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NOVEL PHARMACEUTICAL APPLICATION OF MIXED SOLVENCY IN THE FORMULATION DEVELOPMENT OF SYRUPS (LIQUID ORAL SOLUTIONS) OF POORLY WATER-SOLUBLE DRUGS

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ABSTRACT

Solubilization of poorly water soluble drugs has been a very important issue in screening studies of new chemical entities as well as in formulation research. In the present investigation, mixed-solvency approach has been utilized for solubility enhancement of poorly water-soluble drug, Naproxen and Furosemide (as model drugs). Sixteen blends (having total 40% w/v strength) containing various solubilizers among the commonly used hydrotropes (urea, sodium benzoate and sodium citrate), cosolvents (glycerin, ethanol, propylene glycol, PEG 600 and PEG 400) and water-soluble solids (PEG 4000 and PEG 6000) were made to study the influence on solubility of Naproxen and Furosemide individually. Most of the blends were found to increase the solubility of both drugs. 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 produce a desirable aqueous solubility of poorly water-soluble drugs.

Keywords: Solubility enhancement, Mixed Solvency, Hydrotropic agents.

INTRODUCTION

Hydrotropes[1-15] and co-solvents have been observed to enhance the aqueous solubilities of poorly soluble drugs. Solubility is defined in quantitative terms as the concentration of the solute in a saturated solution at a certain temperature and in the qualitative terms it may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion[16]. Mixed Solvency is one of the important technique (concept) recently developed to increase the solubility of poorly soluble drugs. In this technique solubilizers from the category of hydrotropes (sodium benzoate, sodium citrate, sodium acetate, urea and niacinamide), cosolvents (PEG 200, PEG 300, PEG 400, PEG 600, propylene glycol, ethanol) and water soluble solids (PEG 4000, PEG 6000) are employed. Enhancement in solubility can be achieved by mixing, say, five hydrotropes and / or cosolvents (each in one fifth concentration), then the toxic level of the solubilizing agents can be reduced by fivefold. The application of the same principle has been employed in the present work to increase the solubility of the poorly water-soluble drugs, Naproxen and Furosemide employing the solubilizers from the category of hydrotropes (sodium benzoate, sodium citrate, urea, niacinamide), cosolvents (PEG 400, propylene glycol, ethanol) and water soluble solids (PEG 4000, PEG 6000)[16-25].

EXPERIMENTAL

Materials and Methods[1, 3]: Naproxen and Furosemide were obtained as a generous gift sample from RPG Life Sciences, Ankleshwar and Torrent Pharmaceuticals, Ahmedabad respectively. All chemicals and solvents used were of analytical reagent grade.

Solubility determination of Naproxen and Furosemide : Solubility of Naproxen in solutions of individual solubilizers (40% w/v propylene glycol,

40% w/v glycerin, 40 % w/v ethanol, 40% w/v PEG 4000, 40% w/v Niacinamide, 40% w/v PEG 6000, 40% w/v Sodium Benzoate and 40% w/v urea and various blends were determined. Excess amount of Naproxen was added to screw capped amber colored glass vials containing fixed volumes (10 ml) of the solutions of solubilizers separately. The vials were shaken for 12 hours at room temperature in orbital flask shaker. The solutions were allowed to equilibrate for next 24 hours and then centrifuged for 5 minutes using a centrifuge (Remi Instruments Limited, Mumbai, India). The supernatants of each vial were filtered through whatsman filter paper # 41. Same procedure was applied to Furosemide. An aliquot of each filtrate was diluted suitably with distilled water and the resulting solutions were analyzed on UV/visible spectrophotometer (Shimadzu 1700) at 331 nm and 333 nm for Naproxen and Furosemide respectively against respective reagent blank solutions. The solubilities of both the drugs was determined using the corresponding regression equations is given in Table 1.

Devlopment of Liquid Syrup Formulation: In the present study, the use of mixed-solvency has been explored to develop liquid oral solutions (syrups) of poorly water soluble drugs Naproxen and Furosemide, to give quick onset of action and better bioavailability (in comparison to suspensions).

Procedure for syrups (Solution): The required quantities of all solubilizers were transferred to a volumetric flask (100 ml capacity) containing 50 ml of distilled water and the flask was shaken until complete dissolution of solubilizers. Then required amount of drug was added and the flask was shaken to dissolve the drug completely. Then required amount of sucrose was added and again the flask was shaken to dissolve it. Then the volume was made up to the mark with distilled water and the syrup was filtered through filter paper. First few ml of syrup was discarded. Filtered syrup was preserved in airtight container. On the basis of the results obtained from the solubilization studies of Naproxen and Furosemide the syrup of individual drug was developed to contain 1% w/v and 3%w/v of drug respectively. On the basis of solubility studies nine syrup formulations were prepared for Naproxen (FN1-FN9) and ten formulations were prepared for Furosemide (FF1-FF9) and shown in table 6 and 7, respectively.

