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HYDROTROPIC SOLUBILIZATION: A PROMISING TECHNIQUE TO ENHANCE SOLUBILITY OF POORLY WATER SOLUBLE DRUG LUMEFANTRINE

S. Agrawal and M. Kasturi*

Department of Pharmaceutics, Swami Vivekanand College of Pharmacy, Khandwa Road, Near Toll Naka, Indore - 452020, Madhya Pradesh, India.

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Correspondence to Author:
Madhavi Kasturi

Department of Pharmaceutics, Swami Vivekanand College of Pharmacy, Khandwa Road, Near Toll Naka, Indore - 452020, Madhya Pradesh, India.

E-mail: madhavi2386@gmail.com

ABSTRACT: Solubility of drug is considered to be one of the crucial parameter to achieve its desired concentration in systemic circulation and better pharmacological response. As most of the drugs available are poorly aqueous soluble, solubility enhancement has become major challenge to the formulators in the product development of many orally administered drugs. Therapeutic response of drug as well bioavailability can be limited by poor aqueous solubility of drugs. Earlier, many techniques have been developed for enhancing solubility of drugs. Apart from those, hydrotropic solubilization is one of the solubility enhancement techniques applicable to enhance solubility of hydrophobic drugs with the use of hydrotropes like sodium benzoate, urea, piperazine etc. In the present investigation Lumefantrine, an anti malarial drug was selected as model drug for the reason it has very low water solubility of 0.009 mg/ml and belongs to BCS Class IV. The key objective of current research work was to enhance aqueous solubility of this drug using hydrotropic solubilization technique. Solubility studies were performed using various concentrations of hydrotropes like sodium citrate, sodium benzoate, *etc*. The results suggested that solubility of Lumefantrine was increased more than 30 folds when added to 30% sodium citrate solution and marked its importance in pharmaceutical field.

INTRODUCTION: Formulation plays a prominent role and holds several benefits in drug discovery and development. Therapeutic efficacy of drug preliminarily depends upon the bioavailability of drug which ultimately upon the solubility of drug molecules. Poor aqueous solubility of drugs often causes significant problems in developing formulations showing high bioavailability.

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Therefore, solubility is one of the important parameter to be considered in the product development in order to achieve desired concentration of drug in systemic circulation which further gives effective pharmacological response. Currently only 8% of new drug candidates have both high solubility and permeability.

Formerly, several techniques have been developed to enhance the aqueous solubility of poorly water-soluble drugs such as complexation, cosolvency, emulsions, liposomes, particle size reduction, solid state alteration, solid dispersions, prodrugs, salt formation, polymeric micelles, *etc.* Hydrotropic solubilization is one among those techniques wherein addition of large amount of second solute increases aqueous solubility of another solute.

The term 'Hydrotropy' was put forward by Carl Neuberg [1] to describe increase in solubility of a solute by the addition of fairly high concentrations of alkali metal salts of various organic acids. Hydrotropy enhances solubility of drug by many folds with use of hydrotropes like sodium benzoate, sodium citrate, urea, niacinamide *etc*. and have many advantages like; it does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system *etc* [2]. Hydrotropic agents are also a type of solubilizers which increase the solubility of poorly water soluble drugs [3]. Examples of various hydrotropic agents that are used as excipients in order to increase aqueous solubility of drug are urea, nicotinamide, sodium benzoate, sodium salicylate, sodium acetate, piperazine, nicotinamide, sodium toluate [4 - 13].

Here, Lumafantrine was selected as model drug. Lumefantrine, also known as Benflumetol, is basically a long acting anti-malarial drug which is very effective in treatment of resistant *P. falciparum malaria*. It is an erythrocytic schizontocide and acts by inhibiting haeme polymerization in the food vacuole of plasmodia. Lumefantrine belongs to BCS Class IV having low water solubility of 0.009 mg/ml. Hence it is necessary to increase the solubility of drug that may further increase bioavailability and also results in reduction of dose. Lumefantrine is generally given in combination therapy with artemether such as Coartem tablets (strength 20/120 mg; artemether / lumefantrine) in order to treat malaria. Here artemether is short acting where as lumefantrine is long acting anti malarial drug.

