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RECENT ADVANCEMENT ON VARIOUS POSSIBLE FORMULATIONS OF ARTEETHER AND FUTURE ASPECTS: A COMPREHENSIVE REVIEW

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Abstract

Arteether is a well-known antimalarial drug with high commercial success because of its use in drug resistance cases of malariait is a readily accessible antimalarial medicine that may be given intramuscularly as an oily solution (11.).The injection is painful and patient non-compliance so here we are discussing various possible oral dosage form of arteether. Arteether is used to treat both cerebral malaria and chloroquine resistant malaria. However, the primary issues with arteether are its limited solubility (≅17 µg/ml) and ≅ 40 % gastrointestinal breakdown. So these problems are challenge. Because of these issues, developing an oral dose form with high bioavailability is difficult. According to the literature survey we try to develop some possible oral dosage form of arteether(i.e. Spheroids, liposomes, Nano lipid carriers, self-emulsifying drug delivery system (seddss), colon targeted matrix tablets, Enteric coated tablets).Arteether oral formulations can be optimised for rapid and full medication absorption.

Keywords: Arteether, Anti-malarial, Solubility, Bio-availability, Oral delivery.

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Introduction

Malaria has had the most historical ramifications of any infectious illness. Plasmodium species infect 300-500 million people globally each year, killing 1.5-2.7 million people, the great majority of whom are children. Malaria affects 2400 million people in over 90 countries, accounting for 40% of the world's population (1).

Malaria is most commonly spread by the bite of an infected female anophelelene mosquito, although it can also be acquired through blood transfusion or infected needles, as well as congenital infection. Anopheles mosquitoes have a nearly global distribution, although only 40 of the 430 recognised species are estimated to be significant as malaria vectors (2).

In 1972, a group of Chinese researchers discovered artemisinin, a novel anti-malarial medication. Artemisinin is derived from the traditional Chinese medicinal herb Artemisia annua (3). Arteether is a derivative of artimisinin extracted from the leaves of this plant, and it possesses anti-malaria action against the parasite Plasmodium falciparum. Arteether is an oil-soluble ethyl ether derivative of dihydroartemisinin, a very effective erythrocytic schizonticidal medicine used to treat multidrug-resistant falciparum malaria. It is only accessible as an intramuscular injection. A-β Arteether has a fast schizonticidal effect and results in rapid clinical improvement with a low recrudescence rate in falciparum malaria (4). It also has modest gametocidal activity, which helps to reduce the spread of falciparum malaria. It has been shown to be completely successful in treating individuals with acute chloroquine-resistant, complex, and uncomplicated falciparum malaria (5). It has a longer half-life of elimination (> 20 h) and is more stable and lipophilic than the other artemisinin molecules, but its chief drawbacks are its poor solubility (17 g/ml) and 40% breakdown in the stomach. (6) Because of these constraints, arteether (is only accessible as an intramuscular injection.

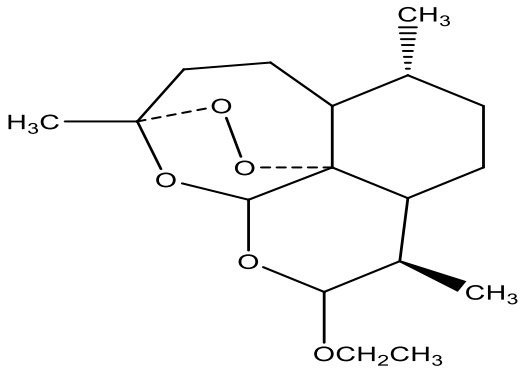

Figure1: α, β-Arteether

Challenges

Arteether is an oil-soluble ethyl ether derivative of dihydroartemisinin, a very effective erythrocytic schizonticidal medicine used to treat multidrug-resistant falciparum malaria. It can only be administered intramuscularly. - In falciparum malaria, arteether has a quick schizonticidal impact and resulting in rapid clinical improvement with a low recrudescence rate (7) It also has modest gametocidal activity, which helps to reduce the spread of falciparum malaria. It has been shown to be completely successful in treating individuals with acute chloroquine-resistant, complex, and uncomplicated falciparum malaria (8). Since it has a longer elimination half-life (> 20 h) and is more stable and lipophilic than other artemisinin compounds, it is a promising treatment for both cerebral malaria and chloroquine-resistant malaria. However, the primary issues with arteether are its poor solubility (17 g/ml) and 40% breakdown in the stomach (9). As a result, these issues provide a hurdle. Because of these issues, developing an oral dose form with good bioavailability is difficult.

