RESEARCH ARTICLE

Solubility and Taste Masked Behaviour of Cyclodextrin Molecular Inclusion Complex of Lumefantrin

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ABSTRACT

Lumefantrine is an antimalarial drugs used especially for pediatric persons. β-Cyclodextrine is used to improve the taste of lumefantrine by forming complexes with them by the solvent evaporation method, respectively. β-Cyclodextrine prevent the release of drug in the saliva. Lumefantrine is a bitter drug. So masking of bitter taste in the formulation is a prerequisite as it improves the compliance of the patient and product value. Lumefantrine with β-cyclodextrin in a drug-polymer ratio 1:1 gave complete taste masking with a satisfactory result obtained in term of *in-vivo* and *in-vitro* evaluation visual inspection revealed that lumefantrine was yellow-crystalline. The melting point of lumefantrine was found to be 127°C, respectively. The standard calibration curve of Lumefantrine shows a slope 0.0108 and a correlation coefficient of 0.9997. Compatibility studies show that drugs are compatible with polymers. Solubility study show that the solubility of both drugs are increased in phosphate buffer 6.8 by successfully forming a complex with β-cyclodextrin. The solubility of lumefantrine in saliva (pH 6.8) is 0.408 mg/mL, after complex forming with β-cyclodextrine the solubility of (Lumefantrine complex) is 0.526 mg/mL. In an i*n-vitro* drug release investigation, taste masking occurs when the amount of drug substance in dissolved media is either below the detection threshold for recognizing its taste or is undetectable in the early time points (between 0 and 5 minutes). Taste masking (Taste perception test) 11 volunteers are selected for this test, results show that complex is taste masked successfully. Lumefantrine with β-Cyclodextrine complex is a hopeful approach to enhance solubility, dissolution and drug taste.

Keywords: Antimalarial, Lumefantrine, β-cylcodexrine, Solubility enhancement, Taste masking

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INTRODUCTION

While lumefantrine is an important part of artemisinin-based combination medicine for treating malaria, it has some problems, such as not dissolving well in water and not passing through cells easily. To enhance its solubility profile, this research looked into a lumefantrine-β-cyclodextrin complex. Lumefantrine has low water solubility, yet the inclusion complex could help the medicine be absorbed by the body and have a more beneficial effect on patients.[1] The crystalline malaria pigment hemozoin forms as a result of this binding process and prevents the haem from being detoxified. Free hemoglobin builds up and kills the parasites. When used in conjunction with artemisinin, lumefantrine becomes an essential part of the treatment. Combining it with artemether makes it a more effective oral antimalarial drug for both adults and children. It has been shown to enhance the efficacy of lumefantrine by reducing the prevalence of lingering *Plasmodium*. The prolonged half-life of lumefantrine's elimination makes it useful for prophylaxis after treatment has ended. Concerns persist concerning its limited bioavailability after oral administration due to its association with low aqueous solubility. The biopharmaceutical categorization system (BCS) places lumefantrine in class IV because of its low permeability and low aqueous solubility (0.02 mg/mL).[2]

Cyclodextrins (CDs) are similar to molecular-sized empty capsules. They are cyclic oligosaccharides formed from the breakdown of starch by cyclodextrin gluconotransferase (CGTase). Successful commercial CDs include those with 6, 7, or 8 glucose molecules. These are known as α-CDs, β-CDs, and γ-CDs, respectively. Critical to CDs' usefulness is their ability to create a "inclusion complex" with a wide range of hydrophobic guest molecules. This combination seals off the hydrophilic hydroxyl groups on the cyclodextrin's surface while exposing the hydrophobic functionality in its internal cavity. The hydrophobic visitor molecule is physically a part of one of the molecules, called the "host," either whole or partially.[3]

The structural formula Lumefantrine and β-Cyclodextrine is shown in Figures 1 and 2.

