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Review Article

PHARMACOKINETIC, SOLUBILITY AND DISSOLUTION PROFILE OF ANTI-MALERIAL DRUGS

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Abstract

Pharmacokinetic data and solubility profile of drugs are the basic requirement of any researcher, for selecting an appropriate drug for any kind of formulation development. To get such data of all drugs of any category at one place is very difficult task; we by our review article have tried to give all such data of Anti-malerial drugs.

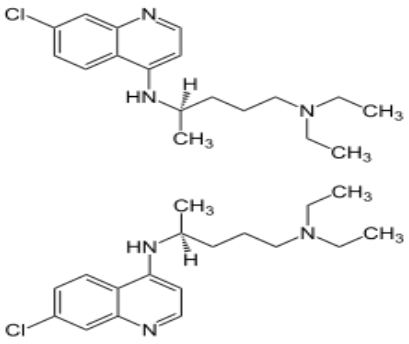
Keywords: Solubility profile, Pharmacokinetic data, Mechanism of action, Dissolution profile.

Introduction:

Classification: -

1. **4-Aminoquinolines:** - Chloroquine, Amodiaquine, Piperaquine.
2. **Quinoline- Methanol: -** Mefloquine.
3. **Cinchona alkaloid:** - Qunine, Quinidine.
4. **Biguanides: -** Proguanil (Chlorguanil, Chlorproguanil).
5. **Diaminopyrimidines:** - Pyrimethamine.
6. **8-aminoquinoline:** - Primaquine, Bulaquine.
7. **Sulfonamides and Sulfones: -** Sulfadoxine, Sulfamethopyrazine, Dapsone.
8. **Tetracyclines:** - Tetracycline, Doxycycline.
9. **Sesquiterpine lactones: -** Artesunate, Artemether, Arteether.
10. **Amino alcohols:** - Halofantrine, Lumifantrine.
11. **Mannich Base: -** Pyronaridine.
12. **Naphthoquinone: -** Atovaquone.

Chloroquine [2]



Systematic (IUPAC) nameN'-(7-chloroquinolin-4-yl)-N,N-diethyl-pentane-1,4-diamine

Chemical data

Formula: - $C_{18}H_{26}ClN_3$

Mol. mass: - 319.872 g/mol

Boiling Point: - 460.6 °C at 760 mmHg **[3]**

Melting Point: - 200 °C

Pharmacology: -

Mechanism of Action: - The mechanism of plasmodicidal action of Chloroquine is not completely certain. Like other quinoline derivatives, it is thought to inhibit heme polymerase activity. This results in accumulation of free heme, which is toxic to the parasites. **[4]**

Description: -White or slightly yellow, crystalline powder. Is odorless and has a bitter taste. **[5]**

Solubility Profile: -Very slightly soluble in water, soluble in dilute acid, in chloroform and in ether. **[USP]**

Chloroquine hydrochloride injection: -

Solubility Profile: -Colorless liquid. **[USP]**

Chloroquine Phosphate: -

Description: -White, Crystalline powder. Is odorless. Has a bitter taste and is discolored slowly on exposure to light. Its solution has a ph of about 4.5. Exists in two polymorphic forms.One melting between 193^0 and 195^0 and the other between 210^0 and 215^0. Mixture of the forms melts between 193^0 and 215^0.

Solubility Profile: -Freely soluble in water, practically insoluble in alcohol, in chloroform and In ether. **[USP]**

Chloroquine Phosphate: -

Solubility Profile: -Freely soluble in water, Very slightly soluble in chloroform, in ethanol, in ether and in methanol. **[IP]**

ChloroquineSulphate: -

Solubility Profile: -Freely soluble in water and in methanol, Very slightly soluble in ethanol (95%), practically insoluble in chloroform and in ether. **[IP][6]**

Pharmaceutics: -

Pharmacokinetic data

Metabolism: - Liver **[2]**

Half-life: - 1-2 months

Protein Binding: - 55% of the drug in the plasma is bound to nondiffusible plasma constituents

Absorption: - Completely absorbed from gastrointestinal tract **[4]**

Excretion: - Urine **[7]**

Nature: - Lipophillic **[8]**

Log P: -4.72**[9]**

PKa**: -** 8.4 and 10.8**[10]**

Dissolution: -

chloroquine tablets: -

Apparatus:

Apparatus 2

Stir rate:

100 rpm

Dissolution medium:

900 ml water

Q-value:

75%

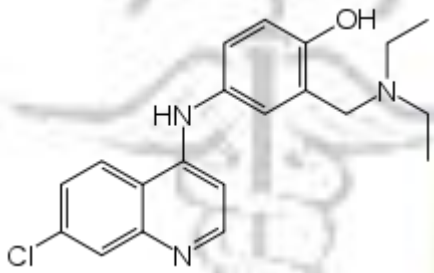
Time:

45 minutes

Sample volume:

5 ml**[11]**

Amodiaquine [12]



Systematic (IUPAC) name4-[(7-chloroquinolin-4-yl) amino]-2-[(diethylamino)methyl]phenol

Chemical data

Formula$C_{20}H_{22}ClN_3O$

Mol. mass 355.861 g/mol

Melting Point: 208°C **[13]**

Boiling Point:478 °C at 760 mmHg **[13]**

Pharmacology: -

Mechanism of Action: - The mechanism of plasmodicidal action of Amodiaquine is not completely certain. Like other quinoline derivatives, it is thought to inhibit heme polymerase activity. This results in accumulation of free heme, which is toxic to the parasites.**[14]**

Description: - Very pale yellow to light tan-yellow, Odorless powder. **[USP][15]**

Solubility Profile: - practically insoluble in water, sparingly soluble in 1.0N Hydrochloric acid, slightly soluble in alcohol. **[USP]**

Amodiaquine Hydrochloride: -

Description: - Yellow, crystalline powder, is odorless and has a bitter taste. **[USP]**

Solubility Profile: - Soluble in water, sparingly soluble in alcohol, very slightly soluble in benzene, in chloroform and in ether. **[USP]**

Amodiaquine Hydrochloride: -

Solubility Profile: - Soluble in water, sparingly soluble in ethanol (95%). Practically insoluble in chloroform and in ether.**[IP][16]**

Pharmaceutics: -

Pharmacokinetic data

Metabolism: - The hepatic first pass **metabolism** is high **[17]**

Half-life: - 5.2 ± 1.7 (range 0.4 to 5.5) minutes **[12]**

Protein Binding: -Not available

Absorption: -Rapidly absorbed following oral administration. **[14]**

Excretion: kidney, liver, red bone marrow and spleen **[18]**

Nature: - amphiphilic **[19]**

Log P: -log rank statistic=4.67, **P**=0.03**[20]**

PKa**: -pKa**1 = 7.1, **pKa**2 = 8.1**[21]**

Dissolution:-

Amodiaquine tablet[22]

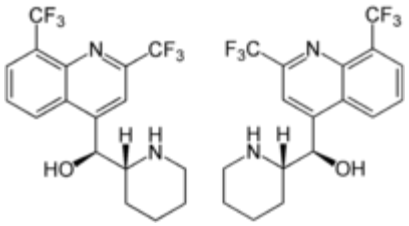
Medium: - Water, 900ml

Apparatus: - 2[USP]

Rpm: - 50 rpm

Time: - 30 minutes.

Mefloquine [23]



Systematic (IUPAC) name(R*,S*)-2,8-bis(trifluoromethyl)quinolin-4-yl]-(2-piperidyl)methanol

Chemical data

Formula$C_{17}H_{16}F_6N_2O$

Mol. mass 378.312 g/mol

Boiling Point: 415.7°Cat760mmHg **[24]**

Melting point = 259-260°C (decomposition).**[25]**

Pharmacology: -

Mechanism of Action: -Mefloquine has been found to produce swelling of the Plasmodium falciparum food vacuoles. It may act by forming toxic complexes with free heme that damage membranes and interact with other plasmodial components. **[28]**

Description: - White or slightly yellow, crystalline powder. It exhibit polymorphism. **[USP][26]**

Solubility Profile: - Freely soluble in methanol, soluble in alcohol, very slightly soluble in water. **[USP]**

Pharmaceutics: -

Pharmacokinetic data

Metabolism: - Extensively hepatic; main metabolite is inactive**.[23]**

Half-life: - 2 to 4 weeks. **[23]**

Protein Binding: -98%.**[27]**

Absorption: -Well absorbed from the gastrointestinal tract. The presence of food significantly enhances the rate and extent of absorption.**[28]**