Optimized formula for liquid syrup formulations
All the syrups were subjected to physical stability at room temperature for two weeks to observe color development or precipitation if any. The Naproxen syrup formulations FN2, FN3 and FN8 no precipitation or color development was there up to fourteen-day. In FN4, FN5 and FN6 formulations the second day precipitation was formed. The FN1 formulations immediate precipitation was formed. The FN7 and FN9 formulation after fourteen-day precipitation was formed. The FF4, FF6 formulations no precipitation or color development was there up to fourteen-day. The FF2, FF3, FF7 formulations the second day precipitation was formed. The FF1, FF5, FF9 formulation after fourteen-day precipitation was formed. The FF8 formulation immediate precipitation was formed. Therefore, the Naproxen syrup formulations FN2, FN3, FN8 and the Furosemide syrup formulations FF4, FF6 were selected for further studies.

Physical and chemical stability testing of formulated syrups[26]: Physical stability testing was performed for seventy five days of all the syrup formulations of Naproxen and Furosemide at three different temperatures i.e. at Room Temperature, at 55ºC and at 40ºC/75% RH. Chemical Stability testing was performed for about seventy days of all the syrup formulations of Naproxen and Furosemide and the readings were taken every seven days.

Freeze thaw cycling testing of syrups: The vials were kept alternately at 40±1°C and 4°C for 24 hour each, and shaken everyday for 5 minutes on a touch-type vortex mixer. Two vials of formulation were taken, one of which was kept at 40±1°C and the other 4°C for first day, followed by subsequent temperature cycling and shaking as described. After 7 such cycles at 4°C and 40±1°C (alternately), the vials were observed to check turbidity and precipitation.

RESULT AND DISCUSSION

Table 1 showed the equilibrium solubility of naproxen and Furosemide in various solubilizers such as 40% sodium benzoate, 40% sodium citrate solution, 40% urea solution, 40% PEG 6000 solution, 40% PEG 4000 solution, 40% PEG 600 solution, 40% PEG 400 solution, 40% propylene Glycol solution, 40% niacinamide solution, 40% urea solution, 40% ethanol Solution, 40% glycerin and 40% sodium Acetate.

Table 2 and 3 showed the advantages of making blends of solubilizers. The equilibrium solubility of Naproxen was increased in all most all blends. Results showed that maximum solubility enhancement in case of blends containing five solubilizers was obtained in blend NB (ET-PG-SB-

NM-EG). In case of blends containing four solubilizers maximum solubility enhancement was obtained in blend YC (UR-SB-PG-ET).

Similarly Table 4 and 5 shows equilibrium solubility of Furosemide was increased in most of the blends. Results showed that maximum solubility enhancement in case of blends containing five solubilizers was obtained in blend FF (SB-SC-EF-EH-ET). In case of blends containing four solubilizers maximum solubility enhancement was obtained in blend XE (SB-EI-PG-ET).

The pH of the blends of various solubilizers was nearly neutral (7.5 to 9.1). Since the pH of all blends of solubilizers is nearly neutral, it may be assumed that there is negligible effect of pH on solubility enhancement of Naproxen and Furosemide.
This physical and chemical stability study indicates that the selected Naproxen and Furosemide formulations are quite stable.

The results of chemical stability studies showed that, the residual drug content at the end of 10th week was more than 90.00% at room temperature in all the syrup formulations of Naproxen and Furosemide. The residual drug content at 10th week time period in the Naproxen syrup formulation FN2 was found to be 95.8% at room temperature, 84.07% at 40°C/75% RH and 81.60% at 55°C, whereas in formulation FN3, the residual drug content was found to be 95.80% at room temperature, 85.31% at 40°C/75% RH and 83.60% at 55°C, whereas in formulation FN8 the residual drug content was found to be 90.91% at room temperature, 83.90% at 40°C/75% RH and 81.56% at 55°C. The residual drug content at 10th week time period in the furosemide formulation FF4 was found to be 93.23% at room temperature, 84.65% at 40°C/75% RH and 80.07% at 55°C, whereas in formulation FF6 the residual drug content was found to be 94.82% at room temperature, 82.78% at 40°C/75% RH and 80.56% at 55°C. This study indicates that the selected naproxen and furosemide formulations are quite stable

The formulated naproxen and furosemide syrups were subjected to freeze-thaw cycling studies by exposing them alternately at 4°C and 40°C (for 24 h at each temperature) during 14 days. There was no precipitation and no turbidity in syrup formulations Table 1: Solubility of Naproxen and Furosemide in distilled water and individual solubilizers[1]

CONCLUSION

Various organic solvents like chloroform dimethyl formamide, methanol, and ethanol have been employed for solubilization of poorly water-soluble drugs. 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. It can be concluded that with the carefully designed experimental technique, solubility of poorly water-soluble drugs can be improved by using "Mixed-solvency approach.'' It would not be surprising that many types of syrup (oral liquid solution) of poorly water-soluble drugs based on these mixed-solvency phenomena would enter into the market.

