HYDROTROPICSOLUBILIZATION:APROMISINGTECHNIQUETOENHANCESOLUBILITYOFPOORLYWATERSOLUBLE DRUG LUMEFANTRINE

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ABSTRACT: One of the most important parameters for achieving the target concentration in the systemic circulation and improving the pharmacological response is the drug's solubility. When developing new products for oral administration, formulators face the formidable task of increasing solubility, as the majority of currently marketed medications are only weakly soluble in water. When medications have a low water solubility, it may impair their bioavailability and therapeutic effect. The solubility of pharmaceuticals has been the subject of several earlier methods. In addition to these methods, hydrotropic solubilization may be used to increase the solubility of hydrophobic medications by using hydrotropes such as sodium benzoate, urea, piperazine, and others. Because of its low water solubility of 0.009 mg/ml and membership in BCS Class IV, the antimalarial medication lumefantrine was chosen as the model drug in the current experiment. The primary goal of this study was to find a way to make this medicine more water-soluble by using a hydrotropic solubilization approach. Hydrotropes, such as sodium citrate and sodium benzoate, were used in solubility investigations at different concentrations. The findings highlighted the significance of Lumefantrine in the pharmaceutical area, suggesting that its solubility was enhanced by more than 30 times when added to a 30% sodium citrate solution.

Keywords: Lumefantrine, Hydrotropy,Solubility,Sodiumbenzoate, Solubilityenhancementratio

INTRODUCTION:

Drug research and development rely heavily on formulation because of its many advantages. The solubility of drug molecules is the deciding factor in the bioavailability of drugs, which in turn determines the therapeutic effectiveness of drugs. The development of formulations demonstrating high bioavailability is sometimes hindered by the poor water solubility of medications.In order to attain the required concentration of the medication in the systemic circulation and elicit an adequate pharmacological response, solubility is a key criterion to consider during product development. At now, only 8% of potential novel drugs exhibit excellent solubility and permeability.

Past research has explored many methods to improve the water solubility of medications that aren't very water-soluble. These include complexation, cosolvency, emulsions, liposomes, particle size reduction, solid state change, solid dispersions, prodrugs, salt creation, polymeric micelles, and more. One of these methods is hydrotropic solubilization, which involves increasing the aqueous solubility of a solute by adding a significant quantity of a second solution.

Carl Neuberg 1 used the word "hydrotrophy" to characterize the process by which a solute's solubility is enhanced by the incorporation of relatively large quantities of alkali metal salts of different organic acids. One of the several benefits of hydrotropy is that it greatly increases the solubility of pharmaceuticals without the need for chemical modification of hydrophobic medications, organic solvents, or the development of an emulsion system. Hydrotropes such as sodium benzoate, sodium citrate, urea, niacinamide, etc., are used in this process. An other class of solubilizers, hydrotropic compounds, may improve the water solubility of medications that are otherwise insoluble in water. 3. A number of hydrotropic agents, such as urea, nicotinamide, sodium benzoate, sodium salicylate, sodium acetate, piperazine, nicotinamide, and sodium toluate, are used as excipients to enhance the drug's solubility in water.

Lumafantrine was chosen as the model medicine in this case. One effective therapy for resistant P. falciparum malaria is lumefantrine, which is also known as benflumetol. It is a long-acting anti-malarial medication. It suppresses haeme polymerization in the plasmodia's feeding vacuole, making it an erythrocyticschizontocide. Lumefantrine has a low water solubility of 0.009 mg/ml and is a member of BCS Class IV. Therefore, it is important to make the medication more soluble, which might boost bioavailability and lead to a decrease in dosage. Coartem tablets (strength 20/120 mg; artemether) are a common form of artemether used in combination treatment with lumefantrine. lumefantrine) to alleviate the symptoms of malaria. In this case, lumefantrine is a long-acting anti-malarial medicine, while artemether is a short-acting one.

This is why the current study is devoted to developing a hydrotropic solubilization strategy to increase the solubility of lumefantrine. The solubility of Lumefantrine was examined in relation to hydrotropes such as sodium benzoate, sodium citrate, sodium gluconate, ammonium acetate, piperazine, and others.

MATERIALS: Lumefantrinewaskindlygiftedfrom Cipla, Pithampur,India. Sodiumgluconate,PiperazineanhydrousandL-ascorbicacidwerepurchasedfromMolychem,Mumbai,India.Sodiumbenzoate,Tri-sodiumcitratedihydratewerepurchasedfromRankem,Haryana,India.