Excretion: Primarily bile and feces; urine (9% as unchanged drug, 4% as primary metabolite. **[23]**

Nature: - Lipophillic **[29]**

Log P: -3.10**[28]**

PKa**: -**4.5**[30]**

Dissolution:-

Mefloquine HCL tablet[31]

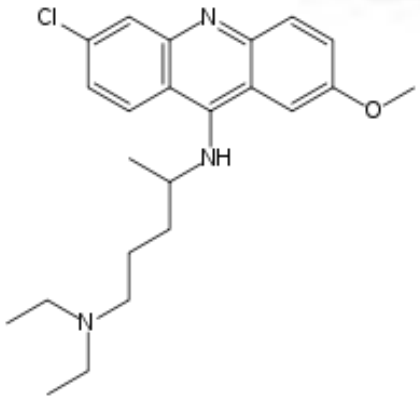
Medium: - Sgf without enzyme, 900ml

Apparatus: - 1[Basket]

Rpm: - 100 rpm

Time: - 10, 20,30,45,60 minutes.

Quinacrine [32]



Systematic (IUPAC) name (RS)-N'-(6-chloro-2-methoxy-acridin-9-yl)-N, N-diethyl-pentane-1,4-diamine.

Chemical data

Formula=$C_{23}H_{30}ClN_3O$

Mol. mass= 399.957 g/mol

Boiling Point:574.1 °C **[33]**

Melting point =248-250 °C **[34]**

Pharmacology: -

Mechanism of Action: - The exact mechanism of antiparasitic action is unknown; however, quinacrine binds to deoxyribonucleic acid (DNA) in vitro by intercalation between adjacent base pairs, inhibiting transcription and translation to ribonucleic acid (RNA). Quinacrine does not appear to localize to the nucleus of Giaridiatrophozoites, suggesting that DNA binding may not be the primary mechanism of its antimicrobial action. Fluorescence studies using Giardia suggest that the outer membranes may be involved. Quinacrine inhibits succinate oxidation and interferes with electron transport. In addition, by binding to nucleoproteins, quinacrine suppress the lupus erythematous cell factor and acts as a strong inhibitor of cholinesterase. **[35]**

Description: - yellow crystals or powder. Bright yellowish needles or bright yellow

powder. Odorless.pH of a 1% aqueous solution is about 4.5**.[36]**

Solubility: Soluble in cold water**.[37]**

Pharmaceutics: -

Pharmacokinetic data

Metabolism: - Not available.

Half-life: - 5 to 14 days. **[32]**

Protein Binding: - 80-90%.**[32]**

Absorption: -Absorbed rapidly from the gastrointestinal tract following oral administration.**[35]**

Excretion: Primarily bile and feces; urine (9% as unchanged drug, 4% as primary metabolite. **[23]**

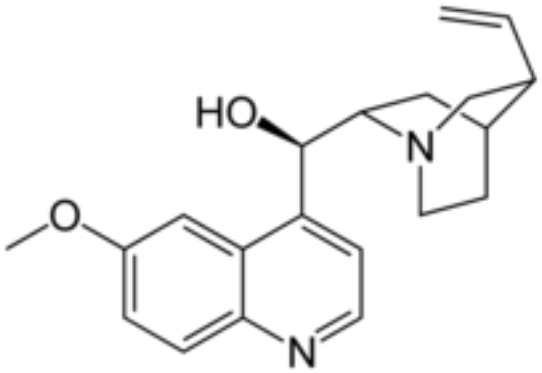
Nature: - Lipophilliccationic drug. **[38]**

Log P: -**(LogP** 5.67).**[39]**

PKa**: -**9.4 and 10.7. **[40]**

Dissolution: - Not reported as yet.