Table 1: Solubilities of both the drugs

S. No.		Solubility (% w/v)	
		Naproxen	**Furosemide**
1	Distilled water	0.065	0.0085
2	40% Urea (UR)	0.258	0.3562
3	40% Sodium Benzoate (SB)	4.17	6.72
4	40% Sodium Citrate(SC)	0.228	0.20
5	40% Niacinamide(NM)	0.28	-
6	40% PEG 6000 (EF)	0.307	2.84
7	40% PEG 4000 (EG)	0.418	0.493
8	40% PEG 400 (EH)	0.156	0.3
9	40% PEG 600 (EI)	0.19	0.25
10	40% PG(PG)	0.115	0.24
11	40% Glycerin(GL)	0.0817	0.19
12	40% Ethanol(ET)	0.754	0.32
13	40% Sodium Acetate(SA)	-	0.34

Table 2: Equilibrium solubility data of Naproxen in blends containing five solubilizers

Blend codes	Solubilizers (%w/v)												Equilibrium solubility(%w/v)
	UR	SB	SC	NM	EF	EG	EH	EI	SA	PG	GL	ET	
NA	8	8	-	-	-	8	-	-	-	-	8	8	1.117
NB	-	8	-	8	-	8	-	-	-	8	-	8	2.253
NC	8	8	-	-	8	8	-	-	-	8	-	-	1.52
ND	8	-	-	-	8	-	-	8	-	8	8	-	0.141
NE	-	8	8	-	-	8	8	-	-	-	-	8	1.27
NF	8	8	-	-	-	8	8	8	-	-	-	-	1.07
NG	8	8	-	-	8	-	8	-	-	-	-	8	1.587
NH	8	8	-	-	-	8	-	-	-	8	8	-	1.0425
NI	8	8	-	-	-	8	-	-	-	8	-	8	1.96
NJ	8	8	-	-	8	-	-	8	-	-	-	8	1.84

The codes of mixed solvents blends used were **NA**=UR-SB-EG-GL-ET, **NB**= ET-PG-SB-NM-EG, **NC**= PG-UR-SB-EG-EF, **ND**= GL-EI-UR-EF-PG, **NE**= EH-ET-SB-SC-EG, **NF**= EI-EH-UR-SB-EG**, NG**= ET-EH-SB-UR-EF**, NH**= PG-GL-SB-UR-EG**, NI**= ET-PG-SB-UR-EG**, NJ**= ET-EI-SB-UR-EF**.**

Table 3: Equilibrium solubility data of Naproxen in blends containing four solubilizers

Blend codes	Solubilizers (%w/v)												Equilibrium solubility(%w/v)
	UR	SB	SC	NM	EF	EG	EH	EI	SA	PG	GL	ET	
YA	10	10	-	-	10	10	-	-	-	-	-	-	1.711
YB	-	-	10	10	10	-	10	-	-	-	-	-	0.785
YC	10	10	-	-	-	-	-	-	-	10	-	10	2.05
YD	10	-	-	10	-	-	-	-	-	10	-	10	0.540
YE	10	-	-	10	-	-	-	10	-	-	10	-	0.275
YF	10	10	10	10	-	-	-	-	-	-	-	-	1.972

The codes of mixed solvents blends used were **YA**=UR-SB-EF-EG**, YB**=SC-NM-EF-EH**, YC**=UR-SB-PG-ET**, YD**=UR-NM-PG-ET**, YE**=UR-NM-EI-GL**, YF**=UR-SB-SC-NM**.**

Table 4: Equilibrium solubility data of Furosemide in blends containing five solubilizers

