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Original Article

SOLUBILITY ENHANCEMENT OF NORFLOXACIN BY HYDROTROPY TECHNIQUE

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ABSTRACT

The objective of this study is to improve the solubility of poorly water soluble anti-bacterial drug Norfloxacin by hydrotropic solubilization technique. For the present study sodium benzoate was used as hydrotropic agent. By using this hydrotropic agent as water soluble carrier, hydrotropic solid dispersions of Norfloxacin were prepared.in 1:1, 1:2, 1:3 and 1:4 ratios (drug: hydrotropic agent). Equilibrium solubilization of pure drug and hydrotropic solid dispersions of Norfloxacin in distilled water by excess solute method and solubility enhancement ratios were calculated by measuring the absorbance of the solutions at 274.80 nm using UV spectrophotometer. The hydrotropic agent did not interfere in analysis. The results showed that there was an increase in the solubility of Norfloxacin with hydrotropic solid dispersions compared to pure drug in distilled water. There was 9.56 fold enhancement in aqueous solubility of Norfloxacin with hydrotropic solid dispersion of 1:4 ratio compared to 1:1 (6.29), 1:2 (7.09) and 1:3 (8.59) ratios.

Keywords: Hydrotropy, Solubility enhancement, Norfloxacin.

INTRODUCTION

The term hydrotropic agent was first introduced by Neuberg (1916) to designate anionic organic salts which at high concentrations, considerably increase the aqueous solubility of poorly soluble solutes[1].Hydrotropy is a solubilization phenomenon whereby addition of large amount of second solute results in an increase in the aqueous solubility of another solute. However, the term has been used in the literature to designate non-micelle-forming substances, either liquids or solids, organic or inorganic, capable of solubilizing insoluble compounds. Neuberg conventional hydrotropic salts generally consist of two parts, a hydrophobic aromatic ring or ring system and anionic group.

The prerequisite for a hydrotropic substance is anionic group which is responsible for bringing high aqueous solubility. There is a minor effect on the type of anion or metal ion[2]. On the flip side planarity of hydrophobic part also plays a crucial role in hydrotropic solubilization mechanism [3].

Those salts or additives which increases solubility in a given solvent are referred to as "salt in" and which decreases solubility are referred to as "salt out". Hydrotropism refers to as salting in of non-electrolytes which are highly soluble in water. The mechanism involved in hydrotropy is related to complexation which involves interaction between lipophilic drugs and the hydrotropic agents such as urea, nicotinamide, sodium alginate, sodium benzoate etc [4].

Advantages of hydrotropic solubilization

- This process doesn't require emulsification, highly selective and solvent character is independent of pH so it is preferred over other solubilization methods such as cosolvency, micellarsolubilization.
- It primarily involves the mixing of hydrotropic agent and drug directly into solvent which is water.
- It precludes the chemical modification of hydrophobic drugs or preparation of emulsion system.

Materials

Norfloxacin drug sample was supplied as gift sample by Teena Bio Labs, Hyderabad. Sodium benzoate was purchased from Ranbaxy fine chemicals.

Equipment

UV visible spectrophotometer - UV 1601 PC, Shimadzu, Japan.

Rotospin –Tarson.

Magnetic stirrer – Remi, Mumbai.

Hot air oven – Osworld laboratory oven.

Methodology

Preparation of hydrotropic solid dispersion

Hydrotropic solid dispersions were prepared using sodium benzoate as a water soluble hydrotropic agent in different ratios based on moles (1 mole = 1 gram/molecular weight). For preparation hydrotropic solid dispersion containing Norfloxacin and sodium benzoate in 1:1 ratio, Norfloxacin (g) and sodium benzoate (g) were accurately weighed. Minimum possible quantity of water was taken in a beaker and maintained at 80-85°c for the quick dissolution of hydrotropic agent. Then slowly drug was added to the beaker (maintained at 30-40°c) and teflon coated magnetic bead was dropped in beaker, temperature was maintained for optimum stirring and stirring was continued until semisolid mass is obtained. This semisolid mass was spread on several watch glasses and placed in oven maintaining a temperature of 50-60°C. Then the trituration was done with mortar and pestle and after drying it was passed through sieve no.60 and kept in desiccator. Same procedure was repeated to prepare hydrotropic solid dispersion of 1:2, 1:3 and 1:4 ratio.

$$\text{Solubility enhancement ratio} = \frac{\text{Solubility of drug in hydrotropic dispersion}}{\text{Solubility of pure drug in water}}$$

Table 1: Ingredients and their hydrotropic ratios

S. No.	Ingredients	Quantity in grams			
		1:1	1:2	1:3	1:4
1	Norfloxacin	0.313	0.313	0.313	0.313
2	Sodium benzoate	0.694	1.388	2.082	2.776

Determination of interference of hydrotropic agent in the spectroscopic estimation of drug

For determination of interference of hydrotropic agents in the spectrophotometric estimation of Norfloxacin, the absorbance of the standard solutions of drugs were determined in distilled water alone and in the presence of the maximum concentration of the hydrotropic agent using UV spectrophotometer. The absorbance was recorded against respective reagent blanks at appropriate wavelength.

