RESEARCH ARTICLE

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

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ABSTRACT

Artemether by forming a complex with β-cyclodextrine (βCD) is used to improve solubility and taste masked by the kneading method. Artemether with β-cyclodextrine complex prepared with βCD in a drug-polymer ratio 1:1 gave complete taste masking with the satisfactory result obtained in term of *in-vivo* and *in-vitro* evaluation. The standard calibration curve of Artemether shows a slope of 0.0154 and a correlation coefficient of 0.9992. Compatibility studies show that drugs are compatible with polymers. Solubility studies show that the solubility of drug are increased in Phosphate buffer 6.8 by successfully forming a complex with βCD. *In-vitro* dissolution results showed that a maximum of 97.05% of Artemether, drug release less than 15 minutes in formulation. The solubility of Artemether in saliva (PH 6.8) is 0.00735 mg/mL, After complex forming with β-cyclodextrin the solubility of (Artemether complex) is 0.124 mg/mL. *In-vitro* drug release investigation, taste masking occurs when the amount of drug substance in the dissolve medium is either not identified or is below the threshold for recognizing its flavor in the early time points (between 0 and 5 minutes). Taste masking (Taste perception test) 11 volunteers were selected for this test, results show that complex is taste masked. Artemether with βCD complex is a hopeful method to augment the solubility, dissolution and taste masking of the drug.

Keywords: Antimalarial, *β*-cylcodexrine, Solubility Enhancement, Taste Masking

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INTRODUCTION

Malaria has a devastating effect on people in tropical and subtropical areas. Between 1.5 and 2.7 million people die every year, and it is believed that there are 300 to 500 million clinical cases. Most malaria deaths can be traced back to the protozoan *Plasmodium falciparum*. Due to extensive drug resistance caused by older, quinine-dominated regimens, artemisinin-based chemotherapy has replaced quinine as the gold-standard treatment for malaria. Among the artemisinin derivatives, 1,2-benzodioxepin is lipid-soluble and has shown efficacy in treating malaria, particularly malignant malaria. Artemether changes the ultrastructure, disrupts the function of the mitochondria, and stops *P. falciparum* from absorbing nutrients. This causes them to lose cytoplasm and nutrients, which they can't get back, and they die soon after. The effectiveness of artemether in treating malaria is now under review. Its clinical potential is constrained by its insolubility in water. This research is meant to aid in the expansion of an inclusion complex of artemether with βCD that can increase the drug's solubility and oral bioavailability.[1]

The WHO recognizes artemether as an important drug due to its efficacy in treating severe, multi-resistant malaria. It is effective against *P. vivax* and *P. falciparum*, including chloroquine-sensitive and chloroquine-resistant strains, and has been licensed for the treatment of cerebral malaria. Artemether is broken down into dihydroartemisinin, which is then used by the body. By blocking both nucleic acid and protein synthesis, the medication is effective against *P. falciparum* in its erythrocytic phases. For maximum effectiveness, lumefantrine is given together with artemether. Artemether starts working quickly and leaves the body just as quickly. Artemether is considered to relieve malaria symptoms quickly by decreasing parasite numbers. Produces cytotoxic radical species via contact by ferriprotoporphyrin IX ("heme") or ferrous ions in acidic parasite food vacuole. Here is a byproduct of hemoglobin breakdown that is released during the proteolysis of red blood cells, and it is widely believed that peroxide antimalarials work by interacting with this peroxide. It is hypothesized that a wide variety of potentially dangerous oxygen and carbon-centered radicals are formed as an outcome of this interaction.[2]

The molecular size of cyclodextrins (CDs) allows them to be thought of as empty capsules. They are derived from starch degradation by the enzyme cyclodextrin gluconotransferase

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(CGTase) and are cyclic oligosaccharides. Successful commercial CDs include those with 6, 7, or 8 glucose molecules. These are known as -CDs, -CDs, and -CDs, respectively. Critical to CDs' usefulness is their ability to create an "inclusion complex" with an extensive assortment 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 moderately.[3]

The structural formula Artemether and βCD is shown in Figures 1 and 2.