Keeping this point in view, the present research work is focused to enhance solubility of Lumefantrine using hydrotropic solubilization technique. The effect of hydrotropes like sodium benzoate, sodium citrate, sodium gluconate, ammonium acetate, piperazine, *etc*. on the solubility of Lumefantrine was investigated.

MATERIALS: Lumefantrine was kindly gifted from Cipla, Pithampur, India. Sodium gluconate, Piperazine anhydrous and L-ascorbic acid were purchased from Molychem, Mumbai, India. Sodium benzoate, Tri-sodium citrate dihydrate were purchased from Rankem, Haryana, India. Sodium salicylate, N, N- dimethyl urea, Pyrogollol, Pyridoxine HCl, Nicotinamide was purchased from Loba Chemie, Mumbai. Urea and Ammonium acetate were purchased from Qualigens, Mumbai, India. All the chemicals and reagents used were of analytical grade.

Experimental Methods:

UV Spectral Studies: Identification of Lumefantrine was done by UV Spectrophotometric method using Shimadzu Spectrophotometer UV-1800 (Shimadzu Corp., Japan). About 20 mg of drug was accurately weighed and dissolved in 200 ml of methanol R by sonication for about 15 minutes. The solution was allowed to cool to room temperature and diluted five times with methanol R. The absorption spectrum of the diluted solution when observed between 275 and 325nm, exhibits a maximum at about 302 nm; the specific absorbance (A 1% 1 cm) is between 314 and 348 [14].

Preparation of Calibration Curve of Lumefantrine in 0.1 M methanolic HCl (λ_{max} 332 nm): Standard stock solution of Lumefantrine was prepared by dissolving 100 mg of drug in 100 ml of 0.1 M methanolic HCl (1000 µg/ml). From the above stock solution 10 ml was taken and diluted upto 100 ml in methanolic HCl (100 µg/ml). From the above solution 1, 2, 3, 4, 5 and 6 ml was taken and diluted upto 10ml with 0.1M methanolic HCl to get concentrations ranging from 10 to 60 µg/ml of Lumefantrine. Absorbance was noted using UV-VIS Spectrophotometer at λ_{max} of 332 nm against blank (methanolic HCl). Calibration curve values of Lumefantrine in methanolic HCl (λ_{max} 332 nm) were given in **Table 1** and also graph plotted was shown in **Fig. 2**.

IR Analysis: The IR analysis of Lumefantrine sample was carried out using IR Affinity-1 (Shimadzu Corp., Japan). Here, diamond is the preferred choice for most applications because of its robustness and durability. The solid material is placed onto the small crystal area and then the pressure arm is positioned over the crystal/sample area.

Force is applied on to the sample, pushing it onto the diamond surface. Transmittance was measured from wave number 4000 cm^{-1} to 400^{-1} applying Happ-Gensel apodization.

Qualitative Solubility Studies: Qualitative solubility analysis for Lumefantrine was done by dissolving 10 mg of drug in 10 ml of solvent (aqueous / non aqueous) taken in conical flask. After shaking, the samples were examined for the presence of any undissolved suspended particles and clarity. The results of qualitative solubility of Lumefantrine in various solvents were reported in **Table 3**.

Quantitative Solubility Studies: An excess amount of solute is dissolved in 10 ml of selected solvent till saturated solution was obtained. The conical flasks were stoppered and agitated in thermostatically controlled orbital shaker (Tanco, Pitampura, New Delhi, India) at 25 ± 1 °C. After 24 hrs equilibrium was attained and the samples were filtered through Whatman filter paper (No.1). The individual samples were analyzed after suitable dilution to determine concentration of drug dissolved using UV-VIS spectrophotometer [4]. The solubility study was carried out in triplicate and the observations were given in **Table 4**.

pH Dependent Solubility Studies: An excess quantity of drug was added to a series of stoppered conical flasks containing 10 ml of phosphate buffer solutions (of varying pH) until saturated solution was obtained. The flasks were mechanically shaken at room temperature for 24 hrs, in thermostatically controlled orbital shaker (Tanco, Pithampura, Delhi) at 25 ± 1 °C. These suspensions were filtered through Whatman filter paper (No.1). [4] Aliquots of filtrate obtained were diluted with distilled water and analyzed using UV spectrophotometer at 332 nm against blank. The solubility study was carried out in triplicate and the results were shown in **Table 5**.