Possibilities

There are bare minimum possibilities to develop an oral dosage form of arteether. The major problems arise with arteether is

low solubility and degradation of drug in the acidic environment of stomach. There are numerous ways for improving solubility and shielding pharmaceuticals from the stomach's acidic environment(10).

A drug must be in solution in order to enter the systemic circulation and exert a therapeutic effect. Incomplete or uneven absorption is common in somewhat insoluble substances(11). It has a longer elimination half-life (> 20 h) and is more stable and lipophilic than other artemisinin compounds, making it a viable treatment for both cerebral malaria and chloroquine-resistant malaria(12).

- ❖ Crystal habits of drug substance
- ❖ Micronization
- ❖ Solubilization and Complexation – use of surfactants and cyclodextrins
  - ○ Physical mixing
  - ○ Kneading
  - ○ Spray Drying
  - ○ Lyophilization
  - ○ Rota evaporator
- ❖ Salt formation
- ❖ Solid dispersion

Drug degradation can be preventing by coating of the polymer. Coating can be done by using Natural (Ex: Guar Gum and Xanthan Gum) Or Synthesize Polymer (Eudrazit)(12).

Various Possible Oral Dosage Forms of Arteether:

1) Spheroid
2) Nano lipid carrier
3) Liposome
4) Self-emulsifying drug delivery system (SEDDS)
5) Colon targeted Matrix tablets
6) Enteric coated tablets

1) Spheroid

Spheroids are also known as pallets. There are various layers present in spheroids. The inner most layers are known as core granules or crystals (13). Then the drug is present in the second layer. After that there is the outermost layer of polymer which is for control release. Sometimes a protective layer is present on drug layer after which the polymer layer is present. The spheroid is made up of a water-insoluble medication and a controlled release matrix, with the matrix containing between 70% and 99.5% polymer and 0.5% to 4% at least one cellulose derivative(14).

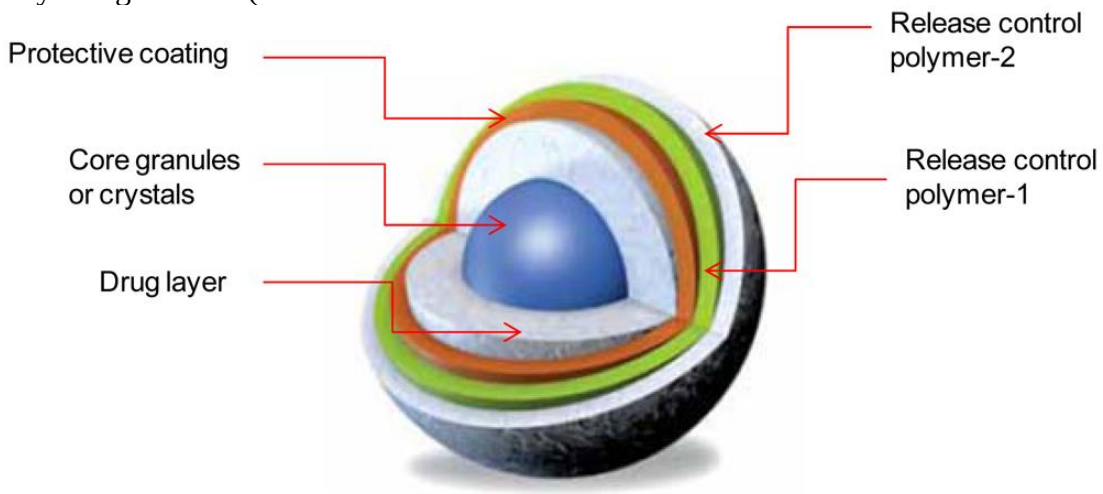

Figure 2 : various layers of spheroids

Method of preparation of spheroids

Pellets can be prepared by extrusion-spheronization process. Spheroids can be prepared by using polyvinyl pyrrolidone (PVP) K 30 as binder, sodium starch glycollate as disintegrant and microcrystalline cellulose (MCC or Avicel 101) as filler. All the ingredients accurately weighed and blended with required quantity of drug (15). Then water would be