Sodium salicylate, N, N- dimethyl urea, Pyrogollol,Pyridoxine HCl, Nicotinamide was purchased fromLobaChemie,Mumbai.UreaandAmmoniumacetate were purchased from Qualigens, Mumbai,India. All the chemicals and reagents used were ofanalyticalgrade.

ExperimentalMethods:

UVSpectralStudies: IdentificationofLumefantrine was done by UV SpectrophotometricmethodusingShimadzuSpectrophotometerUV-1800(ShimadzuCorp.,Japan).About20mgofdrug was accurately weighed and dissolved in 200mlofmethanolRbysonicationforabout15minutes. The solution was allowed to cool to roomtemperatureanddilutedfivetimeswithmethanol R. The absorption spectrum of the diluted solutionwhen observed between 275 and 325nm, exhibits amaximum at about 302 nm; the specific absorbance(A1% 1cm) is between314 and 348[14].

PreparationofCalibrationCurveofLumefantrine in 0.1 M methanolicHCl (λ_{max} 332nm): Standard stock solution of Lumefantrine waspreparedbydissolving 100mg ofdrugin100ml of 0.1MmethanolicHCl(1000µg/ml).Fromtheabove stock solution 10 ml was taken and dilutedupto 100 ml in methanolicHCl (100 µg/ml). Fromthe above solution 1, 2, 3, 4, 5 and 6 ml was takenanddilutedupto10mlwith0.1MmethanolicHClto get concentrations ranging from 10 to 60 µg/mlof Lumefantrine. Absorbance was noted using UV-VIS Spectrophotometer at λ_{max} of 332 nm againstblank (methanolicHCl).Calibration curve valuesof Lumefantrine in methanolicHCl (λ_{max} 332 nm)were given in **Table 1** and also graph plotted wasshownin **Fig. 2**.

IRAnalysis: TheIRanalysisofLumefantrinesamplewascarriedoutusingIRAffinity-1(ShimadzuCorp.,Japan).Here,diamondisthepreferredchoice for most applications because ofits robustness and durability. The solid material isplacedontothesmallcrystalareaandthenthepressure arm is positioned over the crystal/samplearea.

Force is applied on to the sample, pushing it ontothe diamond surface. Transmittance was measuredfromwavenumber4000cm^{-1}to400^{-1}applyingHapp-Genselapodization.

QualitativeSolubilityStudies: Qualitativesolubility analysis for Lumefantrine was done bydissolving10mgofdrugin10mlofsolvent(aqueous/nonaqueous)takeninconicalflask.After shaking, the samples were examined for thepresenceofanyundissolvedsuspendedparticlesand clarity. The results of qualitative solubility ofLumefantrine in various solvents were reported in**Table 3**.

QuantitativeSolubilityStudies: Anexcessamount of solute is dissolved in 10 ml of selectedsolventtillsaturatedsolutionwasobtained.Theconicalflaskswerestopperedandagitatedinthermostatically controlledorbitalshaker(Tanco,Pitampura,NewDelhi,India)at25±1°C.After24 hrs equilibrium was attained and the sampleswere filtered through Whatman filter paper (No.1).The individual samples were analyzed after suitabledilutiontodetermineconcentrationofdrugdissolved using UV-VIS spectrophotometer [4]. Thesolubility study was carried out in triplicate and theobservationsweregivenin**Table4**.

pHDependentSolubilityStudies: Anexcessquantity of drug was added to a series of stopperedconical flasks containing 10 ml of phosphate buffersolutions (of varying pH) until saturated solutionwas obtained. The flasks were mechanically shakenat room temperature for 24 hrs, in thermostaticallycontrolledorbitalshaker(Tanco,Pithampura,Delhi)at25±1°C.Thesesuspensionswerefilteredthr oughWhatmanfilterpaper(No.1).[4]AliquotsoffiltrateobtainedweredilutedwithdistilledwaterandanalyzedusingU Vspectrophotometerat332nmagainstblank.Thesolubility study was carried out in triplicate and theresultswereshown in**Table 5**.

Solubility Studies using Hydrotropes: An excessquantity of drug was added to a series of stopperedconicalflaskscontaining10mlofhydrotropicsolutions until saturated solution was obtained. Theflaskweremechanicallyshakenatroomtemperaturefor12hrs,inthermostaticallycontrolledorbitalshaker(T anco,Pithampura,Delhi)at25±1°C.ThesesuspensionswerefilteredthroughWhatmanfilterpaper(No.1)[4].Aliquo tsoffiltrateobtainedweredilutedwithsuitable quantity of required solvent and analyzedusingUVspectrophotometerat332nm.Thesolubility study wascarriedoutintriplicateandobservationswereshowninTable 6.