Solubility Studies using Hydrotropes: An excess quantity of drug was added to a series of stoppered conical flasks containing 10 ml of hydrotropic solutions until saturated solution was obtained. The flasks were mechanically shaken at room temperature for 12 hrs, in thermostatically controlled orbital shaker (Tanco, Pithampura, Delhi) at 25 ± 1 °C. These suspensions were filtered through Whatman filter paper (No. 1) [4]. Aliquots of filtrate obtained were diluted with suitable quantity of required solvent and analyzed using UV spectrophotometer at 332 nm. The solubility study was carried out in triplicate and observations were shown in **Table 6**.

Solubility Enhancement Ratio Determination: Solubility enhancement ratio is another parameter that determines the extent to which the drug is soluble in a particular solvent compared to that of water. The solubility enhancement ratios for drug in different hydrotropic solutions were calculated and the results were shown in **Table 7**.

Solubility enhancement ratio was calculated by using following formula:

Solubility enhancement ratio = Solubility in hydrotropic solution / Solubility in water

RESULTS AND DISCUSSION:

UV Spectral Studies: UV spectroscopic analysis for the drug was performed and the maximum absorption *i.e.* λ_{max} of Lumefantrine was observed at 332 nm Lumefantrine. UV analysis was carried out using 0.1M methanolic HCl as the drug is not completely soluble in methanol and require acidic environment because it is weakly basic in nature. The drug spectrum was shown in **Fig. 1**.

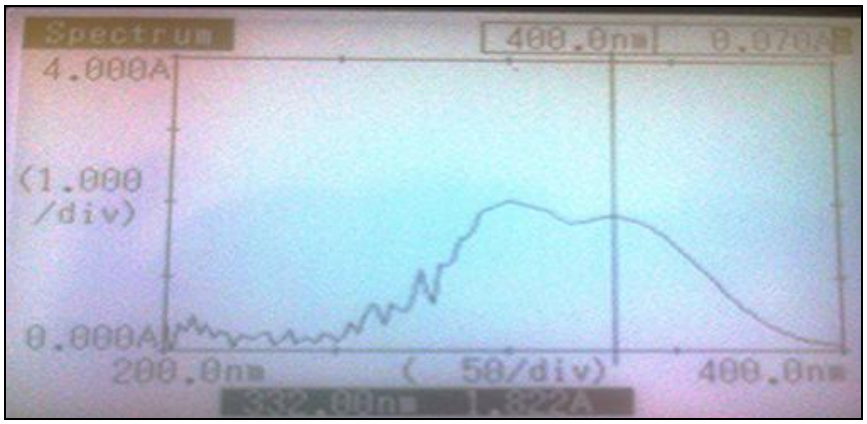

FIG. 1: UV SPECTRUM OF LUMEFANTRINE IN 0.1M METHANOLIC HCl

Preparation of Standard Curve of Lumefantrine in 0.1 M methanolic HCl (λ_{max} 332 nm): Calibration curve in of Lumefantrine was plotted using 0.1M methanolic HCl at λ_{max} of 332 nm and the readings were shown in **Table 1**. The linear standard curve of Lumefantrine including the graph equation was depicted in **Fig. 2**.

