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SOLUBILIZATION OF POORLY WATER SOLUBLE CLASS II DRUG

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ABSTRACT

Solubilization is distinct from dissolution because the resulting fluid is a colloidal dispersion involving an association colloid. This suspension is distinct from a true solution, and the amount of the solubilize in the micellar system can be different (often higher) than the regular solubility of the solubilize in the solvent.

In non-chemical literature and in everyday language, the term "solubilization" is sometimes used [citation needed] in a broader meaning as "to bring to a solution or (non-sedimenting) suspension" by any means, e.g., leaching by a reaction with an acid.

KEYWORDS: Micellarsolubilization, Solubilization, Dexibuprofen.

INTRODUCTION:

Dexibuprofen is a class II drug with low solubility and high permeability. In order to formulate Dexibuprofen in predissolved form with enhanced solubility, attempts were made to develop solvent systems with improved solubility. Various novel solvents and nonionic surfactants reported to solubilize lipophilic drugs were tried to develop solvent systems for solubilization of Dexibuprofen.

Following strategies were tried for solubilization of Dexibuprofen:

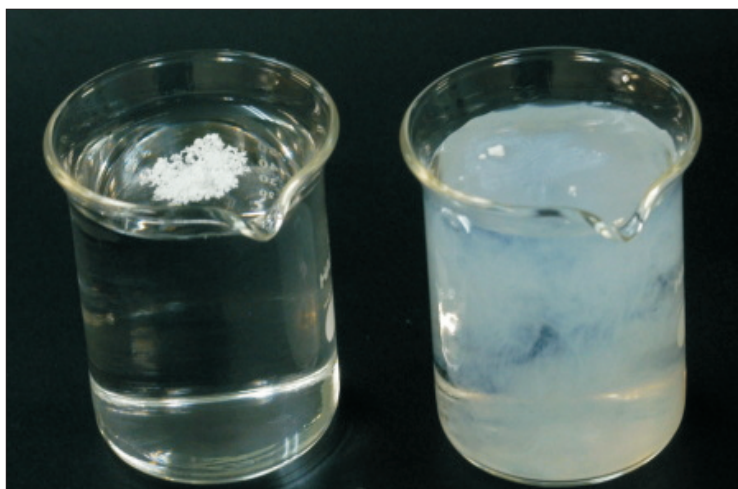
- 1) Solubilization using novel solvents.
- 2) Use of solvent synergism effect on solubilization of Dexibuprofen.
- 3) Micellarsolubilization using various nonionic surfactants

Lipid based formulations

- 1) Formation of microemulsions.
- 2) Formation of selfmicroemulsifying drug delivery systems (SMEDDS)

3.2 Determination of Solubility of Dexibuprofen

Initially solubility of Dexibuprofen was checked in various solvents by dissolving approximately 5mg of Dexibuprofen in 1ml of each solvent. Some solvents were sonicated for 5 minutes. Some solvents were warmed up to 40°C cooled and observed for formation of crystals. Transcutol, Arlasolve, PEG400, propylene glycol, Crodamol, Triacetin, sesame oil, oleyl alcohol, propylene carbonate, tributylcitrate, triethyl citrate and Labrafac



were initially used as solvents for solubilization of Dexibuprofen. Results of solubility studies are mentioned in table 3.1.

Table 3.1
Solubility studies of Dexibuprofen in various solvents

Sr.no.	Solvents	Observation	Remarks
1	Transcutol	Soluble	Freely soluble
2	Arlasolve	Soluble	Freely soluble
3	PEG200	Soluble	Sonicated for 5 mins
4	PEG400	Soluble	Sonicated for 5 mins
5	Propylene glycol	Soluble	Sonicated for 5 mins
6	Triacetin	Soluble	Freely soluble
7	Sesame oil	Soluble	Warmed up to 40 ^o C
8	Soya bean oil	Soluble	Warmed up to 40 ^o C
9	Oleyl alcohol	Soluble	Warmed up to 40 ^o C
10	Triethyl citrate	Soluble	Warmed up to 40 ^o C
11	Tributyl citrate	Soluble	Warmed up to 40 ^o C
12	Crodamol	Soluble	Warmed up to 40 ^o C
13	Propylene carbonate	Soluble	Sonicated for 5 mins
14	Labrafac	Soluble	Warmed up to 40 ^o C
15	Ethanol	Soluble	Freely soluble
16	Acetone	Soluble	Freely soluble
17	Chloroform	Soluble	Freely soluble
18	Water	Insoluble	--