Blend codes	Solubilizers (%w/v)												Equilibrium solubility(%w/v)
	UR	SB	SC	NM	EF	EG	EH	EI	SA	PG	GL	ET	
FA	8	8	-	-	-	8	-	-	-	8	-	8	3.50
FB	8	8	-	-	8		-	8	-	-		8	4.11
FC	8	8	-	-	-	8	-	-	-	-	8	8	2.72
FD	8	8	-	-	-	8	8	8	-	-	-	-	3.718
FE	8	-	8	-	-	8	-	-	-	8	8	-	4.251
FF	-	8	8	-	8	-	8	-	-	-	-	8	5.305
FG	-	8	8	-	8	-	-	-	-	8	8	-	3.80
FH	8	-	-	-	-	8	-	-	8	-	8	8	2.94
FI	-	-	8	-	8	-	-	-	-	8	8	8	3.35
FJ	8	8	8	-	-	-	-	8	8	-	-	-	2.1

The codes of mixed solvents blends used were **FA**=UR-SB-EG-PG-ET**, FB**=UR-SB-EF-EI-ET**, FC**=UR-SB-EG-GL-ET**, FD**=UR-SB-EG-EH-EI**, FE**= UR-SC-EG-PG-GL**, FF**= SB-SC-EF-EH-ET**, FG**=SB-SC-EF-PG-GL**, FH**=UR-EG-SA-GL-ET**, FI**=SC-EF-PG-GL-ET**, FJ**=UR-SB-SC-EI-SA**.**

Table 5: Equilibrium solubility data of Furosemide in blends containing four solubilizers

Blend codes	Solubilizers (%w/v)												Equilibrium solubility(%w/v
	UR	SB	SC	NM	EF	EG	EH	EI	SA	PG	GL	ET	
XA	10	-	-	-	10	10	-	-	10	-	-	-	2.08
XB	10	-	-	-	-	-	10	10	10	-	-	-	1.209
XC	10	10	-	-	-	-	10	-	-	10	-	-	3.260
XD	-	-	10	-	-	10	-	-	-	-	10	10	1.05
XE	-	10	-	-	-	-	-	10	-	10	-	10	3.42
XF	10	10	10	-	-	-	-	-	10	-	-	-	3.21

The codes of mixed solvents blends used were **XA=** UR-EF-EG-SA**, XB=**UR-EH-EI-SA**, XC=**UR-SB-EH-PG**, XD=** SC-EG-GL-ET**, XE=** SB-EI-PG-ET**, XF=** UR-SB-SC-SA.

Table-6 Formulation development with drug Naproxen

Ingredients	Formulation Code								
	FN1	FN2	FN3	FN4	FN5	FN6	FN7	FN8	FN9
Naproxen (gm)	1	1	1	1	1	1	1	1	1
Ethanol (gm)	8	8	8	8	-	8	-	10	-
Propylene glycol	8	8	-	-	8	-	-	10	-
PEG 400	-	-	-	8	-	8	-	-	-
PEG 600	-	-	8	-	-	-	-	-	-
Sodium benzoate	8	8	8	-	8	8	10	10	10
Sodium citrate (gm)	-	-	-	-	-	8	-	-	10
Niacinamide (gm)	8	-	-	-	-	-	-	-	8
Urea (gm)	-	8	8	8	8		10	10	10
PEG 4000 (gm)	8	8	-	-	8	8	10	-	-
PEG 6000 (gm)	-	-	8	8	8	-	10	-	-
Sucrose (gm)	20	20	20	20	20	20	20	20	20
Distilled water q.s.	100	100	100	100	100	100	100	100	100

Table-7 Formulation development with drug Furosemide

Ingredients	Formulation Code								
	FF1	FF2	FF3	FF4	FF5	FF6	FF7	FF8	FF9
Furosemide (gm)	3	3	3	3	3	3	3	3	3
Ethanol (gm)	8	8	-	-	8	-	8	-	10
Propylene glycol	8	-	-	8	-	8	8	10	10
PEG 400	-	-	8	-	8	-	-	10	-
PEG 600	-	8	8	-	-	-	-	-	10
Sodium benzoate	8	8	8	-	8	8	-	10	10
Sodium citrate (gm)	-	-	-	8	8	8	8	-	-
Glycerin	-	-	-	8	-	8	8	-	-
Urea (gm)	8	8	8	8	-		-	10	-
PEG 4000 (gm)	8	-	8	8	-	-	-	-	-
PEG 6000 (gm)	-	8	-	-	8	8	8	-	-
Sucrose (gm)	20	20	20	20	20	20	20	20	20
Distilled water q.s.	100	100	100	100	100	100	100	100	100

REFERENCES

1. Maheshwari RK. Solubilization of Ibuprofen by Mixed Solvency Technique. Indian Pharmacist 2009; 8: 81-84.
2. Maheshwari RK, Chaturvedi SC, Jain NK. Novel Application of Hydrotropic solubilization in the analysis of some NSAIDs and their solid dosage forms. Indian Journal of Pharmaceutical Sciences 2007; 69(1):101-106.