MATERIAL AND METHODS

Preparation of Standard Calibration Curve Artemether

The stock solution (1000 µg/mL) of Artemether was prepared by dissolving 5 mg in 25 mL of 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, 10, 15, 20, and 25 µg/mL were obtained by pipetting 0.5, 1.0, 1.5, 2.0, and 2.5 mL of stock solution into a 10.0 mL volumetric flask and bringing 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. λ_{max} was traced and a calibration curve of absorbance at 240.5 nm versus the concentration of standard solutions was constructed.[4]

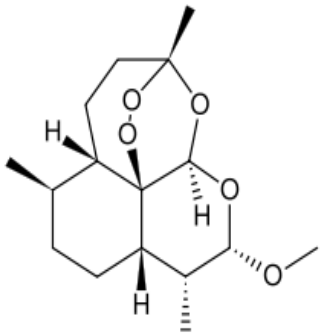

Figure 1: Artemether

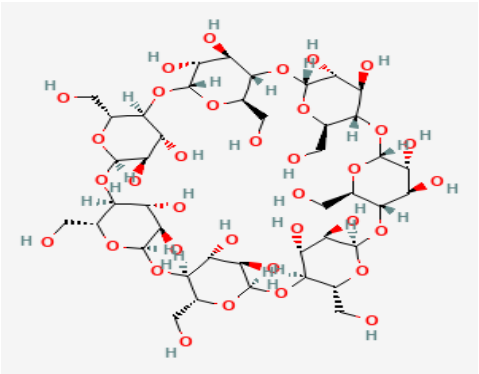

Figure 2: β-Cyclodextrine

Determination of Solubility

Artemether is free soluble in dichloromethane, and methanol, and practically insoluble in Water.[5]

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 to 400 cm^{-1}. In these tests, the medication was combined with each excipient at a 1:1 ratio.

Preparation of Artemether- β-Cyclodextrin Complex

Artemether- βCD complex is prepared by kneading method in the ratio 1:1 Drug: Polymer, respectively. The procedure is combining βCD and water in a glass mortar until a paste is formed, before adding artemether and kneading the resulting slurry for 90 minutes. To keep the right consistency, just the right amount of water is added. After being vacuum-dried at 400°C for 48 hours, the product is next sieved through 150-micron mesh.[6]

Evaluation of Complex

Drug content of artemether - β-Cyclodextrin Complex

- *Preparation of standard solution-Artemether*

In a 10 mL desiccated volumetric flask, precisely measure 10 mg of Artemether and recirculate the volume to 10 mL using phosphate buffer 6.8 as the standard solution. 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]

Preparation of Test Solution-Artemether Complex

Prepare a test solution by carefully placing 20 mg of Artemether 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 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 Artemether and βCD in the ratio 1:1 and then complexes 40 mg is filled in the empty capsule shell separately. The dissolution medium is phosphate buffer 6.8, the capsule is placed in baskets separately and rotated at 50 rpm at having temperature of 37.5°C. Artemether's absorption at 240 nm is noted when liquid is withdrawn from both containers at 5-minute intervals and a volume of 10 mL is made up with phosphate buffer 6.8. When the drug ingredient in the dissolving medium is undetectable or identified at a concentration below the threshold for recognizing its taste in the early time points (between 0 and 5 minutes), the drug's taste is effectively masked.[8]

Taste Perception Test

A taste perception test was conducted to see how effective inclusion complexation is at masking flavors. Artemether, a bitter medication, appears to work by binding to taste bud receptors on the tongue. The drug's harsh taste is blocked since β-CD encapsulates it. Artemether prevents bitter taste receptors from binding to their corresponding proteins in the tongue. The pleasant aftertaste of β-CD also helps to mask the bitterness. Kneading was found to be effective in complexing artemether in the hydrophobic cavity of β-CD, so preventing the medication from coming into direct touch 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 sample in the mucosa. After that the complexes kept in the mouth for 5 seconds and volunteers recorded the taste level.[9]

Solubility Study of Artemether 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 240 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 240 nm spectrophotometrically using a UV spectrophotometrically. Both readings were compared.[10]

RESULT AND DISCUSSION

Standard Calibration Curve

The concentration-absorbance curve used as a standard for Artemether was obtained. Table 1 tabulates the absorbance values. The slope of the typical calibration curve is 0.0154 and the correlation coefficient is 0.9992 (Figure 3).

Table 1: Standard calibration readings of Artemether

Concentrations (µg/mL)	*Absorbance*
5	00.077
10	0.146
15	0.232
20	0.305
25	0.382

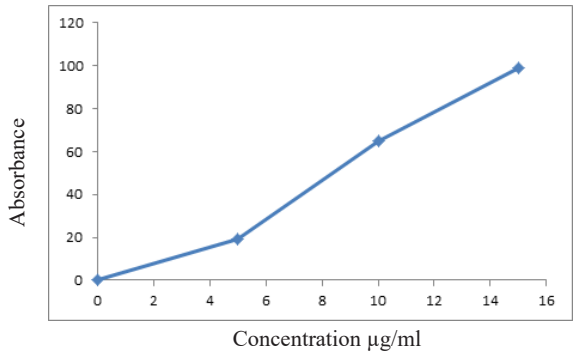

Figure 3 : Artemether calibration curve in phosphate buffer 6.8

Determination of Solubility

The solubility of Artemether were shown in Table 2. Artemether is free soluble in Dichloromethane, methanol and practically in soluble in water.