added to the blended ingredients so as to form wet mass or dough. When this dough willpass through extruder; cylindrical shaped extrudates will be formed. The extrudates will be collected in spheronizer for rounding the extrudates.

We can prepare spheroids of arteether by extrusion spheronization process(16). The main problem occur with arteether is that it is degraded in the acidic environment of stomach this problem can be solved by coating of enteric coating polymer on the drug layer present in spheroids after that we can coat a control release polymer on it. The second problem of arteether is low solubility (≅17 µg/ml)that problem can be solved by made a complex with any solubility enhancer polysaccharide (ex. Cyclodextrin) and this complex (AE + Solubility enhancer) is applied as second layer of the spheroid. So it is a possible oral dosage form of arteether.

Nano lipid carrier

Nlcs are the slns second generation (solid lipid nanoparticles). NLC is a hybrid carrier composed of a binary mixture of solid lipid and spatially differentiated liquid lipid. The average size of nlcs is 10-500 nm. NLC is composed of a carefully blended blend of solid lipid (long chain) and liquid lipid (short chain), preferably in a 70:30 to 99.9:01 ratio (17.).

The particle size and physical state of the lipid phase are crucial determinants in lipid dispersions' durability. Nlcs are partially crystallized lipid particles with mean radii of 100 nm suspended in an aqueous phase including emulsifiers. In some cases, NLC may be preferable to other colloidal carriers. Because of their high drug loading, encapsulation efficacy, and durability, NLC are an appealing nutraceutical delivery approach. They have the potential to increase bioavailability and stability of bioactive chemicals, as well as food system shelf life, consumer acceptability, functionality, nutritional value, and safety (18).

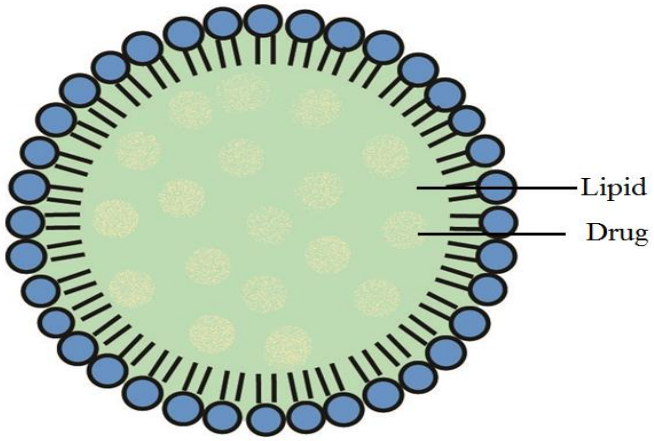

Figure 3: General structure of Nano lipid carrier

Method of Preparation of Nanolipid Carrier

The particle size and physical condition of the lipid phase are important factors in the durability of lipid dispersions. Nanostructured lipid carriers (NLC) are a promising delivery technology that distributes partially crystalline lipid particles with mean radii of 100 nm(19). The lipid and aqueous phases would be formed separately. Pluronic F 68 surfactant would be dissolved in aqueous phase by dissolving the surfactant in water and stirring continuously at 50 rpm using a magnetic stirrer. Combine the required amount of liquid lipids (glyceryl

monostearate and oleic acid) and solid at 70 degree celcius. Arteether would be introduced to the lipid phase since it is insoluble in water. By combining the aqueous and lipid phases, both phases with the same temperature will be fused. The mixture would now be homogenized for 10 minutes at 8000 rpm. The resultant emulsion would next be sonicated for 2 minutes to further reduce its size (20).