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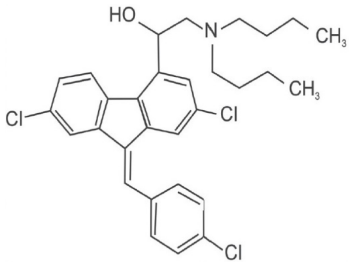

Figure 1: Lumefantrine

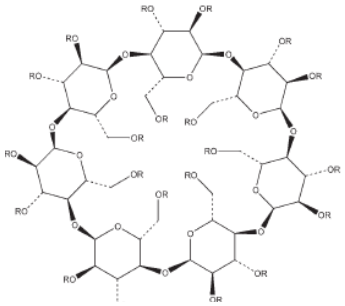

Figure 2: β-Cyclodextrine

MATERIAL AND METHODS

Preparation of Standard Calibration Curve of Lumefantrine

lumefantrine stock solution (1000 µg/mL) was prepared using dichloromethane. To make a solution with a concentration of 100 ng/mL, remove 1-mL with a pipette and add 10 mL of phosphate buffer 6.8. Concentrations of 5 to 25 µg/mL were obtained by pipetting 0.5 to 2.5 mL of stock solution into a 10.0 mL volumetric flask and bringing the volume up to 10 mL with mobile phase (phosphate buffer 6.8). After being sonicated for 5 minutes, the entire sample was run through a UV spectrophotometer and scanned between 200 and 400 nm. λmax was traced and calibration curve was constructed.[4]

Determination of Solubility

Lumefantrine are free soluble in dichloromethane, methanol and practically insoluble in water.

Drug Excipients Compatibility Study

This research was conducted to ensure there would be no negative interactions between the medicine and the excipients by analyzing their IR spectra. We captured the spectrum from 4000–400 cm^{-1}. In these tests, the medication was combined with each excipient at a 1:1 ratio.

Preparation of Lumefantrine-β-Cyclodextrine Complex

Lumefantrine- β-Cyclodextrine complex is prepared by solvent evaporation technique in ratio 1:1 Drug: Polymer, respectively. In this method, the drug is dissolved in dichloromethane and β-Cyclodextrine in water both separately, then mix both solutions together and finally evaporating the solvent under a vacuum at 45°C for 24 hours. The dried product is sieved through 60 µm mesh.[5]

Evaluation of Complex

Drug content of lumefantrine - β-cyclodextrine complex

- *Preparation of standard solution-Lumefantrine*

Prepare a standard solution by carefully weighing 10 mg of Lumefantrine into a 10 mL dry volumetric flask and bringing the volume up to 10 mL with phosphate buffer 6.8. Sonicating the standard solution for 5 minutes and then analyzing it at 240 nm allowed for a more accurate reading from the UV spectrophotometer.[6]

- *Preparation of test solution-Lumefantrine complex*

Prepare a test solution by carefully placing 20 mg of lumefantrine complex in a 10 mL dry volumetric flask and bringing the volume up to 10 mL with phosphate buffer 6.8. Sonicating the standard solution for 5 minutes and then analyzing it at 240 nm allowed for a more accurate reading from the UV spectrophotometer.[7]

Drug content was determined by the following equation:

$$\text{Drug Content} = \frac{\text{Absorbance of test solution}}{\text{Absorbance of standard solution}} \times 100$$

Taste Masking Evaluation of Complexes

In-vitro drug release

The complex form between Lumefantrine with β-cyclodextrine in the ratio 1:1. Then complexes 240 mg is filled in the empty capsule shell. The dissolution medium is phosphate buffer 6.8, the capsule is placed in a basket separately and rotated at 50 rpm having a temperature of 37.5°C. Lumefantrine absorption notice at 234 cells for the evacuation of liquid from both jars at 5 minutes interval and the creation of up to 10 mL with phosphate buffer 6.8. Taste masking occurs when the drug ingredient in the dissolving medium is either undetectable or discovered in quantities below that at which it can be identified by taste in early time points (between 0 and 5 minutes).[8]

Taste perception test

A taste perception test was conducted to see how effective inclusion complexation is at masking flavors. Lumefantrine, a bitter medication, seems to work by binding to taste-bud receptors on the tongue. The drug's harsh taste is blocked since β-CD encapsulates it. Because lumefantrine prevents attachment to taste bud receptors, it lessens bitter tastes. The pleasant aftertaste of β-CD also helps to mask the bitterness. Lumefantrine was successfully complexed in the hydrophobic cavity of β-CD utilizing the kneading process and solvent evaporation method, which aid in preventing direct interaction of pharmaceuticals with taste bud receptors. Eleven people are chosen at random to take a taste test. The medicines were kept in the mouths of the volunteers for 5 seconds. After swallowing the drugs, the volunteers spit them back out and rated how bitter they tasted. The mouth was washed with tap water after each test to get rid of any leftover samples in the

mucosa. After 5 seconds, volunteers rated how the complexes tasted in their mouths.[9]