TABLE 1: STANDARD CURVE OF LUMEFANTRINE IN 0.1M METHANOLIC HCl (λ_{max} 332 nm)

Concentration (µg/ml)	Absorbance
0	0
10	0.339
20	0.633
30	0.899
40	1.19
50	1.473
60	1.811

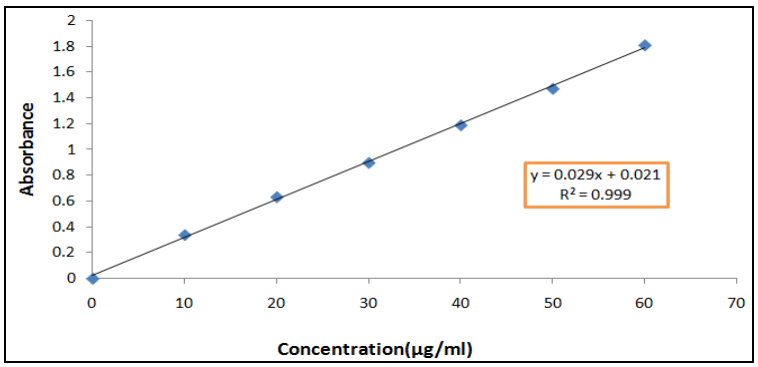

FIG. 2: STANDARD CURVE OF LUMEFANTRINE IN 0.1M METHANOLIC HCl (λ_{max} 332 nm)

IR Analysis: The IR Spectra of samples of Lumefantrine were shown in **Fig. 3**. The characteristic peaks attributable to various functional groups present in drug molecule were recorded in **Table 2**.

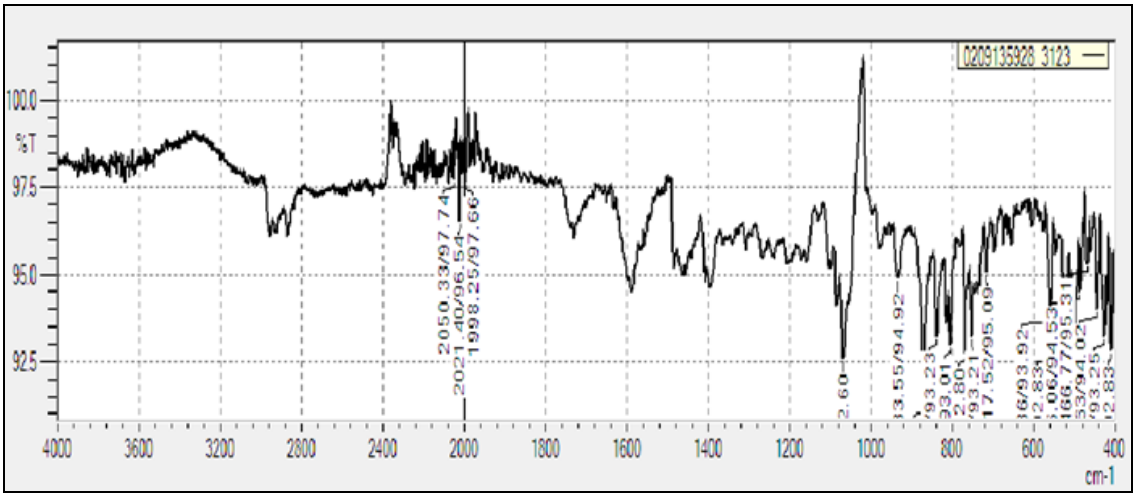

FIG. 3: IR SPECTRUM SPECTRUM OF LUMEFANTRINE DRUG SAMPLE

The following table represents various peaks of different functional groups in Lumefantrine.

TABLE 2: INTERPRETATION OF IR SPECTRUM OF LUMEFANTRINE

Standard peaks (cm^{-1})	Group	Observed peak (cm^{-1})
2200-2000	O-H stretching	2050.33
2000-1900	C=C stretching	1998.25
1250-1020	C-N stretch, aliphatic amines	1068.56
850-700	C-H bending, aromatic	839.63
850-550	C-Cl stretch alkyl halide	752.24

The peaks which were observed were in the corresponding range of standard peak for the respective functional group. Hence the results reveal that the sample refers to Lumefantrine structure.

All the peaks values were found to be near the standard values to confirm the purity of the drug molecule.

Qualitative Solubility Studies: The results of qualitative solubility of Lumefantrine shown in **Table 3** reveal that the drug is freely soluble in dichloromethane, ethyl acetate and chloroform.

Quantitative Solubility Studies: The quantitative solubility of Lumefantrine determined in different solvents was illustrated in **Table 4**.