Quinine [41]



Systematic (IUPAC) name (*R*)-(6-methoxyquinolin-4-yl)((2*S*,4*S*,8*R*)- 8-vinylquinuclidin-2-yl)methanol

Chemical data

Formula$C_{20}H_{24}N_2O_2$

Mol. mass 324.417 g/mol

Boiling Point: - 633 °C at 760 mmHg **[42]**

Melting point = 173 - 175 C. **[43]**

Pharmacology: -

Mechanism of Action: - The theorized mechanism of action for quinine and related anti-malarial drugs is that these drugs are toxic to the malaria parasite. Specifically, the drugs interfere with the parasite's ability to break down and digest hemoglobin. Consequently, the parasite starves and/or builds up toxic levels of partially degraded hemoglobin in itself.**[44]**

Description: - White, fine, needle like crystals. Usually lusterless, making a light and readily compressible mass. is odorless. It darkens on exposure to light. Its saturated solution is neutral or alkaline to litmus. **[USP][45]**

Solubility Profile: - Slightly soluble in water, in alcohol and in chloroform. Very slightly soluble in ether, freely soluble in alcohol at 80^0 and in a mixture of 2 volumes of chloroform and 1 volume of dehydrated

alcohol. Sparingly soluble in water at 100^0.**[USP]**

Quinine Bisulphate: -

Solubility Profile: - Freely soluble in boiling water and in boiling ethanol (95%), soluble in water, sparingly soluble in ethanol(95%), slightly soluble in chloroform. **[IP][46]**

Quinine Dihydrochoride: -

Solubility Profile: - Very soluble in water, soluble in ethanol (95%), slightly souble in chloroform, very soluble in ether. **[IP]**

Quinine Sulphate: -

Solubility Profile: - Freely soluble in a mixture of 2 volumes of chloroform and 1 volume of ethanol, sparingly soluble in boiling water and in ethanol (95%), slightly soluble in water, very slightly soluble in chloroform, practically insoluble in ether. **[IP]**

Pharmaceutics: -

Pharmacokinetic data

Bioavailability 76 to 88%

Protein binding ~70%

Metabolism Hepatic (mostly CYP3A4 and CYP2C19-mediated)

Half-life ~18 hours

Excretion Renal (20%)

Absorption: - 76 - 88% **[44]**

Nature: - Hydrophobic. **[47]**

Log P: -2.1.[**48]**

PKa**:** -8.7.**[49]**

Dissolution:-

Quinine sulfate capsule.[50]

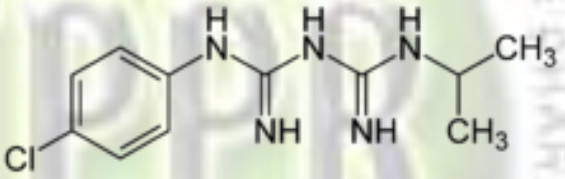
Medium: - 0.1 N Hydrochloric acid,900 ml

Apparatus: - 1[Basket]

Rpm: - 100 rpm

Time: - 45 minutes.

Proguanil [51]



Systematic (IUPAC) name: - 1-(4-chlorophenyl)-2-(N'-propan-2-ylcarbamimidoyl) guanidine.

Chemical data

Formula: - $C_{11}H_{16}ClN_5$

Mol. mass: - 253.731 g/mol

Boiling Point: - 340.2°Cat760mmHg. **[52]**

Melting point = 130 °C to 133 °C.**[53]**

Pharmacology: -

Mechanism of Action: - Proguanil inhibits the dihydrofolate reductase of plasmodia and thereby blocks the biosynthesis of purines and

pyrimidines, which are essential for DNA synthesis and cell multiplication. This leads to failure of nuclear division at the time of schizont formation in erythrocytes and liver. **[54]**

Description: - White, crystalline powder; odourless.**[55]**

Solubility Profile: - Soluble in **ethanol (95%)***;* slightly soluble in **water**; practically insoluble in **chloroform** and in ether.

Pharmaceutics: -

Pharmacokinetic data

Bioavailability: - Proguanil hydrochloride extensively absorbed from the GI tract. **[56]**

Protein binding: - Approximately 75%.**[54]**

Metabolism: - Proguanil metabolized principally by CYP2C19 to the active metabolite cycloguanil and to 4-chlorophenylbiguanide. **[56]**

Half-life: - 20 h.**[51]**

Excretion: - 40–60% of a dose of Proguanil excreted in urine. **[56]**

Absorption: - Rapidly and well absorbed in humans following oral doses ranging from 50 to 500 mg. **[54]**

Nature: - Lipophillic cationic. **[57]**

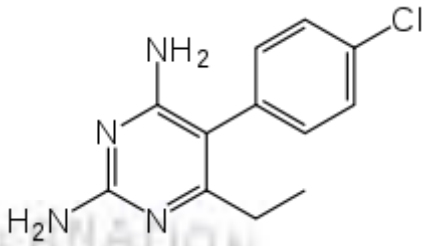
Log P: -< 0.03. **[58]**

PKa**:** -2.3. **[59]**

Dissolution: -

Not repoted as yet.