We may develop arteether NLC. The biggest issue with arteether is its breakdown in the acidic environment of the stomach, thus it may be protected by covering the lipidic layer or the innermost layer with enteric coating, and the second issue is its poor solubility (21).

Solubility can be enhanced by using cyclodextrin in complex with arteether. So it is possible that we can prepare nanostructured lipid carriers of arteether.

3) Liposome

Liposomes are small vesicles that contain an aqueous volume enclosed by a lipid-based membrane. Liposomes are concentric bilayered vesicles with an aqueous volume entirely encapsulated by a lipid bilayer made up mostly of natural and synthetic phospholipids.

Liposomes are lipid and phospholipid-based structures(22).

Liposomes are mostly composed of a lipid mixture. Amphoteric lipids, which can form bilayers and hence are an important component of the liposomal system, are among the lipid phospholipids.A phospholipid is made up of two acyl chains connected by a glycerol backbone to a headgroup. Saturated and unsaturated acyl chains are represented by R1 and R2, respectively, while the polar head group is represented by R3(24).

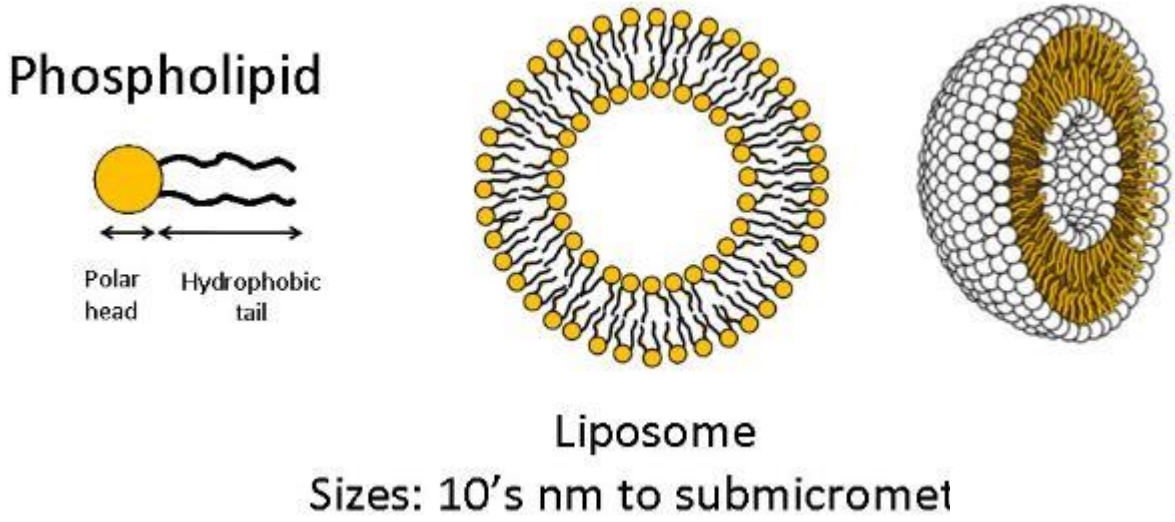

Figure 4: The General structure of liposomes.

Method of Preparation of liposomes

Hand shaking method can be used to prepare liposomes. First, we'd put the lipid solution and organic solvents in a round bottom flask and shake it by hand. It will result in the production of a film, which we will subsequently dry with a vacuum. Then we put some water in it to hydrate it. After that, the film stacks are distributed in aqueous phase, where lipids expand and peel away from the round bottom flask to produce liposomes. We can make arteether liposomes (25). The film stacks are then disseminated in aqueous phase, where lipids expand and peel off from the round bottom flask, resulting in the creation of liposomes. We can make arteether liposomes. Because liposomes are a target drug delivery mechanism, we can simply pass/bypass liposomes from the stomach to

minimise drug degradation in the acidic environment of the stomach, and we can readily boost arteether solubility by complexation with cyclodextrins. As a result, liposomes may be the best formulation for arteether oral administration. (26.).