Solubility study of Lumefantrine and its Complexes

Fifty milligrams of the medication was diluted into ten milliliters of phosphate buffer 6.8, the sample was filtered and analyzed at 234 nm spectrophotometrically using a UV spectrophotometrically. Similarly 100 mg of complex 10 mL of phosphate buffer 6.8, the sample was filtered and analyzed at 234 nm spectrophotometrically using a UV spectrophotometrically. Both readings were compared.[10]

RESULT AND DISCUSSION

Standard Calibration Curve

The absorbance versus concentration calibration curve was plotted to obtain the lumefantrine standard curve. The absorbance values are given in Table 1 and Figure 3. Standard calibration curve shows a slope 0.0108 and a correlation coefficient of 0.9997.

R	=	0.9997
Slope	=	0.0108

Determination of Solubility

The solubility of lumefantrine were shown in Table 2. Lumefantrine is free soluble in dichloromethane, methanol and practically in soluble in water.

From IR-spectrum of lumefantrine and β-cyclodextrine, it is clear that, there is no appreciable change in the positions of bonds of lumefantrine and β-cyclodextrine (Table 3 and Figures 4-6). It can be concluded that, the lumefantrine maintains its identity in pure form without undergoing any chemical interaction, So all the aspects show that there is no incompatibility between lumefantrine and β-cyclodextrine.

Evaluation of Complex

Drug content

Drug contented was found to be 96.25% for Lumefantrine, respectively.

Taste Masking Evaluation for Complex

In-vitro drug release study for lumefantrine

The drug substance, lumefantrine, was detected in the dissolution media (phosphate buffer 6.8) in the early stages from 0 to 5 minutes, although the observed amount was below the threshold value. So, the drug is not bind to the taste receptor in 0 to 5 minutes which prevents the fullness of the bitter taste