TABLE 3: QUALITATIVE SOLUBILITY OF LUMEFANTRINE IN VARIOUS SOLVENTS

Solvent	Solubility of Lumefantrine
Water	Practically insoluble
Ethanol	Slightly soluble
Methanol	Slightly soluble
Chloroform	Freely soluble
Acetone	Soluble
Ethyl acetate	Freely soluble
Dichloromethane	Freely soluble
0.1N HCl	Slightly soluble
0.1 N NaOH	Practically insoluble
Phosphate buffer pH7.4	Sparingly soluble

TABLE 4: THE QUANTITATIVE SOLUBILITY OF LUMEFANTRINE IN DIFFERENT SOLVENTS

S. no.	Solvent	Solubility* of Lumefantrine
1	Water	0.0092 mg/ml
2	Acetone	7.214 mg/ml
3	Chloroform	19.53 mg/ml
4	Ethanol	2.744 mg/ml
5	Methanol	2.396 mg/ml
6	Dichloromethane	24.582 mg/ml
7	Ethyl acetate	5.422 mg/ml

*Average of three determinations

pH Dependent Solubility Studies: The pH dependent solubility of Lumefantrine in different phosphate buffers ranging from pH 1.2 to 10 were shown in **Table 5**. Lumefantrine was found to be more soluble at lower pH indicating basic nature of drug.

TABLE 5: pH DEPENDENT SOLUBILITY OF DRUGS IN PHOSPHATE BUFFERS

Solvent (water and different pH of PB)	Lumefantrine solubility* (mg/ml)
Water	0.0092
1.2	0.152
2.2	0.128
4.6	0.102
6.8	0.097
7.4	0.084
8	0.062
9	0.031
10	0.022

PB indicates Phosphate buffer, *Average of three determinations

Solubility of Lumefantine in water was 0.009 mg/ml and that of in that of pH 1.2 was 0.152 mg/ml and hence solubility of Lumefantrine in pH 1.2 was increased by 17 times.

Solubility Studies using Hydrotropes: Hydrotropes or hydrotropic agents are molecules having planar hydrotropic structure brought into solution by a polar group. Hence it seems rational to propose that molecules with a planar hydrophobic part and a polar group, which is not necessarily anionic, can act as hydrotropic agent [15]. The results of hydrotropic solubilization of Lumefantrine were given in **Table 6**.

TABLE 6: SOLUBILITY OF LUMEFANTRINE IN VARIOUS HYDROTROPES

S. no.	Hydrotropic solution	Solubility* of Lumefantrine in mg/ml			
		5% (w/v)	10% (w/v)	20% (w/v)	30% (w/v)
1	Sodium benzoate	0.0034	0.0072	0.0136	0.0185
2	Sodium salicylate	0.0017	0.0031	0.0058	0.0076
3	Sodium gluconate	0.0031	0.0068	0.0112	0.0151
4	Tri-sodium citrate dihydrate	0.0552	0.1059	0.1987	0.2864
5	Urea	0.0041	0.0089	0.0167	0.0243
6	N,N- dimethyl urea	0.0458	0.0905	0.1812	0.2612
7	Ammonium acetate	0.0035	0.0076	0.0149	0.0212
8	L-ascorbic acid	0.0017	0.0038	0.0071	0.0112
9	Piperazine anhydrous	0.0194	0.0422	0.0798	0.1197
10	Pyrogollol	0.0068	0.0148	0.0266	0.0415
11	Pyridoxine HCl	0.0025	0.0048	0.0096	0.0144
12	Nicotinamide	0.0084	0.0181	0.0352	0.0513

*Average of three determinations

Among the different hydrotropes used highest solubility of Lumefantrine was found to be in Tri-sodium citrate dihydrate > N, N- dimethyl urea > Piperazine anhydrous > Nicotinamide > Pyrogollol >Urea> Ammonium acetate > Sodium benzoate. Solubility of Lumefantrine in various hydrotropes was also represented in graphical form in **Fig. 4**.