R = 0.9995

Slope = 0.0153

Table 2: Solubility of Artemether

Sr. No	*Drug*	*Soluble*	*Insoluble*
1	Artemether	Dichloromethane, Methanol	Water

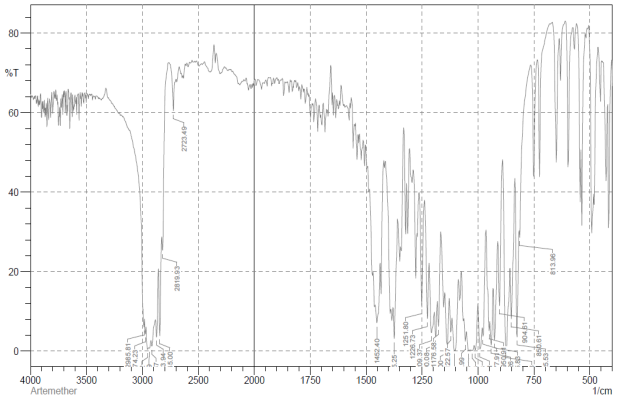

Figure 4: IR spectra of Artemether pure drug

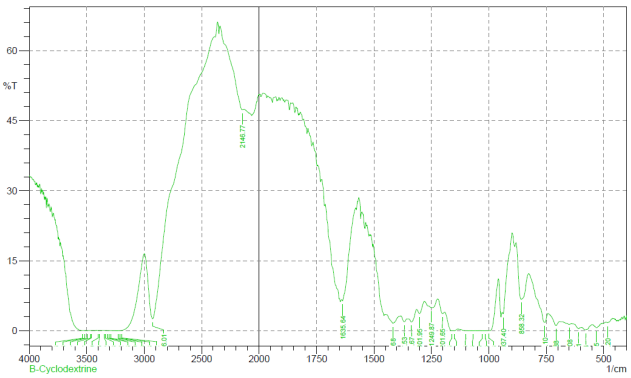

Figure 5: IR spectra of β-cyclodextrine

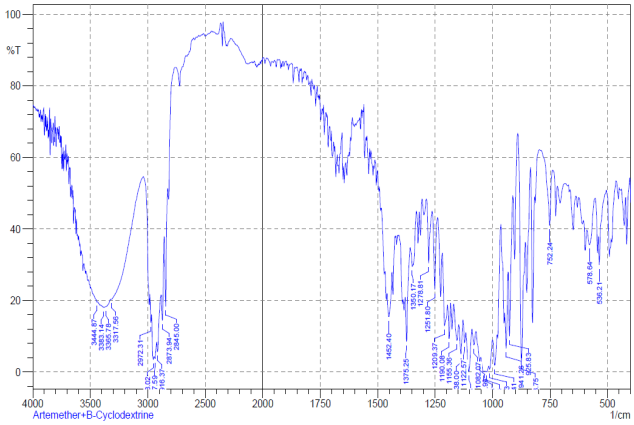

Figure 6: IR spectra of Artemether + β-cyclodextrine

Table 3: Interpretation

Sr.No	*Funtional Group*	*Artemether*	*B-cyclodextrine*	*Complex*
1	C-O-C	1100 cm^{-1}	--	1100 cm^{-1}
2	O-CH_3	1500-1400 cm^{-1}	--	1500-1400 cm^{-1}
3	C-O-CH_3	3100-3000 cm^{-1}	--	3100-3000 cm^{-1}
4	Alcoholic O-H	--	3500-3200 cm^{-1}	--
5	Alcoholic C-O	--	1250-1050 cm^{-1}	--

The infrared spectra of Artemether and βCD shows that the bonding configurations of the two molecules have not changed much (Figures 4 and 5). It can be determined that, Artemether keeps its distinctiveness in pure form deprived of undergoing any chemical interaction, So all aspects shows that there is no incompatibility between Artemether and B-cyclodextrine (Table 3 and figure 6).

Evaluation of Complex

Drug content

Drug content was found to be 94.43% for Artemether.

Taste Masking Evaluation for Complex

In vitro drug release study

Drug material in the dissolution media (phosphate buffer 6.8) was discovered in the early points from 0 to 5 minutes, although the observed amount was below the threshold value, according to an *in-vitro* drug release study of Artemether. So the drug is not bind to taste receptor in 0 to 5 minutes which prevent the fellness of bitter taste of drug thus it shows that taste masking is achieved for Artemether (Table 4 and Figure 7).