SolubilityEnhancementRatioDetermination: Solubility enhancement ratio is another parameterthatdeterminestheextenttowhichthedrugissoluble in a particular solvent compared to that ofwater.The solubility enhancementratiosfor drugin different hydrotropic solutions were calculatedandtheresults wereshown in**Table 7**.

Solubilityenhancementratiowascalculatedbyusingfollowingformula:

Solubilityenhancementratio=Solubilityinhydrotropicsolution/ Solubilityin water

RESULTSANDDISCUSSION:

UV Spectral Studies: UV spectroscopic analysisforthedrugwasperformedandthemaximumabsorption*i.e.* λ_{max} ofLumefantrine was observedat 332 nm Lumefantrine. UV analysis was carriedout using 0.1M methanolicHCl as the drug is notcompletely soluble in methanol and require acidicenvironment because it is weakly basic in nature.Thedrugspectrum was shown in **Fig. 1**.

FIG.1:UVSPECTRUMOFLUMEFANTRINEIN0.1MMETHANOLICHCl

Preparation of Standard Curve of Lumefantrinein0.1MmethanolicHCl(λ_{max}332nm): Calibration curve in of Lumefantrine was plottedusing0.1MmethanolicHClatλ_{max}of332nmandthe readings were shown in**Table 1**. The linearstandard curve of Lumefantrine including the graphequationwas depicted in**Fig.2**.

TABLE1:STANDARDCURVEOFLUMEFANTRINEIN0.1MMETHANOLICHCl(λ_{max}332nm)

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

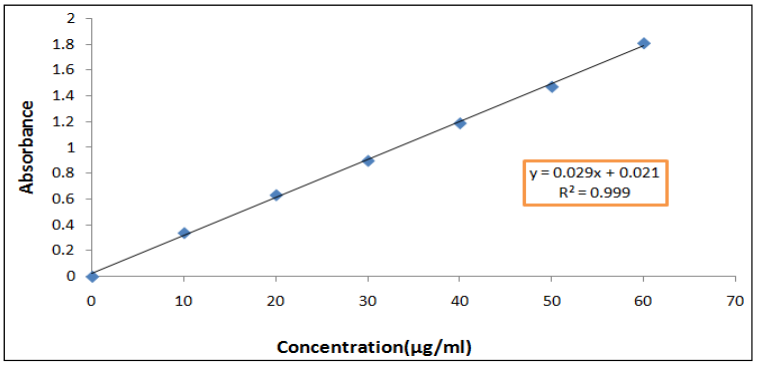

FIG.2:STANDARDCURVEOFLUMEFANTRINEIN0.1MMETHANOLICHCl(λ_{max}332nm)

IRAnalysis: TheIRSpectraofsamplesofLumefantrinewereshowninFig.3.Thecharacteristicpeaksattributabletovarious

functionalgroupspresentindrugmoleculewererecordedin**Table 2**.

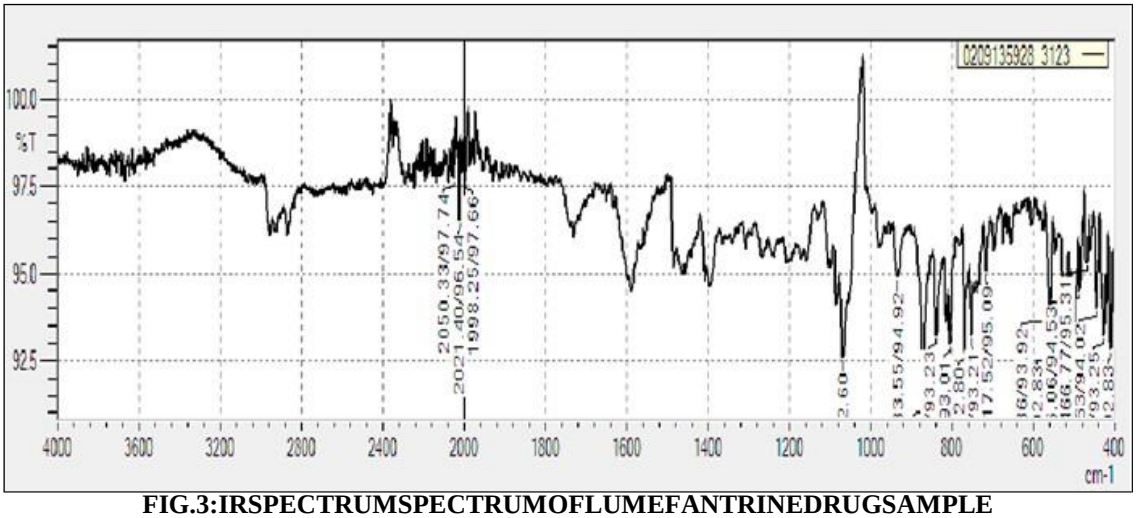

FIG.3:IRSPECTRUMSPECTRUMOFLUMEFANTRINEDRUGSAMPLE

Thefollowingtablerepresentsvariouspeaksofdifferentfunctionalgroupsin Lumefantrine.