4) Self-emulsifying drug delivery system

SEDDS are isotropic mixtures of natural and synthetic oils, solid and liquid surfactants, and co-solvents/surfactants. When seddss are placed in an aqueous phase with gentle agitation, they spontaneously emulsify to form fine oil-in-water emulsions that readily pass through the gastro intestinal system (6). SEDDS typically produce emulsions with droplet sizes of 100 to 300 nm, whereas smeddss produce transparent micro-emulsions with droplet sizes of less than 50 nm (27.).

Method of preparation of seddss

For the production of seddss, a precisely weighed quantity of the drug (Arteether) would be put in a glass vial, followed by oil, surfactant, and co-surfactant. The combination would next be combined for 30 minutes with moderate stirring and vortex mixing. This mixture would be heated on a magnetic stirrer at 40°C until the medication was completely dissolved. This will result in the development of a self-emulsifying medication delivery system(28).

We can easily prepare seddss of arteether because we know it is a low soluble drug, so we can increase its solubility by creating inclusion complexes with cyclodextrins and save the drug from degradation in the acidic environment of the stomach by using any enteric coated polymer (natural/synthetic). So we may prepare the arteether seddss.

5) Colon Targeted matrix tablets

The colon is the greatest place for the delivery of medications used in the treatment of colon illness and other ailments. The colon is an appealing destination for poorly absorbed drug molecules, which may increase bioavailability and minimize gastrointestinal discomfort caused by many medications. It has a longer retention time, which improves the absorption of medications that are poorly absorbed. Because it has a low hostile environment and reduced peptidase activity, it can be used to deliver peptides, oral vaccinations, insulin, and growth hormones (29).

Matrix tablets are defined as "oral solid dosage forms in which the medication or active component is homogeneously disseminated within hydrophilic or hydrophobic matrices that function as release rate retardants." To constantly release pharmaceuticals, these devices employ dissolution-controlled and diffusion-controlled approaches (30)

Method of preparation of Matrix tablets

Matrix tablets would be made with varied amounts of colon target polymer or enteric coated polymer (guar gum and xanthan gum) as the binder. Wet granulation might be used to create matrix tablets of,- arteether. A mortar would be filled with precisely weighed amounts of medication, polymers (guar gum and xanthan gum), filler (lactose), and micro-cystalline cellulose as an anti-adherent. To produce a granulation-ready mass, the needed amount of binder (starch in water as a 10% solution) was added and thoroughly mixed. The dough mixture was then strained through sieve # 22 to produce granules that would be dried for 20 minutes in a 120° oven (9). The granules were mixed with the proper proportions of lubricant (talc) and glidant (Mg stearate), which decreased friction between the tablet and the walls of the die cavity as well as tablet adherence to the die and punch. The mixture is subsequently crushed to form tablets in a single station rotary tablet machine Karnavati) utilising 9 mm round concave punches at an ideal pressure. The method of preparation of matrix tablets is written below:

- **Weighing and Blending** - The active ingredient (α, β-arteether: β-CD equimolar complex) and other ingredients (microcystalline cellulose and lactose) would be weighed accurately and mixed properly.
- **Granulation:** The wet granulate might be prepared by adding starch paste (10%) used as a granulating agent.
- **Screening:** The damp mass would be converted into granules by passing through sieve #22
- **Drying:** The prepared granules could be dried at 120 ± 2° C for 20 min.
- **Dry screening:** After drying, the granules would be passed through a sieve bigger in size than the one used for the wet mass to pick granules of uniform size to allow even filling in the die cavity.
- **Lubrication:** A lubricant (talc) and a glidant (magnesium stearate) would be blended with the granules. It decreases friction between the tablet and the die cavity walls. It also helps to keep the tablet from adhering to the die and punch.
- **Compression:** Then the granules might be subjected to compression in tablet (31).