Taste Perception Test

The data highlighted in bold (Table 5) indicate that most participants reported a comparable degree of bitterness. The 11 healthy volunteers held the drug in the mouth for 30 seconds and the taste sensation felt was recorded. 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

For Artemether pure drug most of volunteers opinion that it was strong bitter.

The data highlighted in bold (Table 6) indicate that most participants reported a comparable degree of bitterness. The 11 healthy volunteers held the drug in the mouth for 30 seconds and the taste sensation felt was recorded. Volunteers opinion for taste level was recorded by giving different score value i.e.

A mathematical measure was used with following values:

0 = Tasteless 1 = Bitter

2 = Slightly bitter 3 = Slightly sweet 4 = Sweet

For Artemether complex most of volunteers opinion was that it was slightly bitter.

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

Sr. No	*Time (min)*	*% Drug release*
		Artemether
1	0	0
2	5	33.23
3	10	97.05

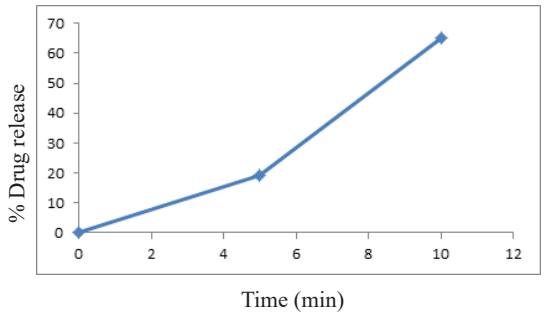

Figure 7: %Drug release of Artemether

Solubility Studies

Solubility studies were carried in buffer solution pH 6.8 .Solubility of Artemether + βCD complex have showed highest solubility in buffer pH 6.8 (0.124 mg/mL) as compared with the pure drug i.e Artemether (0.0735 mg/mL). From above it show that the complexes was formed have good solubility in Phosphate buffer 6.8 as compared with pure drug (Table 7).

Artemether is antimalarial drugs used especially for pediatric patients. Artemether is a bitter drug. So masking of bitter taste in the formulation is a prerequisite as it improve the compliance of the patient and product value. βCD is use to improve taste of Artemether by forming complex with them by Kneading method . βCD prevents the release of drug in the saliva. The result obtained shows that the drug- polymer complex prepared with βCD in drug-polymer ratio 1:1 gave complete taste masking with satisfactory result obtained in term of *in-vivo* and *in-vitro* evaluation Visual inspection

Table 5: Bitterness evaluation results (For pure drug):

Sr. No.	*Drugs*	*0 (Tasteless)*	*1 (Slightly bitter)*	*2 (Moderately bitter)*	*3 (Strong bitter)*
1	Artemether	--	--	1	10

Table 6: Bitterness evaluation results (For complex)

Sr.No	*Complexes*	*0 (Tasteless)*	*1 (Bitter)*	*2 (Slightly bitter)*	*3 (Slightly sweet)*	*4 (Sweet)*
1	Artemether compex	--	2	9	--	--

Table 7: Solubility studies of pure drug and drug complex

Sr.no	*Drug / Complex*	*Solubility (mg/ml)*
1	Artemether drug	0.0735 mg/ml
2	Artemether + β-cyclodextrine Complex	mg/ml

revealed that Artemether was white crystalline powder and it is bitter in taste.. The melting point of Artemether was found to be 87°C. The standard calibration curve of Artemether shows the slope of 0.0154 and correlation coefficient of 0.9992. Values were initiate to be in the range of 17°13' ± 0.03 to 19°45'± 0.01. Compatibility study show that drug are compatible with polymer. Solubility study shows that solubility of drug is increased in Phosphate buffer 6.8 by successfully forming complex with βCD. *In-vitro* dissolution results showed that maximum 97.05% of Artemether, drug release less than 15 minutes in formulation. Solubility of Artemether in saliva (pH 6.8) is 0.00735 mg/ml, After complex forming with βCD the solubility of (Artemether complex) is 0.124 mg/mL. When the drug ingredient in the dissolve media is either not detected or identified at a concentration below the threshold for detecting its taste in early time points (from 0 to 5 minutes, according to an *In-vitro* drug release research), the drug's flavor is effectively masked. Taste masking (Taste perception test) 11 volunteers were selected for this test, results show that complex is taste masked successfully.[11]

CONCLUSION

From the results of these studies it was possible to increase the solubility and also the taste was masked for reducing the bitterness by forming complexes of Artemether with βCD by kneading method. Because of this, combining artemether with βCD complex could help in creating new medicines that use artemether to fight malaria.

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