3.3 Temperature Related Solubility

Temperature related solubility studies were carried out to solubilize drug to the extent of 1-2.5 gm/ml as dose of Dexibuprofen is very high. Temperature was maintained at 40^oC. Solutions were cooled and they were observed for formation of crystals during or after cooling process. The results are given in table 3.2

Table 3.2
Temperature related solubility of Dexibuprofen

Sr no	Solvents	Amount of solute added			
		1gm/ml	1.5gm/ml	2gm/ml	2.5gm/ml
1	Transcutol	clear	clear	clear	clear
2	Arlasolve	clear	clear	clear	clear
3	PEG200	clear	Crystals after cooling	-	-
4	PEG400	clear	clear	clear	clear
5	Propylene glycol	clear	clear	clear	Crystals after cooling
6	Triacetin	clear	clear	Crystals after cooling	-
7	Sesame oil	Crystals after cooling	-	-	-
8	Soya bean oil	Crystals after cooling	-	-	-
9	Oleyl alcohol	Crystals after cooling	-	-	-
10	Triethyl citrate	Crystals after cooling	-	-	-
11	Tributyl citrate	Crystals after cooling	-	-	-
12	Crodamol	clear	Crystals after cooling -	-	-
13	Propylene carbonate	Crystal after cooling	-	-	-
14	Labrafac	Crystals after cooling	-	-	-

3.4 Saturation Solubility

Saturation solubility at room temperature was determined by dissolving Dexibuprofen in solvents with the help of magnetic stirrer. Dexibuprofen was stirred with the solvents till no more of drug could be dissolved. The amount of drug dissolved was determined by estimating drug content in aliquots of filtered solution. The results are given in table 3.3.

Table 3.3
Saturation solubility of Dexibuprofen at room temperature

Sr. no	Solvents	Solubility (gm/ml)
1	Arlasolve	1.7
2	Transcutol	1.000
3	PEG 400	0.849
4	Propylene glycol	0.821
5	Triacetin	0.700

3.5 Synergistic Effect

Synergistic effect refers to the phenomenon in which two or more discrete agents acting together create an effect greater than that predicted by knowing separate effects of the individual agents.

Solubility of Progesterone has been reported to be increased by synergistic effect of PEG400 and cyclodextrin complex formation¹¹⁰. Hence we attempted to study if there is any effect of solvent synergism on solubility of Dexibuprofen. Solvents that showed maximum solubility for Dexibuprofen were selected to study if their combination had any synergistic effect. As discussed earlier in section 3.4 solvents Transcutol, PEG400, propylene glycol, Arlasolve and Triacetin showed maximum saturation solubility, so attempts were made to determine synergistic effects of varying proportions of lipophilic solvents. Hydrophilic and lipophilic solvents were mixed in various ratios. Triacetin and triethyl citrate were used as lipophilic solvents.

PEG 400, Transcutol, propylene glycol, Arlasolve (hydrophilic solvents): Triacetin and triethyl citrate (lipophilic solvents) were used in the ratios of 3:1, 1:1, 1:3. Initially temperature related solubility study was carried out. Dexibuprofen was dissolved in above combination of solvents by maintaining the temperature of water bath at 40°C. Then solution of Dexibuprofen was observed for formation of any crystals or separation of particles during and after cooling. Saturation solubility of Dexibuprofen was determined in combination of solvents to study synergistic effect. Saturation solubility was determined by dissolving Dexibuprofen in combination of solvents with the help of magnetic stirrer. Dexibuprofen was stirred till no more of drug could be dissolved. Aliquot of filtered solution was used to determine the drug content. The results are given in table 3.4.

