy is one of many processes that can increase solvency, and it is particularly significant. Hydrotrophy refers to a solubilization process in which the expansion of several second solutes results in an increase in the watery solubility of a third solute. The synthetic substances used in hydrotrophy are known as hydrotropes. For instance, solubility can be increased by a variety of systems, and the number of folds increase in dissolvability is also taken into account. Examples include sodium benzoate, urea, sodium salicylate, and sodium ibuprofen. Solvency enhancement becomes crucial since the bioavailability of many drugs is impacted by their dissolvability issues, which makes it important. With the aid of the various systems mentioned earlier, it is currently possible to increase the solvency of drugs that are not sufficiently solvent. Currently, this method is developing its qualities and may one day be proven to be the most effective one.

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