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Solubility Enhancement of Theophylline Drug Using Mixed Solvency Approach

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Abstract

It is difficult to work in "Solubility enhancement" while formulating oral drugs that possess low aqueous solubility. Low aqueous solubility is important as it does not allow creation of formulations with sufficiently high bioavailability, leading to poor utility of these drugs. With the introduction of the concept of "mixed-solvency," it has become possible to enhance the solubility of poorly water-soluble drugs in aqueous solutions containing blends of hydrotropic agents/co-solvents/water soluble solutes that provides synergistic enhancement on drug solubility. In the present study, approach of mixed-solvency is used to enhance the aqueous solubility of a poorly water-soluble drug "theophylline" (model drug), by generating blends of randomly selected water-soluble materials from among the hydrotropic solutes (e.g., urea, sodium acetate), water-soluble solutes (e.g., PEG4000 and/or PEG6000); and cosolvents (e.g., PEG200, PEG400). The aqueous solubility of theophylline was observed at room temperature in randomly selected blends of solubilizers that contained varying combinations keeping the total concentration 50% (w/v) constant. Theophylline has λ_{max} 274 nm and obeys Beers law in concentration range of 10–60 µg/mL. The results suggest that mixed solvency approach greatly enhance the solubility of theophylline when it contains blend of varying combinations.

Keywords: hydrotropes, mixed-solvency, solubility, theophylline

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INTRODUCTION

It 1916, Neuberg while dissolving organic substances *viz.*, carbohydrates, lipids, esters, oil and drugs in aqueous solutions containing hydrotropes, came forth with the idea of "hydrotropy,".[1–6] Later, Booth and Everson demonstrated that concentrated aqueous solutions of organic salts (*e.g.*, sodium benzoate, salicylate, benzene sulfonate, and cumene sulfonate) can increase the solubility of compounds. They also reported for the first time that the solubility increase does not occur in a linear fashion, but increases with the increase in the concentration of hydrotrope. This finding lays the foundation for improved understanding of the mechanism of hydrotropy. Balasubramanian and Friberg while analyzing the recent developments in hydrotropy, highlighted the similarities between aggregation behavior of hydrotropes and surfactants.[7–9]

McKee highlighted some of the important features and advantages of hydrotropy particularly for chemical engineering and industrial applications. He mentioned that most hydrotropic solutions precipitate the solute upon dilution. This enables in separation and recovery of the hydrotope to be used further.[10–16]

With the use of hydrotropes, co-solvents and water-soluble solutes, it has now

become possible to enhance the aqueous solubility of poorly water-soluble drugs. The concept of mixed solvency helps to induce a synergistic effect. Hydrotropy is used for titrimetric and spectrophotometric assessments of several poorly water-soluble drugs. The mixed-solvency approach discourages the use of organic solvents in large concentrations, due to their possible toxic effects, for development of dosage forms. Many solubilizers that are taken in low concentrations curtailing their toxic levels, shows significant improvements in the solubility of poorly water-soluble drugs.[17–21] Based on the principle of mixed solvency, Maheshwari put forward that all substances possess a solubilizing capability. Irrespective of physical state, all soluble subtances enhance the aqueous solubility of other poorly soluble drugs. Solubility studies were carried out for the solutions containing hydrotropic agents (urea and sodium acetate), cosolvents (PEG 200 and PEG 400) and water-soluble solids (PEG 4000 and PEG 6000), in varyingly prepared blends but maintaining the total concentration constant (50%, w/v). Results have shown a synergistic effect on solubility enhancement of the drug.[21–28]

MATERIALS AND METHODS

Analytical grade chemicals bought from Sisco Research Laboratories Pvt. Ltd. (Mumbai, India) were used for the study. Theophylline tablets were purchased from the local market. Purified water was used to prepare all the solutions. A spectrophotometer (UV-1800 Shimadzo) was used for quantitative analysis.