Preparation of stock solution

The standard stock solution (1mg/ml) of the drug was prepared in distilled water. The stock solution was further diluted with distilled water, to obtain various dilutions. Solution containing 10 µg/ml of drug was scanned between 200 and 400 nm λ_{max} was found.

Equilibrium solubility determination of pure drug and hydrotropic solid dispersion

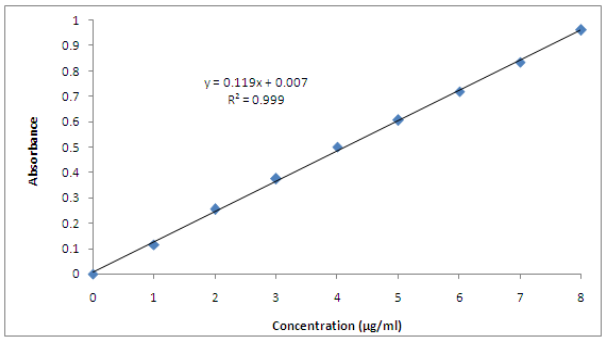
Solubility of pure drug and hydrotropic solid dispersion were determined at room temperature. Sufficient excess amount of pure drug and hydrotropic solid dispersion were added to ria vials containing 3 ml of distilled water. The vials were shaken for 24 hrs at 100 rpm using rotospin. The solution of each vial was filtered through whatman filter paper no.41.

The filtrates were diluted suitably, and analyzed spectro photometrically against blank. Equilibrium solubility of pure drug and hydrotropic solid dispersions were determined by intrapolation on the calibration curve. Enhancement ratio in solubility were also determined by following formula

RESULTS AND DISCUSSION

Calibration curve of drug in distilled water

Solution containing 10 µg/ml of drug was scanned between 200 and 400 nm and λmax was found at 274.80 nm. A linear relationship was observed at 1 to 10 µg/ml concentration with a regression value of 0.9992.



Graph 1: Standard plot of pure drug (Norfloxacin) in distilled water

Determination of interference of hydrotropic agent in the spectroscopic estimation of drug:

The absorbance of the standard solutions of drug was determined in distilled water alone and in the presence of the maximum concentration of the hydrotropic agent at 274.80 nm using UV-visible spectrophotometer. There was no interference of hydrotropic agent in the spectroscopic estimation of drug.

Determination of equilibrium solubility and solubility enhancement ratio:

Solubility studies of pure drug and hydrotropic solid dispersion were determined in distilled water at room temperature. The solubility of pure drug and hydrotropic solid dispersions of ratios 1:1, 1:2, 1:3, 1:4 and 1:5 in distilled water was found to be 0.213, 1.338, 1.506, 1.825, 2.033, and 1.731 mg/ml respectively. This confirms that there was an increase in the solubility of Norfloxacin with hydrotropic solid dispersions compared to pure drug in distilled water. There was 9.56 fold enhancement in aqueous solubility of Norfloxacin with hydrotropic solid dispersion of 1:4 ratio compared to 1:1 (6.29), 1:2 (7.09) and 1:3 (8.59) and ratios

Table 2: Solubility of pure drug and hydrotropic solid dispersions of Norfloxacin in distilled water

Ratio	Trial 01	Trial 02	Trial 03	Average
	Solubility in mg/ml	Solubility in mg/ml	Solubility in mg/ml	Solubility in mg/ml
Pure drug	0.2012	0.2235	0.2141	0.2129
1:1	1.329	1.3034	1.3803	1.3375
1:2	1.5512	1.4401	1.5256	1.5056
1:3	1.8675	1.782	1.8247	1.8247
1:4	2.0042	1.9615	2.1324	2.0327

Table 3: Solubility enhancement ratio of pure drug and hydrotropic solid dispersions of Norfloxacin in distilled water

Ratio	Trial 01	Trial 02	Trial 03	Average
	Enhancement ratio	Enhancement ratio	Enhancement ratio	Enhancement ratio
1:1	6.6029	5.8317	6.4471	6.2939
1:2	7.707	6.4435	7.1257	7.0920
1:3	9.2781	7.9732	8.5229	8.5914
1:4	9.9575	8.7765	9.96	9.5646

CONCLUSION

So we conclude that the present work is the novel application of hydrotropic solubilization technique in the formulation development of poorly water soluble drug Norfloxacin. Equilibrium solubility studies concluded that there was an increase in the solubility of Norfloxacin with hydrotropic solid dispersions compared to pure drug in distilled water.

CONFLICT OF INTERESTS

Declared None

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