RESEARCH ARTICLE

"Mixed-solvency approach" – Boon for solubilization of poorly water-soluble drugs

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Based on a large number of experiments on solubilization of poorly water-soluble drugs, the author is of the opinion that hydrotropy is another type of cosolvency and all water-soluble substances whether liquids, solids, or gases may act as solubilizers for poorly water-soluble drugs. In the present investigation, a mixed-solvency approach has been utilized for solubility enhancement of poorly water-soluble drug, salicylic acid (as a model drug). Sixteen blends (having total 40% w/v strength of solubilizers) containing various solubilizers among the commonly used hydrotropes (urea and sodium citrate), cosolvents (glycerin, propylene glycol, PEG 300 and PEG 400), and water-soluble solids (PEG 4000 and PEG 6000) were made to study the influence on solubility of salicylic acid. Twelve blends were found to increase the solubility of salicylic acid, synergistically. This approach shall prove a boon in pharmaceutical field to develop various formulations of poorly water-soluble drugs by combining various water-soluble excipients in safe concentrations to give a strong solution (say 25% w/v or so) to produce a desirable aqueous solubility of poorly water-soluble drugs. In the present investigation, the mixed-solvency approach has been employed to analyze salicylic acid in the bulk drug sample (using six blends) precluding the use of organic solvents (a way to green chemistry).

Key words: *Co-solvents, hydrotropy, mixed-solvency*

INTRODUCTION

Hydrotropic agents[1-20] and cosolvents[21-29] have been observed to enhance the aqueous solubilties of poorly water-soluble drugs. Maheshwari[1] has demonstrated the synergistic solubilizing capability due to a mixed-hydrotropy approach and this approach has been applied to analyze the poorly water-soluble drug, aceclofenac, titrimetrically, precluding the use of organic solvents. He has nicely applied the application of hydrotropy in titrimetric and spectrophotometric estimations of a large number of poorly water-soluble drugs[1-14] precluding the use of organic solvents. He is of the opinion that hydrotopy is another type of cosolvency. This gave a new thought that like mixed-hydrotropy, a mixed-solvency approach may be tried to observe the effect on solubility of poorly water-soluble drugs. Therefore, salicylic acid was selected as a model poorly water-soluble drug. The total concentration of soubilizer(s) was kept constant (40% w/v) in all blends of solubilization systems. The selected solubilizers were among the commonly employed cosolvents (glycerin, propylene glycol, PEG 300, PEG 400), water-soluble solids (PEG 4000, PEG 6000), and hydrotropes (sodium citrate, urea). Sixteen blends containing four randomly selected solubilizers (each 10% w/v) were made to study the influence on solubility of salicylic acid. The strength of each blend was 40% w/v. Twelve blends were found to increase the solubility of salicylic acid, synergistically. This concept shall prove a boon in pharmaceutical field (and also in non-pharmaceutical fields viz. chemical engineering, etc.). In the present investigation, the mixed-solvency approach has been employed to analyze salicylic acid in the bulk drug sample precluding the use of organic solvent (green chemistry).

MATERIALS AND METHODS

Salicylic acid (S. D. Fine Chemicals Limited, Mumbai) was procured from the market. All chemicals and solvents used were of analytical grade. Distilled water was used to prepare the solutions of solubilizers.

Solubility determination

Solubilities of salicylic acid in distilled water, in solutions of individual solubilizers (40% w/v propylene glycol, 40% w/v glycerin, 40%w/v PEG 300, 40% w/v PEG 400, 40% w/v PEG 4000, 40% w/v PEG 6000, 40% w/v sodium citrate and 40% w/v urea and sixteen different blends (compositions are shown in Table 2) were determined

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at 28±1°C. All of the saturated solutions were subjected to titrimetric analysis using 0.1 M sodium hydroxide solution as a titrant and phenolphthalein solution as an indicator. Blank titrations (in the reagent blanks) were conducted for necessary corrections to calculate the solubilities and results are presented in [Tables 1 and 2].