Pyrimethamine [60]



Systematic (IUPAC) name5-(4-chlorophenyl)-6-ethyl- 2,4-pyrimidinediamine.

Chemical data

Formula$C_{12}H_{13}ClN_4$

Mol. mass 248.71 g/mol

Boiling Point: -201 (5 torr). **[61]**

Melting point =233.5 oC.**[62]**

Pharmacology: -

Mechanism of Action: -Pyrimethamine inhibits the dihydrofolate reductase of plasmodia and thereby blocks the biosynthesis of purines and pyrimidines, which are essential for DNA synthesis and cell multiplication. This leads to failure of nuclear division at the time of schizont formation in erythrocytes and liver. **[63]**

Description: -White, odorless, crystalline powder. **[USP][64]**

Solubility Profile: - practically insoluble in water, slightly soluble in acetone, in alcohol and in chloroform. **[USP]**

Solubility Profile: -Sligthy soluble in chloroform and in ethanol (95%), very slightly soluble in ether, practically insoluble in water. **[IP][65]**

Pharmaceutics: -

Pharmacokinetic data

Bioavailability: -well-absorbed. **[60]**

Protein binding: - 87%

Metabolism: -Hepatic

Half-life: -96 hours

Excretion: -Renal

Absorption: -Well absorbed with peak levels occurring between 2 to 6 hours following administration. **[63]**

Nature: - hydrophobic. [66]

Log P: -**0.0008.** [67]

PKa**:** -7.34. **[68]**

DISSOLUTION: - Pyrimethamine Tablet. [USP][69]

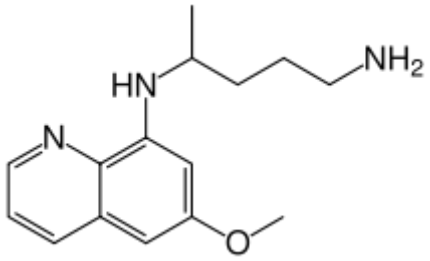
Medium: - 0.1 N Hydrochloric acid, 900 ml

Apparatus: - 2

Rpm: - 50 rpm

Time: - 45 minutes.

Primaquine[70]



Systematic (IUPAC) name: - (*RS*)-*N*-(6-methoxyquinolin-8-yl) pentane-1, 4-diamine.

Chemical data

Formula: -$C_{15}H_{21}N_3O$

Mol. mass: - 259.347 g/mol

Boiling Point: -451.1 °C at 760 mmHg. **[71]**

Melting point =199-205 °C. **[72]**

PHARMACOLOGY: -

Mechanism of Action: -Primaquine's mechanism of action is not well understood. It may be acting by generating reactive oxygen species or by interfering with the electron transport in the parasite. **[73]**

Description: - Orange-red, crystalline powder. Is odorless and has a bitter taste. Its solutions are acid to litmus. Melts at about 200^0.**[USP]**

Solubility Profile: -Soluble in water, insoluble in chloroform and in ether. **[USP][74]**

Solubility Profile: -Soluble in water, practically insoluble in ethanol (95%) and in ether. **[IP][75]**

PHARMACEUTICS: -

Pharmacokinetic data

Bioavailability: - 96%

Metabolism: - Liver

Half-life: - 6 hours

Excretion: -Urinary. **[76]**

Nature: - hydrophilic and amorphous. **[77]**

Log P: -11 mM and 0.74 mM.**[78]**

PKa**:** -3.20. **[79]**

Dissolution: -

Primaquine phosphate Tablet. [USP][80]

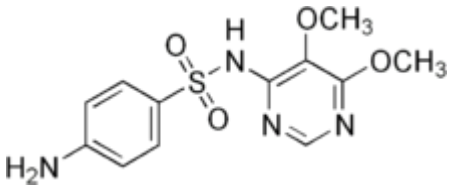
Medium: - 0.1 N Hydrochloric acid, 900 ml

Apparatus: - 2

Rpm: - 50 rpm

Time: - 60 minutes.

Sulfadoxine[81]



Systematic (IUPAC) name: - 4-Amino-*N*-(5,6-dimethoxy-4-pyrimidinyl)benzenesulfonamide.

