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ENHANCEMENT OF SOLUBILITY OF IBUPROFEN USING MIXED SOLVENCY TECHNIQUE

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ABSTRACT

The solubility of a drug has a significant impact on its formulation and bioavailability. The poor aqueous soluble drugs often have limited effectiveness due to this. The conventional solubilization techniques, though effective, often require expensive or toxic reagents. Hydrotropic solubilization is a safer alternative, that enhances the aqueous solubility through non-toxic and easily available hydrotropic agents. Mixed hydrotropic solubilization is advanced extension of hydrotropic solubilization, which includes use of multiple hydrotropic agents instead of single hydrotropic agent in order to increase aqueous solubility of drug. This research study evaluates the efficiency of mixed hydrotropic method for ibuprofen, a poorly water-soluble drug using a blend of urea and sodium citrate as the hydrotropic agents in mixed blend. The results demonstrated that lower volume of solvent is needed with mixed hydrotropic than with hydrotropic method to dissolve ibuprofen. In addition of being eco-friendly and reducing the need for high concentrations of individual hydrotropic agent, mixed hydrotropic method also reduces the toxicity risk. Mixed hydrotropic solubilization offers a highly efficient and cost-effective method for improving the solubility of drugs that are poorly soluble in water.

INTRODUCTION

The solubility of a drug molecule plays an important role during the formulation stage.[1] Low aqueous solubility is a major problem encountered during the development of many novel drug molecules.[2] Furthermore, drugs with poor aqueous solubility often exhibit low bioavailability and poor dissolution rates.[3] Many techniques have been employed by the pharmaceutical industry to improve the water solubility of poorly soluble medications. These include particle size reduction, nanonization, hydrotropy, pH adjustment, sonocrystallization, solid dispersion, polymorphic alterations, complexation, surfactant use, and liquisolid methods.[4] Most of these methods are expensive or use harmful chemicals to enhance the solubility profile of the drug molecule or medication. To preclude the use of these expensive and toxic chemical method, many have started to turn to hydrotropic solubilization technique. A unique method of solubilization includes the use of nontoxic hydrotropic compounds to solubilize poorly water-soluble drug molecules.[5] The credit for hydrotropic method is given to Carl A. Neuberg who used the term hydrotropy in 1916. Neuberg claimed that the addition certain organic salts might greatly enhance the aqueous solubility of hydrophobic compounds.[6] Hydrotropes are amphiphilic in nature and thus have both hydrophobic and hydrophilic portions within their structures. The hydrotropic potency of a molecule is directly proportional to its hydrophobic part; thus, any increase in the hydrophobic component increases its hydrotropic property.[7] Hydrotropy is considered a superior solubilization technique because, in this method, the solvent properties are not affected by pH and emulsification is required. The hydrotropic method is highly selective. No chemical modification, addition of toxic organic solvents or expensive machinery are required for this method. Simple mixing of the drug with a hydrotropic agent is required to increase the aqueous solubility of the drug.[8] The mechanics of the hydrotropic solubilization have been the subject of many investigative studies. A recent study utilized H-NMR and concluded that the origin of hydrotropy can be attributed to the water-mediated aggregation of hydrotrope molecules around the solute, and the extrapolation of both solute and hydrotrope is the driving force of hydrotropy.[9] Drugs with low aqueous solubility profiles may easily dissolve in hydrotropic solutions of sodium benzoate, urea, nicotinamide, sodium citrate, and sodium acetate. These hydrotropes do not have a critical concentration, and self-aggregation occurs step-by-step when a solubilizer is added.[10] Mixed hydrotropy refers to the strategic use of hydrotropic blends at a fixed ratio to increase the aqueous solubility of drug molecules through the synergistic effect of hydrotropes. The mixed hydrotropic method decreases the concentration of individual hydrotropes and minimizes the possible side effects of using a single hydrotropic agents at large concentration. Instead of using a large quantity of one

hydrotropic agent, the mixed hydrotropic method utilizes hydrotropic blends, resulting in lower concentrations and reducing the individual toxicities of hydrotropes.[11] Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID). Ibuprofen is widely used for its analgesic, antipyretic and anti-inflammatory properties. Ibuprofen exerts its pharmacological effects are due to inhibition of COX-2 which decreases the synthesis of prostaglandins involved in mediating inflammation, pain, fever and swelling. Ibuprofen belongs to BCS class II category of drug and thus possesses low solubility which leads to low oral bioavailability.[12] The current research study aims to increase the aqueous solubility of ibuprofen using mixed solvency approach and also compare the solubility enhancement using single vs blends of hydrotropic agents in same ratio.

Advantages of mixed hydrotropic solubilization[13]

1. Mixed hydrotropy reduces the total concentration of hydrotropic agents used to enhance the solubility of poorly soluble drugs, by employing a combination of agents at lower concentrations.
2. Compared to other solubility enhancement techniques, mixed hydrotropy is simple, economic, A safer and environmentally friendly approach to increase solubility and for the analysis (Titrimetric and Spectrophotometric) of poorly water-soluble drugs, precluding the use of organic solvents.