Methods

Theophylline (40 mg) was accurately weighed and transferred to 50 mL volumetric flask. To this 40 mL of distilled water was added. The flask was shaken to dissolve the drug and volume was made up to the mark with distilled water. Stock solutions were diluted further using distilled water to prepare dilutions in the range of 10-60 µg/mL. Absorbance was noted at 274 nm against reagent blanks to get the calibration curve. The solubility of theophylline in distilled water was observed and shown in Table 1.

Table 1. *Solubility of Theophylline in Purified Water.*

Sl. no.	**Concentration** (µg/mL)	**Absorbance**
1	10	0.18
2	20	0.24
3	30	0.37
4	40	0.52
5	50	0.61

Solvents were used in different volumes and concentrations to prepare varying combinations (50% w/v constant) of solubilizers. Blend-1 containing sodium salicylate, PEG4000, PEG400, nicotinamide and sodium salicylate, Blend-2 contains sodium salicylate, PEG6000, PEG200 and nicotinamide, Blend-3 contains sodium salicylate, PEG200, PEG400, and nicotinamide and Blend-4 contains sodium salicylate, PEG400, PEG6000, and nicotinamide as shown in Table 2.

Initially, the bulk drug was dissolved in 10 mL of Blend-1. The solution was shaken vigorously for a defined period with regular intervals until a supersaturated solution was obtained.

The resulting solution was diluted up to 1000 mL with the blend. Absorbance of this solution was noted at 274 nm against the solvent blend. The same procedure was followed with other blends, *viz.,* Blend-2, Blend-3 and Blend-4, respectively, and absorbance at the same wavelength was measured for all.

The corresponding concentration gives an idea about of the drug solubility. The increased solubility can then be calculated by comparing with solubility of the drug in water.

RESULTS AND DISCUSSION

The results obtained are shown in Table 3 for the solubility of theophylline in different blends. From the table it is evident that there was improvement in the solubility of theophylline in blend (50% w/v) containing sodium salicylate, PEG-200, PEG-400, PEG-4000, PEG-6000, and nicotinamide in varying concentrations. On comparing Tables 2 and 3, the drug solubility was found to be enhanced by 1.94-, 2.36-, 2.69-, and 2.98-folds with Blend-1, Blend-2, Blend-3, and Blend-4, respectively. Highest solubility enhancement was observed for Blend-4 and lowest for Blend-1. These results validate the concept of mixed-solvency, according to which water soluble substances (hydrotropic solvents or solids) can be combined arbitrarily in variable concentrations giving rise to poorly or highly water-soluble drugs. Blends of water-soluble substances can be prepared at safe level of concentrations of individual solubilizers, giving a concentrated solution that act as solubilizing system for development of different dosage forms.

Table 2. *Contents of Blends.*

Blend-1		**Blend-2**		**Blend-3**		**Blend-4**	
Hydrotrope	%	Hydrotrope	%	Hydrotrope	%	Hydrotrope	%
Sodium salicylate	10	Sodium salicylate	10	Sodium salicylate	15	Sodium salicylate	15
PEG-4000	10	PEG-6000	10	PEG-200	10	PEG-400	15
PEG-400	15	PEG-200	15	PEG-400	15	PEG-6000	10
Nicotinamide	15	Nicotinamide	15	Nicotinamide	10	Nicotinamide	10

Table 3. *Solubility of Theophylline in Different Blends.*

Sl. no	**Blend no.**	**Absorbance**	**Saturated Solubility** (μg/mL)
1	Blend-1	1.135	125
2	Blend-2	1.382	160
3	Blend-3	1.574	184
4	Blend-4	1.746	196

CONCLUSION

The solubility of the theophylline containing different combinations of sodium salicylate, PEG-200, PEG-400, PEG-4000, PEG-6000, and nicotinamide in varying concentrations was enhanced significantly, using this mixed-solvency approach. Thus, the results suggest that mixed-solvency approach can be successfully used for the enhancement of solubility of other poorly water-soluble drugs.

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