Table 1: Standard calibration readings of lumefantrine

Concentration (mg/mL)	*Readings*
5	0.090
10	0.142
15	0.200
20	0.252
25	0.305

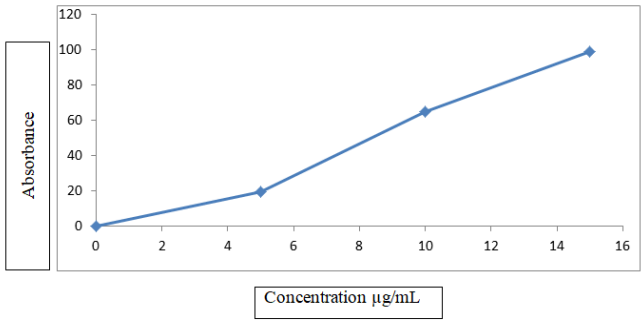

Figure 3: Standard calibration curve of lumefantrine in phosphate buffer 6.8

Table 2: Solubility of lumefantrine

S. No	*Drug*	*Soluble*	*Insoluble*
1	Lumefantrine	Dichloromethane, Methanol	Water

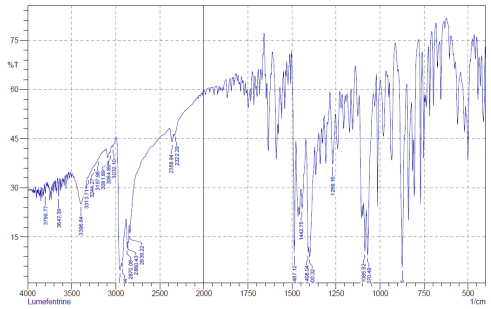

Figure 4: IR of lumefantrine pure drug

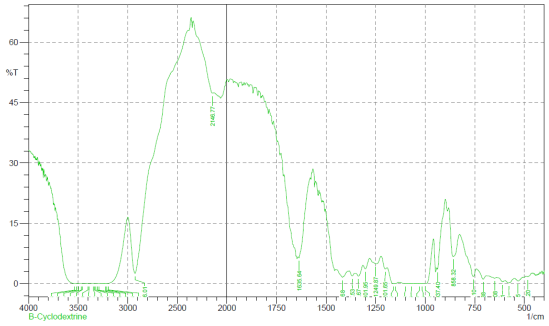

Figure 5: IR spectra of β-cyclodextrine

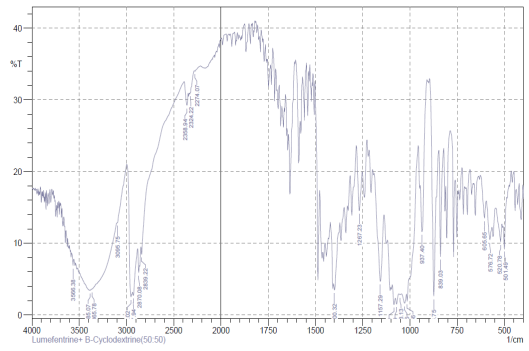

Figure 6: IR spectra of lumefantrine + β-cyclodextrine

Table 3: IR interpretation

S. No	*Functional group*	*Lumefantrine (cm^{-1})*	*B-cyclodextrine (cm^{-1})*	*Complex (cm^{-1})*
1	Alcoholic O-H	3610–3645	--	3610–3645
2	Intramole H Bond	3600–4350	--	3600–4350
3	Intermole H Bond	3500–3200	--	3500–3200
4	Tertitery amine	1250–1020	--	1250–1020
5	Alkyl C-H	3000–2800	--	3000–2800
6	Alcoholic O-H	--	3500–3200	--
7	Alcoholic C-O	--	1250–1050	--

Table 4: *In-vitro* drug release study for Lumefantrine

S. No	*Time (min)*	*%Drug release of Lumefantrine*
1	0	0
2	5	19.32
3	10	64.98
4	15	98.76

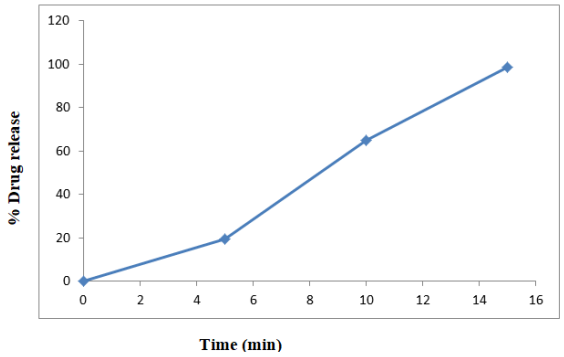

Figure 7: %release of drug Lumefantrine taste perception test

Table 5: Bitterness evaluation results (For pure drug)

S. No.	*Drugs*	*0 (Tasteless)*	*1 (Slightly bitter)*	*2 (Moderately bitter)*	*3 (Strong bitter)*
1	Lumefantrine	--	--	3	8

of the drug thus it shows that taste masking is achieved for Lumefantrin (Table 4 and Figure 7).

The data highlighted in bold indicate that most participants reported a comparable degree of bitterness (Tables 5 and 6). Eleven healthy volunteers took 30 seconds to hold the medication in their mouths and report how it tasted. Volunteers' opinion for bitter levels was recorded by giving different score value i.e.

0 = Tasteless, 1 = Slightly bitter

2 = Moderately bitter 3 = Strong bitterness

From Table 5, for lumefantrine pure drug most of the volunteers opinion that it was strongly bitter in taste.

Table 7: Solubility studies of pure drug and drug complex

S. No.	*Drug/Complex*	*Solubility (mg/mL)*
1	Lumefantrine drug	0.408
2	Lumefantrine + β-cyclodextrine complex	0.526

The results highlighted in bold indicate that a majority of participants found the same degree of sweetness in their samples. Eleven healthy participants took 30 seconds to hold the medication in their mouths and report how it tasted. Volunteer's opinion for taste level was recorded by giving different score value, i.e.,

An algebraic measure was used with the following values:

0 = Tasteless 1 = Bitter

2 = Slightly bitter 3 = Slightly sweet 4 = Sweet

From Table 6, for the lumefantrine complex most of the volunteers opinion that it was slightly sweet in taste.

Solubility Studies

Solubility studies were carried in buffer solution pH 6.8 (Table 7). The solubility of lumefantrine + β-cyclodextrin complex has shown the highest solubility in buffer pH 6.8 (0.526 mg/mL) as compared with the pure drug, i.e., lumefantrine (0.408 mg/mL). From above it shows that the complexes were formed have good solubility in phosphate buffer 6.8 as compared with pure drug.

Lumefantrine is an antimalarial drug used especially for pediatric persons. Lumefantrine is a bitter drug. So masking of bitter taste in the formulation is a prerequisite as it improves the compliance of the patient and product value. β- Cyclodextrine is used to improve the taste of lumefantrine by forming complexes with them by solvent evaporation method, respectively. β-Cyclodextrine prevent the release of drug in the saliva.