TABLE2:INTERPRETATIONOFIRSPECTRUMOFLUMEFANTRINE

Standardpeaks(cm^{-1})	Group	Observedpeak(cm^{-1})
2200-2000	O-Hstretching	2050.33
2000-1900	C=Cstretching	1998.25
1250-1020	C-Nstretch,aliphaticamines	1068.56
850-700	C-Hbending,aromatic	839.63
850-550	C-Clstretchalkylhalide	752.24

Thepeakswhichwereobservedwereinthecorrespondingrangeofstandardpeakfortherespectivefunctionalgroup.Hencetheresultsrevealthatthesamplereferstolumefantrinestructure.

Allthepeaksvalueswerefoundtobenearthestandard values to confirm the purity of the drugmolecule.

QualitativeSolubilityStudies: TheresultsofqualitativesolubilityofLumefantrineshowninTable 3 reveal that the drug is freely soluble indichloromethane,ethylacetateandchloroform.

Quantitative Solubility Studies: The quantitativesolubility of Lumefantrine determined in differentsolvents was illustrated in **Table 4**.

TABLE3:QUALITATIVESOLUBILITYOFLUMEFANTRINEINVARIOUSSOLVENTS

Solvent	SolubilityofLumefantrine
Water	Practicallyinsoluble
Ethanol	Slightlysoluble
Methanol	Slightlysoluble
Chloroform	Freelysoluble
Acetone	Soluble
Ethylacetate	Freelysoluble
Dichloromethane	Freelysoluble
0.1NHCl	Slightlysoluble
0.1 NNaOH	Practicallyinsoluble
PhosphatebufferpH7.4	Sparinglysoluble

TABLE4:THEQUANTITATIVESOLUBILITYOFLUMEFANTRINEINDIFFERENTSOLVENTS

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

*Averageofthreedeterminations

pHDependentSolubilityStudies: ThepHdependent solubility ofLumefantrine in differentphosphatebuffersrangingfrompH1.2to10were shown in **Table 5**. Lumefantrine was found to bemore soluble at lower pH indicating basic nature ofdrug.

TABLE5:pHDEPENDENTSOLUBILITYOFDRUGSINPHOSPHATEBUFFERS

Solvent(wateranddifferentpHofPB)	Lumefantrinesolubility*(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

PBindicatesPhosphatebuffer,*Averageofthreedeterminations

SolubilityofLumefantineinwaterwas0.009mg/mlandthatofinthatofpH1.2was0.152mg/mlandhencesolubilityof LumefantrineinpH
1.2 was increased by17 times.

SolubilityStudiesusingHydrotropes: Hydrotropes orhydrotropicagentsaremoleculeshavingplanarhydrotropicstructurebroughtintosolutionbyapolar group. Hence it seems rational to propose thatmoleculeswithaplanarhydrophobicpartandapolar group, which is not necessarily anionic, canactashydrotropicagent[15].TheresultsofhydrotropicsolubilizationofLumefantrineweregivenin **Table 6**.

TABLE6:SOLUBILITYOFLUMEFANTRINEINVARIOUSHYDROTROPES

S.no.	Hydrotropicsolution	Solubility*ofLumefantrineinmg/ml			
		5%(w/v)	10%(w/v)	20%(w/v)	30%(w/v)
1	Sodiumbenzoate	0.0034	0.0072	0.0136	0.0185
2	Sodiumsalicylate	0.0017	0.0031	0.0058	0.0076
3	Sodiumgluconate	0.0031	0.0068	0.0112	0.0151
4	Tri-sodiumcitratedihydrate	0.0552	0.1059	0.1987	0.2864
5	Urea	0.0041	0.0089	0.0167	0.0243
6	N,N-dimethylurea	0.0458	0.0905	0.1812	0.2612
7	Ammoniumacetate	0.0035	0.0076	0.0149	0.0212
8	L-ascorbicacid	0.0017	0.0038	0.0071	0.0112
9	Piperazineanhydrous	0.0194	0.0422	0.0798	0.1197
10	Pyrogollol	0.0068	0.0148	0.0266	0.0415
11	PyridoxineHCl	0.0025	0.0048	0.0096	0.0144
12	Nicotinamide	0.0084	0.0181	0.0352	0.0513

*Averageofthreedeterminations

Amongthedifferenthydrotropesusedhighestsolubility of Lumefantrine was found to be in Tri-sodium citrate dihydrate> N, N- dimethyl urea >Piperazineanhydrous>Nicotinamide>Pyrogollol >Urea>Ammoniumacetate>Sodiumbenzoate.Solubility of Lumefantrine in various hydrotropeswasalsorepresentedin graphicalforminFig. 4.