Objectives

1. To study the mixed hydrotropic solubilization technique and compare it to hydrotropic method.
2. To increase aqueous solubility of ibuprofen using hydrotropic blends.

Research method

Simple method to determine approximate solubility of a drug in a solvent

Approximate solubility method

Take 1 ml of solvent in a 10 ml volumetric flask and add 5 mg of drug and shake the flask vigorously and try to dissolve it.

Condition 1 – Suppose 5 mg drug does not dissolve even by 30 minutes shaking, then add 0.5 ml more of solvent and again shake the flask vigorously. Suppose drug is not dissolved completely by shaking for 30 minutes, then again 0.5 ml more of solvent is added and same process is repeated. Suppose, 5 mg is dissolved completely by 4 ml of solvent, then approximate solubility shall be 5 mg per 4 ml, means 125 mg per 100 ml, means 0.125 gm per 100 ml, means 0.125 % w/v. So, approximate solubility of drug in solvent is 0.125 % w/v.

Condition 2 – Suppose 5 mg drug gets dissolved in 1 ml solvent by shaking, add 5 mg more of drug and shake the flask vigorously. Suppose again we get a clear solution by shaking. This process is continued, means addition of 5 mg drug and shaking. A time will come when we get a turbid solution even after 30 minutes shaking. Means, at this stage 1 ml solvent has been nearly saturated with drug. Suppose, 70 mg drug is dissolved completely by 1 ml solvent and when 5 mg more of drug (total 75 mg drug) is added and we get a turbid solution (even after shaking for 30 minutes), approximate solubility of drug in solvent is 70 mg per ml, means 7000 mg per 100 ml, means 7 gm per 100 ml, means 7 % w/v.

Preparation of hydrotropic solution

Solution A- 40% w/v urea solution was prepared in water.

Solution B- Hydrotropic blend of urea and sodium citrate in 1:1 ratio was prepared, keeping the collective concentration same (40%) as solution A.

1. Determination of approximate solubility

The method of approximate solubility mentioned was used. Due to its low solubility condition 1 procedure was followed.

For solution A- 5 mg ibuprofen needed 4.5 ml of solution A.

Approximately, 111 mg per 100 ml means 0.111 g per 100 ml, means 0.111% w/v.

For solution B- 5 mg ibuprofen needed 2.5 ml of solution B.

Approximately, 200 mg per 100 ml means 0.200 gm per 100 ml, means 0.2% w/v.

2. The solubility enhancement for the hydrotropic agent and hydrotropic blend was calculated using the formula[14]

Enhancement ratio=Solubility of drug in hydrotropic/Solubility of drug in distilled water

The solubility of ibuprofen in water is approximately 0.021 mg/ml.[15]

Enhancement ratio for single hydrotropic agent (Urea) = 0.111 mg/ml / 0.021 mg/ml

= 5.28

Enhancement ratio for mixed hydrotropic blend (Urea and Sodium citrate)

= 0.2 mg/ml / 0.021 mg/ml

= 9.5

RESULT

In the research study, the solubility enhancement of ibuprofen using mixed hydrotropic agent (urea and sodium citrate) was found almost twice to the single hydrotrope solvent system consisting of urea only. The results demonstrated that 5 mg of ibuprofen drug required approximately 4.5 ml of 40% w/v of urea solution for its effective dissolution while the mixed hydrotropic agents (Urea and Sodium citrate) at same concentration required only 2.5 ml of the solvent mixture while also increasing solubility. This demonstrates a significant improvement in solubility when employing the mixed solvent approach.

DISCUSSION

The research study compared the effectiveness of hydrotropic solubilization as well as the mixed hydrotropic solubilization for poorly water-soluble drug,

ibuprofen. Results show that the mixed hydrotropy approach which combined urea and sodium citrate had greater solubility than that from a single hydrotropic agent (Urea) only.

The increase in aqueous solubility by mixed hydrotropy results from the synergistic effects of the combined hydrotropic agents. The hydrotropic blends increase the solubility while reducing the need of high concentrations of one single hydrotropic agent which in turn reduces potential toxicity and side effects caused by higher doses of individual hydrotropic agent. The results demonstrated that the mixed hydrotropic approach required less volume for effective dissolution. Mixed hydrotropy is particularly relevant in recent pharmaceutical formulations with low aqeous solubility drug where achieving desired bioavailability is crucial for therapeutic efficacy.

CONCLUSION

Mixed hydrotropy is a simple yet effective method that promises direction for further research in pharmaceutical development especially for substances, with limited solubility.

The current research study determined that mixed hydrotropic solubilization has potential to improve the water solubility of poorly soluble medications such, as ibuprofen The solubility enhancement achieved through mixed hydrotropy does not require toxic or expensive chemicals for increasing solubility. The future research studies should utilize the novel method of solubility enhancement using multiple hydrotropic agents and investigate combinations of hydrotropic agents and their effectiveness. In conclusion mixed hydrotropic solubilization offers a feasible answer, to an issue encountered in drug formulation nowadays.

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