The result obtained shows that the drug-polymer complex prepared with β-cyclodextrine in a drug-polymer ratio 1:1 gave complete taste masking with satisfactory results obtained in terms of *in-vivo* and *in-vitro* evaluation visual inspection revealed that lumefantrine was yellow crystalline. It is intensely bitter. The melting point of lumefantrine was found to be 127°C, respectively. The standard calibration curve of lumefantrine

Table 6: Bitterness evaluation results (For complex)

S. No	*Complexes*	*0 (Tasteless)*	*1 (Bitter)*	*2 (Slightly bitter)*	*3 (Slightly sweet)*	*4 (Sweet)*
1	Lumefantrine complex	--	-	01	10	--

shows a slope 0.0108 and a correlation coefficient of 0.9997. Compatibility studies show that drugs are compatible with polymers. Solubility study shows that the solubility of both drugs are increased in phosphate buffer 6.8 by successfully forming a complex with β-cyclodextrin.

The solubility of lumefantrine in saliva (pH 6.8) is 0.408 mg/mL. After the complex forms with β-cyclodextrine, the solubility of (Lumefantrine complex) is 0.526 mg/mL. From 0 to 5 minutes, when the drug substance is first added to the dissolving medium, either it can't be found or its amount is too low to be able to tell what it tastes like (by *in-vitro* drug release study). Taste masking (Taste perception test). Eleven volunteers are selected for this test, results show that the complex is taste masked successfully.

CONCLUSION

From the results of these studies, it's possible to increase the solubility and to mask the bitter taste of both drugs by forming complexes (Lumefantrin with β-Cyclodextrine by Solvent Evaporation Method). Lumefantrine with β-Cyclodextrine complex could consequently verify beneficial in the design of novel medicinal Lumefantrine formulation to provoke blight of malaria.

REFERENCES

1. Walsh J, Cram A, Woertz K, Breitkreutz J, Winzenburg G, Turner R, Tuleu C, European Formulation Initiative. Playing hide and seek with poorly tasting paediatric medicines: do not forget the excipients. Advanced drug delivery reviews. 2014 Jun 30;73:14-33.
2. Zheng X, Wu F, Hong Y, Shen L, Lin X, Feng Y. Developments in taste-masking techniques for traditional Chinese medicines. Pharmaceutics. 2018 Sep 12;10(3):157.
3. Pawar S, Shende P. A comparative outlook on pharmacokinetics and antimalarial studies of artemether and lumefantrine-loaded microneedle patches and a dry suspension containing nanosponges. Journal of Drug Delivery Science and Technology. 2020 Dec 1;60:102055.
4. Deng J, Chen QJ, Li W, Zuberi Z, Feng JX, Lin QL, Ren JL, Luo FJ, Ding QM, Zeng XX, Ma L. Toward improvements for carrying capacity of the cyclodextrin-based nanosponges: recent progress from a material and drug delivery. Journal of Materials Science. 2021 Apr;56:5995-6015.
5. Khater AJ, Almurisi SH, Mahmood S, Alheibshy F, Alobaida A, Abdul-Halim N, Chatterjee B. A review on taste masked multiparticulate dosage forms for paediatric. International journal of pharmaceutics. 2022 Dec 29:122571.
6. Iravani S, Varma RS. Nanosponges for drug delivery and cancer therapy: Recent advances. Nanomaterials. 2022 Jul 16;12(14):2440.
7. Utzeri G, Matias P, Murtinho D, Valente AJ. Cyclodextrin-based nanosponges: Overview and opportunities. Frontiers in Chemistry. 2022 Mar 24;10:859406.
8. Salazar Sandoval S, Bruna T, Maldonado-Bravo F, Bolaños K, Adasme-Reyes S, Riveros A, Caro N, Yutronic N, Silva N, Kogan MJ, Jara P. β-Cyclodextrin Nanosponges Inclusion Compounds Associated with Silver Nanoparticles to Increase the Antimicrobial Activity of Quercetin. Materials. 2023 May 5;16(9):3538.
9. Kekani LN, Witika BA. Current advances in nanodrug delivery systems for malaria prevention and treatment. Discover Nano. 2023 Apr 20;18(1):66.
10. Garnero C, Zoppi A, Aloisio C, Longhi MR. Technological delivery systems to improve biopharmaceutical properties. InNanoscale Fabrication, Optimization, Scale-Up and Biological Aspects of Pharmaceutical Nanotechnology 2018 Jan 1 (pp. 253-299). William Andrew Publishing.