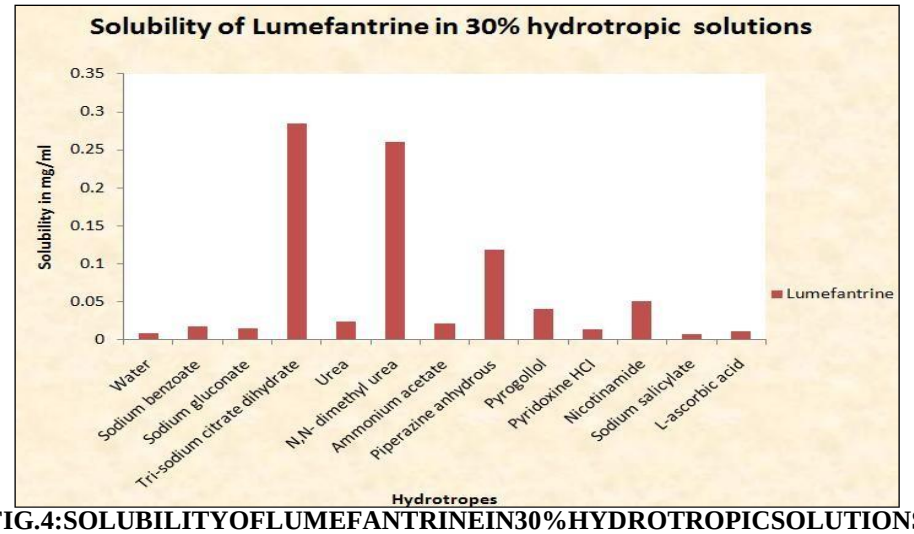

FIG.4:SOLUBILITYOFLUMEFANTRINEIN30%HYDROTROPICSOLUTIONS

SolubilityEnhancementRatioDetermination: SolubilityenhancementratioforLumefantrinewasdetermined and theresults wereshown in**Table 7**.

TABLE7:SOLUBILITYENHANCEMENTRATIOOFLUMEFANTRINEINVARIOUSHYDROTROPICSOLUTIONS

S.no.	Hydrotropicsolution	SolubilityenhancementratioofLumefantrine			
		5%(w/v)	10%(w/v)	20%(w/v)	30%(w/v)
1	Sodiumbenzoate	0.3695	0.7826	1.478	2.011
2	Sodiumsalicylate	0.1848	0.3369	0.6304	0.8261
3	Sodiumgluconate	0.3369	0.7391	1.2173	1.6413
4	Tri-sodiumcitratedihydrate	5.722	11.51	21.597	31.13
5	Urea	0.4456	0.9674	1.8152	2.641
6	N,N-dimethylurea	5.1956	10.597	20.565	30.565
7	Ammoniumacetate	0.3804	0.8261	1.619	2.3043
8	L-ascorbicacid	0.1847	0.4130	0.7717	1.217
9	Piperazineanhydrous	2.1087	4.5869	8.6739	13.010
10	Pyrogollol	0.7391	1.6087	2.8913	4.5108
11	PyridoxineHCl	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%hydrotropicsolutionsofTri-sodiumcitratedihydrate,N,N-dimethylurea,Piperazineanhydrous,Nicotinamide,Pyrogollol,Urea,AmmoniumacetateandSodiumbenzoate.ForLumefantrine,thehighestsolubilitywasobservedin 30% Tri-sodium citrate dehydrate solution andthesolubilityenhancementratiowasobservedas 31.13comparedtothatofwater.

CONCLUSION: To improve the bioavailability of pharmaceuticals that are not very water-soluble, the hydrotropic solubilization approach offers a new, safe, environmentally friendly, and cost-effective solution. The primary issue with Lumefantrine was its poor water solubility; however, the hydrotropic solubilization process improved both its solubility and dissolving rate, and it also offered promising opportunities to boost the bioavailability of the drug.

This would significantly reduce the need for daily dosing, administration frequency, and other Lumefantrine adverse effects.

Research on medication solubility found that adding it to a 30% Tri sodium citrate dihydrate solution boosted its solubility by more than 30 times, highlighting the compound's significance in the pharmaceutical industry.

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