Method of determination for the additive or synergistic effect on solubility in blends

An approximate method of calculation was used to determine the additive or synergistic effect on solubility. The total strength of all solubilizers was 40% w/v (constant) in all aqueous systems containing single solubilizer or combinations of four solubilizers (concentration of each solubilizer was 10% w/v). One example for blend GL-TH-FH-SC (containing 10% w/v glycerin, 10% w/v PEG 300, 10% w/v PEG 400 and 10% w/v sodium citrate) has been explained here. The solubility of salicylic acid in this blend was found to be 10.035% w/v [Table 2]. The contributory solubility based on contribution of individual solubilizer can be calculated a follows –

$$\text{The total contributions in solubility due to individual solubilizers present in the blend} = \frac{\text{Sum of solubilities in individual solutions of solubilizers}}{4}$$

$$= \frac{1.919 + 5.329 + 7.149 + 18.551}{4}$$

$$= 8.237\% \text{ w/v}$$

Therefore, contributory solubility of salicylic acid in blend GL-TH-FH-SC = 8.237% w/v[30,31]

Same method was used to calculate the contributory solubilties in cases of remaining 15 blends and are presented in Table 2.

Analysis of salicylic acid bulk sample by I.P. (1996) method[32]

Accurately weighed (0.3 g) salicylic acid bulk sample was dissolved in 50 ml of ethanol (95%) and was titrated with sodium hydroxide solution (0.1 M) using phenol red solution as an indicator. Necessary blank determination was adjusted to get drug content [Table 3]. Total three such determinations were performed by this method (n=3).

Analysis of salicylic acid bulk sample by proposed PG-FH-FT-UR method

In the proposed PG-FH-FT-UR method, accurately weighed (0.3 g) salicylic acid bulk sample was solubilized in 20 ml of PG-FH-FT-UR blend (composition is shown in Table 2) in a conical flask by shaking for about 5 min and titrated with sodium hydroxide solution (0.1 M) using phenolphthalein

Table 1: Solubilities of salicylic acid in solution of individual solubilizer

Solvent system	Solubility (% w/v)
Distilled water	0.185
40% w/v PEG 400	7.149
40% w/v Sodium citrate	18.551
40% w/v PEG 300	5.329
40% w/v Glycerin	1.919
40% w/v PEG 4000	4.411
40% w/v PEG 6000	4.641
40% w/v Urea	0.993
40% w/v Propylene glycol	2.509

Table 2: Observed solubilities and contributory solubilities (calculated) of salicylic acid in different blends

Blend composition	O. Sol. (%w/v)	C. Sol. (%w/v)
GL-TH-FH-SC (10% w/v each solubilizer)	10.035	8.237
FH-FT-UR-SC (10% w/v each solubilizer)	12.916	7.757
TH-FH-UR-SC (10% w/v each solubilizer)	13.162	8.006
PG-TH-FT-UR (10% w/v each solubilizer)	2.579	3.310
GL-TH-FT-UR (10% w/v each solubilizer)	2.186	3.163
GL-PG-ST-UR (10% w/v each solubilizer)	2.227	2.515
GL-PG-FT-SC (10% w/v each solubilizer)	2.599	2.458
FH-FT-ST-UR (10% w/v each solubilizer)	6.666	4.280
TH-FH-FT-ST (10% w/v each solubilizer)	7.390	5.383
GL-TH-FT-ST (10% w/v each solubilizer)	4.327	4.075
PG-FH-FT-UR (10% w/v each solubilizer)	4.182	3.766
TH-FH-FT-UR (10% w/v each solubilizer)	4.224	4.471
UR-SC-TH-FT (10% w/v each solubilizer)	9.760	7.321
SC-GL-TH-FT (10% w/v each solubilizer)	10.150	7.543
UR-SC-TH-GL (10% w/v each solubilizer)	10.805	6.698
PG-FH-FT-SC (10% w/v each solubilizer)	12.486	8.155

Table 3: Analysis data of salicylic acid bulk drug sample with statistical evaluation (n=3)

Methods of analysis	Mean percent estimated	Standard deviation	Percent coeff. of variation	Standard error
IP Method	99.16	1.310	1.331	0.756
PG-FH-FT-UR method	100.69	0.811	0.805	0.468
UR-SC-TH-FT method	99.36	1.555	1.565	0.898
SC-GL-TH-FT method	98.76	1.330	1.347	0.768
UR-SC-TH-GL method	99.44	0.909	0.914	0.525
PG-FH-FT-SC method	100.31	1.724	1.719	0.995
FH-FT-ST-UR method	100.35	0.862	0.876	0.498

solution as an indicator. Necessary correction was done by conducting blank determination and amount of salicylic acid was calculated [Table 3]. Total three such determinations were performed by this method (n=3).