Table 3.4
Effect of solvent synergism on solubility at 400C

Sr.no	Amount of solute added					
	Ratios	Solvent combination	0.5gm/ml	1gm/ml	1.5gm/ml	2gm/ml
1	1: 3	Triacetin:Arlasolve	Clear	Clear	Clear	Clear
		Triethylcitrate:Arlasolve	Clear	Clear	Clear	Clear
		Triacetin:Transcutol	Clear	Clear	Clear	Clear
		Triethylcitrate:Transcutol	Clear	Clear	Clear	Clear
		Triacetin:PEG400	Clear	Clear	Clear	Crystals
		Triethyl citrate:PEG400	Clear	Clear	Clear	Crystals
		Triacetin:Propylene glycol	Clear	Clear	Clear	Crystals
		Triethylcitrate:Propylene glycol	Clear	Clear	Clear	Crystals
2	1: 1	Triacetin:Arlasolve	Clear	Clear	Clear	Crystals
		Triethylcitrate:Arlasolve	Clear	Clear	Clear	Crystals
		Triacetin:Transcutol	Clear	Clear	Clear	Crystals
		Triethylcitrate:Transcutol	Clear	Clear	Clear	Crystals
		Triacetin:PEG400	Clear	Clear	Clear	Crystals
		Triethyl citrate:PEG400	Clear	Clear	Clear	Crystals
		Triacetin:Propylene glycol	Clear	Clear	Clear	Crystals
		Triethylcitrate:Propylene glycol	Clear	Clear	Clear	Crystals
3	3: 1	Triacetin:Arlasolve	Clear	Clear	Crystals	Crystals
		Triethylcitrate:Arlasolve	Clear	Clear	Crystals	Crystals
		Triacetin:Transcutol	Clear	Clear	Crystals	Crystals
		Triethylcitrate:Transcutol	Clear	Clear	Crystals	Crystals
		Triacetin:PEG400	Clear	Clear	Crystals	Crystals
		Triethyl citrate:PEG400	Clear	Clear	Crystals	Crystals
		Triacetin:Propylene glycol	Clear	Clear	Crystals	Crystals
		Triethylcitrate:Propylene glycol	Clear	Clear	Crystals	Crystals

Table 3.5
Saturation solubility of Dexibuprofen in individual and combination of solvents.

Sr. no	Ratios	solvents	Solubility of Dexibuprofen(gm/ml)
1	-	Arlasolve	1.7
2	-	Transcutol	1
3	-	PEG 400	0.849
4	-	Propylene glycol	0.821
5	-	Triacetin	0.700
6	1:3	Triacetin:Arlasolve	1.200
		Triacetin:Transcutol	0.650
		Triacetin:PEG400	0.557
		Triacetin:Propylene glycol	0.638
7	1:1	Triacetin:Arlasolve	0.870
		Triacetin:Transcutol	0.560
		Triacetin:PEG400	0.500
		Triacetin:Propylene glycol	0.500
8	3:1	Triacetin:Arlasolve	0.750
		Triacetin:Transcutol	0.600
		Triacetin:PEG400	0.450
		Triacetin:Propylene glycol	0.581

RESULTS AND DISCUSSION:

- Dexibuprofen was soluble in selected solvents at room temperature while in most of its solvents it got dissolved by warming up to 40°C or after sonication.
- Hence attempts were made to study the effect of temperature on the solubility of Dexibuprofen.
- The solvents like Transcutol, Arlasolve, PEG400, propyleneglycol and Triacetin exhibited high solubilization capacity. Hence they were selected for further saturation solubility study.
- Arlasolve and Transcutol exhibited maximum saturation solubility for Dexibuprofen.
- To further enhance the solubility of Dexibuprofen, attempts were made to study if any synergistic effect was observed by using combinations of solvents.
- Hence attempts were made to study the effect of solvent synergism on the solubility of Dexibuprofen as discussed in the next section.
- There was no enhancement of solubility observed using combinations of solvents.
- As none of the solvents showed synergistic effect, further studies were discontinued.
- In order to further enhance solubility, it was decided to explore the use of micellar solubilization techniques as described in the next section.

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