3. Maheshwari RK. Spectrophotometric determination of cefixime in tablets by hydrotropic solubilization phenomenon. The Indian Pharmacist 2005; 4: 63-8.
4. Maheshwari RK. Analysis of furosemide by application of hydrotropic solubilization phenomenon. The Indian Pharmacist 2005; 4: 55-8.
5. Maheshwari RK. New application of hydrotropic solubilization in the spectrophotometric estimation of ketoprofen in tablet dosage form. The Pharma Review 2005; 3:123-5.
6. Maheshwari RK. A novel application of hydrotropic solubilization in the analysis of bulk samples of ketoprofen and salicylic acid. Asian J Chem 2006; 18:393-6.
7. Maheshwari RK. Novel application of hydrotropic solubilization in the spectrophotometric analysis of tinidazole in dosage form. Asian J Chem 2006; 18:640-4.
8. Maheshwari RK. Application of hydrotropic solubilization in the analysis of aceclofenac. Asian J Chem 2006; 18:1572-4.
9. Maheshwari RK. Novel application of hydrotropic solubilization in the spectrophotometric analysis of piroxicam in solid dosage form. Indian Drugs 2006; 8:683-5.
10. Maheshwari RK. A novel application of hydrotropic solubilization in the spectrophotometric estimation of furosemide in tablets. The Pharma Review 2006; 4:148-9.
11. Maheshwari RK. Mixed hydrotropy in spectrophotometric analysis of aceclofenac. The Indian Pharmacist 2007; 4: 67-69.
12. Maheshwari RK, Chaturvedi SC, Jain NK. Application of hydrotropic solubilization phenomenon in spectrophotometric analysis of hydrochlorothiazide tablets. Indian drugs 2005; 42:541-4.
13. Maheshwari RK, Chaturvedi SC, Jain NK. Titrimetric analysis of aceclofenac in tablets using hydrotropic solubilization technique. Indian Drugs 2006; 43:516-8.
14. Maheshwari RK, Khera C, Lovlekar A. Novel method of analysis for ibuprofen and flurbiprofen bulk drugs using ibuprofen sodium solution as hydrotropic solubilizing agent. The Pharma Review 2007; 5:167-9.
15. Maheshwari RK, Bisnoi SR. Spectrophotometric analysis of hydrochlorothiazide tablets using chlorpheniramine maleate as hydrotropic solubilizing agent. Asian J Chem 2008; 8:6594-6.
16. Martin A, Bustamante P, Chun AHC. Physical pharmacy. 4th edition. Philadelphia: Lippincott Williams and Wilkins; 2004, pp. 103, 212.
17. Maheshwari RK, Arif D, Mittal P, Manchandani P, Indurkhya A, Jawade S. A novel method for quantitative determination of aceclofenac in bulk drug and tablets using ibuprofen sodium as a hydrotropic solubilizing agent. Journal of Applied Chemical and Research, 2008; 5:63-8.
18. Poochikian GK, Cradock JC. Enhanced chartreusin solubility by hydroxybenzoate hydrotropy. J Pharm Sci 1979; 68:728-32.
19. Etman MA, Hada AH. Hydrotropic and cosolvent solubilization of indomethacin. Acta Pharm 1999; 49:291-8.
20. Darwish A, Florence AT, Saleh AM**.** Effects of hydrotropic agents on the solubility, precipitation and protein binding of etoposide. J Pharm Sci 1989; 78:577-81.
21. Etman MA, Salama RO, Shamsedeen MA, El-Kamel A. Solubilization of etodolac for parenteral administration. Indian J Pharm Sci 2001; 63:459-67.
22. Rasool AA, Hussain AA, Dittert LW. Solubility enhancement of some water-insoluble drugs in the presence of nicotinamide and related compounds. J Pharm Sci 1991; 80:387-93.
23. Jain NK, Agrawal RK, Singhai AK. Formulation of aqueous injection of carbamazepine. Pharmazie 1990; 45:221-5.
24. Williams NA, Amidon GL. Excess free energy approach to the estimation of solubility in mixed solvent system III: Ethanol-Propylene glycol-Water mixtures. J Pharm Sci 1984; 73:18-23.
25. Rowe RC, Sheskey PJ, Owen SC. Handbook of pharmaceutical excipients.5th edition. Britain: Pharmaceutical Press; 2006, pp. 454
26. Parasampuria I., Swarbrick, J., Boylan, J.C., Encyclopedia of Pharmaceutical Technology, 2nd ed., New York; Marcel Dekker Inc., 2002, pp. 1679.