Analysis of salicylic acid bulk sample by other proposed methods

The drug content of salicylic acid bulk drug sample was determined using UR-SC-TH-FT method, SC-GL-TH-FT method, UR-SC-TH-GL method, PG-FH-FT-SC method and FH-FT-ST-UR method were determined adopting the same method (PG-FH-FT-UR method) and the results are presented in Table 3.

RESULTS AND DISCUSSION

From Table 1, it is evident that there was improvement in the solubility of salicylic acid in all solutions containing individual solubilizers. The greatest enhancement in solubility was observed in case of 40% w/v sodium citrate solution and least in case of 40% w/v urea solution. Table 2 illustrates the advantages of making blends of solubilizers. Except in case of PG-TH-FT-UR, GL-TH-FT-UR, GL-PG-ST-UR and TH-FH-FT-UR blends, all remaining 12 blends showed more solubility than contributory (calculated) solubility (hence synergistic solubilities). These results demonstrate the principle of the mixed-solvency concept that water-soluble substances whether hydrotropes or solvents or water-soluble solids (like PEG 4000, PEG 6000 etc) can be combined to give enhancement in solubility for a poorly water-soluble drug. These results demonstrate that in the development of liquid (solution) dosage forms, blends of solubilizers can be employed to reduce the toxicities of solubilizers by reducing the individual concentration of solubilizers (instead of employing one solubilizer in higher concentration which may be toxic for some desired solubility enhancement). Blends of water soluble substances (hydrotropes, cosolvents, water soluble excipients etc.) can be made in safe level of concentrations of individual solubilizer to give a concentrated solution (say 25%, 30% w/v etc.) to act as a solubilizing system for development of liquid (solutions) syrups, or topical solutions, or injections, etc.

The mean percent drug (salicylic acid) estimated using PG-FH-FT-UR, UR-SC-TH-FT, SC-GL-TH-FT, UR-SC-TH-GL, PG-FH-FT-SC, and FH-FT-ST-UR blends was 100.69, 99.36, 98.76, 99.44, 100.31, and 100.35, respectively [Table 3]. These values are very close to 100, indicating the accuracies of the proposed methods of analysis. Also, these values of the mean percent drug estimated are very close to the value of mean percent estimated (99.16) by a standard method of Indian pharmacopoeia, which confirms the accuracy of the proposed methods. The proposed analytical methods are further validated by satisfactorily low values of standard deviation, percent coefficient of variation, and standard error.

Various organic solvents like chloroform, dimethyl formamide, methanol, and ethanol have been employed for solubilization of poorly water-soluble drugs to conduct their titrimetric analysis. Drawbacks of organic solvents include their higher costs, toxicities, and pollution. The present investigation focuses on the application of mixed-solvency concept to discourage the use of organic solvents in analyses to a great extent.

It is, thus, concluded that the proposed titrimetric methods are new, simple, cost-effective, safe, free from pollution, and precise. Just like salicylic acid other poorly water-soluble drugs may be tried to get solubilized by the mixed-solvency concept to carry out their titrimetric analyses precluding the use of organic solvents and the blends of water soluble substances (hydrotropes, cosolvents, water-soluble excipients, etc.) can be made in safe level of concentrations of individual solubilizer for development of liquid (solutions) syrups, or topical solutions, or injections, etc. The proposed solubilizing agents are known to be safe hence toxicities/ safety related issues may not raise concern, suggesting the adoptability for large scale manufacturing i.e. industrial feasibility. The probable mechanism for solubilization of salicylic acid in different blends may be expected due to involvement of hydrogen bonding, weak Van der Wall forces, etc (like the mechanism involved in cases of co-solvents).

O. Sol. refers to observed solubility, C. Sol. refers to contributory solubility, FH refers to PEG 400, FT refers to PEG 4000, ST refers to PEG 6000, UR refers to urea, SC refers to sodium citrate, TH refers to PEG 300, PG refers to propylene glycol and GL refers to glycerin

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