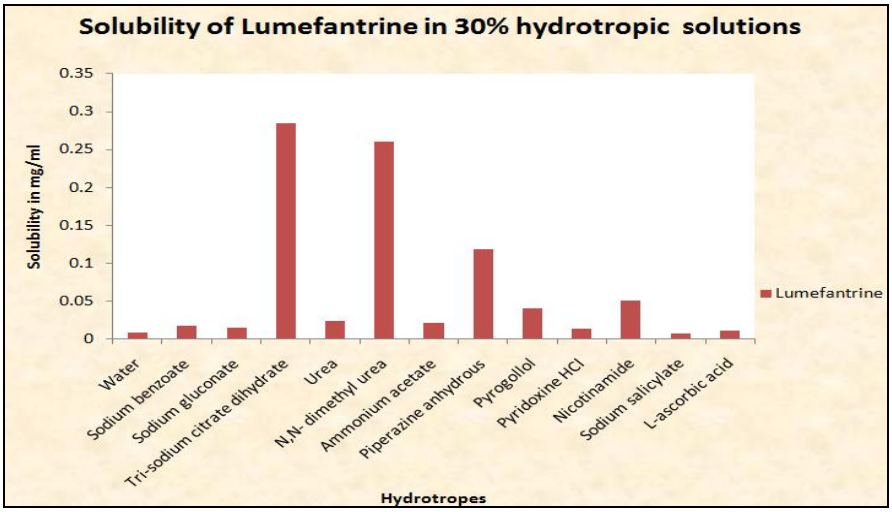

FIG. 4: SOLUBILITY OF LUMEFANTRINE IN 30% HYDROTROPIC SOLUTIONS

Solubility Enhancement Ratio Determination: Solubility enhancement ratio for Lumefantrine was determined and the results were shown in **Table 7**.

TABLE 7: SOLUBILITY ENHANCEMENT RATIO OF LUMEFANTRINE IN VARIOUS HYDROTROPIC SOLUTIONS

S. no.	Hydrotropic solution	Solubility enhancement ratio of Lumefantrine			
		5% (w/v)	10% (w/v)	20% (w/v)	30% (w/v)
1	Sodium benzoate	0.3695	0.7826	1.478	2.011
2	Sodium salicylate	0.1848	0.3369	0.6304	0.8261
3	Sodium gluconate	0.3369	0.7391	1.2173	1.6413
4	Tri-sodium citrate dihydrate	5.722	11.51	21.597	31.13
5	Urea	0.4456	0.9674	1.8152	2.641
6	N,N- dimethyl urea	5.1956	10.597	20.565	30.565
7	Ammonium acetate	0.3804	0.8261	1.619	2.3043
8	L-ascorbic acid	0.1847	0.4130	0.7717	1.217
9	Piperazine anhydrous	2.1087	4.5869	8.6739	13.010
10	Pyrogollol	0.7391	1.6087	2.8913	4.5108
11	Pyridoxine HCl	0.2717	0.5217	1.0434	1.5652
12	Nicotinamide	0.9130	1.9674	3.8260	5.5760

Solubility of Lumefantrine was enhanced in 30% hydrotropic solutions of Tri-sodium citrate dihydrate, N, N- dimethyl urea, Piperazine anhydrous, Nicotinamide, Pyrogollol, Urea, Ammonium acetate and Sodium benzoate. For Lumefantrine, the highest solubility was observed in 30% Tri-sodium citrate dehydrate solution and the solubility enhancement ratio was observed as 31.13 compared to that of water.

CONCLUSION: It can be concluded that the concept of hydrotropic solubilization technique is novel, safe, eco-friendly and economic for enhancing bioavailability of poorly water-soluble drugs. Actually, low aqueous solubility was the major concern for Lumefantrine; hence by the use of hydrotropic solubilization technique not only solubility, dissolution rate increased but also there would be good scope of increase in bioavailability of Lumefantrine.

As a result, daily dose, frequency of administration as well other side effects related to Lumefantrine would be minimized to a great extent.

The solubility studies revealed that the solubility of drug was increased more than 30 folds when added to 30% Tri sodium citrate dihydrate solution and marked its importance in pharmaceutical field.

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