6) PREPARATION OF ENTERIC COATED TABLETS

An enteric coating on a solid dose form might be used to deliver a medicinal substance into the digestive area. There are a variety of enteric coating polymers available that can protect the medication core from the harsh environment of the stomach. Because they are soluble at higher PH values, these polymers breakdown in the colon and release the core for immediate action.

Weighing and Blending - The active ingredient (α, β-arteether: β-CD equimolar complex) and other ingredients (microcystalline cellulose and lactose) would be weighed accurately and mixed properly.

- **Granulation:** The wet granulate might be prepared by adding starch paste (10%) used as a granulating agent.
- **Screening:** The damp mass would be converted into granules by passing through sieve # 22
- **Drying:** The granules so prepared, could be dried at 120 ± 2° C for 20 min.
- **Dry screening:** After drying, granules would be passed through a sieve with a higher mesh size than the one used for the wet mass to pick granules of uniform size to allow even filling in the die cavity.
- **Lubrication:** A lubricant (talc) and a glidant (magnesium stearate) would be blended with the granules. It decreases friction between the tablet and the die cavity walls. It also helps to keep the tablet from adhering to the die and punch.
- **Compression:** Then the granules might be subjected to compression in tablet.
- **Coating:** The Coating might be done on the tablet with enteric coating polymer.

The enteric coating could be done on the granules also; after the granulation process the coating could be done on granules after the coating on granules, granules dried at 120± 2° C for 20 min after that Compression.

Table 1 : Recent advancement on Various formulations for Arteether.

Sr. No.	Delivery System	Method	Excipients used	References

1.	Lipid-based formulations for oral administration of β-arteether	Self-emulsifying drug delivery systems	Groundnut or sesame oil, Maisine 35-1, Tween 80 or Cremophor EL, and absolute ethanol	(32)
2.	Curcumin-loaded lipid-based drug delivery systems combined with β-arteether	Curcumin-loaded lipid-based drug delivery systems	Groundnut or sesame oil, Maisine 35-1, Tween 80 or Cremophor EL, and absolute ethanol	(33)
3.	Arteether loaded solid self-micro emulsifying drug delivery system.	SMEDDS	Arachis oil, Tween-80, and Span-80.	(34)
4.	Solid lipid Nanoparticles	High pressure homogenization (HPH) technique	Glyceryl mono stearate, Soya lecithin, Tween 80, pluronic F68.	(35)
5.	Nanoemulsions	High pressure homogenization	Tween 80, Span 80, PEG 400, methyl cellulose, cremophor EL and SLS.	(36)

FUTURE ASPECTS

Arteether is an oil-soluble ethyl ether derivative of dihydroartemisinin, a highly effective erythrocytic schizonticidal treatment for multidrug-resistant falciparum malaria. It can only be given intramuscularly. - Arteether has a rapid schizonticidal effect in falciparum malaria, resulting in rapid clinical improvement with a low recrudescence rate. It also possesses minor gametocidal activity, which aids in the control of falciparum malaria. It has been proven to be totally effective in treating people with acute chloroquine-resistant, complex, and uncomplicated falciparum malaria. It is a promising treatment for both cerebral malaria and chloroquine-resistant malaria since it has a longer elimination half-life (> 20 h) and is more stable and lipophilic than other artemisinin compounds.

CONCLUSION

Arteether is an oil-soluble ethyl ether derivative of dihydroartemisinin, a highly efficient erythrocytic schizonticidal treatment for multidrug-resistant falciparum malaria. It can only be given intramuscularly. - Arteether has a fast schizonticidal effect in falciparum malaria, resulting in rapid clinical improvement with a low recrudescence rate (Asthana et al., 2001). It also possesses some gametocidal action, which aids in the control of falciparum malaria. It has been demonstrated to be totally effective in treating people with acute chloroquine-resistant, complex, and uncomplicated falciparum malaria (Mandal et al., 2004). It is a potential therapy for both cerebral malaria and chloroquine-resistant malaria since it has a longer elimination half-life (> 20 h) and is more stable and lipophilic than other artemisinin compounds.As a result, these issues provide a hurdle. Because of these issues, developing an oral dose form with good bioavailability is difficult.

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