Chemical data: -

Formula: - $C_{12}H_{14}N_4O_4S$

Mol. Mass: - 310.33 g/mol

Melting point: -190-194. **[82]**

Boiling point: - 522.8 ºCat 760 mmHg. **[82]**

Pharmacology: -

Mechanism of Action: -Sulfadoxine is a sulfa drug, often used in combination with pyrimethamine to treat malaria. This medicine may also be used to prevent malaria in people who are living in, or will be traveling to, an area where there is a chance of getting malaria. Sulfadoxine targets Plasmodium dihydropteroate synthase and dihydrofolate reductase. Sulfa drugs or Sulfonamides are antimetabolites. They compete with para-aminobenzoic acid (PABA) for incorporation into folic acid. The action of sulfonamides exploits the difference between mammal cells and other kinds of cells in their folic acid metabolism. All cells require folic acid for growth. Folic acid (as a vitamin) diffuses or is transported into human cells. However, folic acid cannot cross bacterial (and certain protozoan) cell walls by diffusion or active transport. For this reason bacteria must synthesize folic acid from p-aminobenzoic acid.**[83]**

Description: -white or white crystalline powder.**[84]**

Solubility profile: - Slightly soluble in ethanol (95%) and in methanol. Very slightly soluble in water. Practically insoluble in ether, it dissolves in solutions of alkali hydroxides and in dilute mineral acid. **[85]**

Pharmaceutics: -

Pharmacokinetic data

Bioavailability: - 96%

Metabolism: - kidney. **[86]**

Half-life: -6.7 days. **[87]**

Excretion: -Urine. **[88]**

Nature: - Hydrophillicity. [89]

Log P: -0.55. **[90]**

PKa**: -**6.3. **[91]**

Dissolution: -

Sulpfadoxine Tablet. [USP][92]

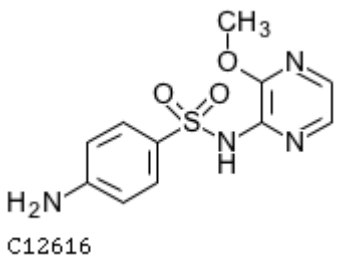
Medium: -ph 6.8 phospahte buffer, 1000ml.

Apparatus: - 2

Rpm: - 75 rpm

Time: - 30 minutes.

Sulfamethopyrazine.[93]



C12616

Systematic (IUPAC) name: - 4-amino-N-(3-methoxypyrazin-2-yl)benzenesulfonamide. **[94]**

Chemical data: -

Formula: - C11H12N4O3S. **[95]**

Mol. Mass: - 280.304 g/mol. **[96]**

Boiling point: - 488.6 °C at 760 mmHg. **[97]**

Melting point: -176°C.**[98]**

Pharmacology: -

Mechanism of Action:-Sulfamethopyrazine is a competitive inhibitor of bacterial para-aminobenzoic acid (PABA), a substrate of the enzyme dihydropteroatesynthetase. The inhibited reaction is necessary in these organisms for the synthesis of folic acid.**[94]**

Description: -A white or yellowish-white crystalline with a little bitter taste and stinkless, **[99]**

Solubility profile: -freely soluble in diluted hydrochloric acid or sodium hydroxide, slightly soluble in ethanol, hardly soluble in water. **[99]**

Pharmaceutics: -

Pharmacokinetic data

Half-life: -65 hrs. **[100]**

Protein binding: -65%. **[101]**

Excretion: -**Biliary.** [102]

Bioavailability: -**Not available**

Dissolution: -

Sulpfamethopyrazine Tablet. [USP][103]

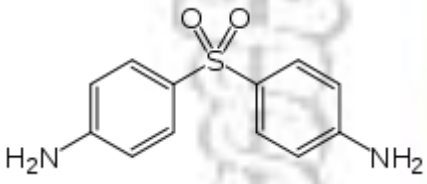
Medium: -0.01 M pH 6.8 phosphate buffer solution (sodium hydroxide and potassium dihydrogen orthophosphate). **[103]**

Apparatus: - 2

Rpm: - 75 rpm

Time: - 40 minutes.

Dapsone. [104]



Systematic (IUPAC) name4-[(4-aminobenzene)sulfonyl]aniline.

Chemical data

Formula: - $C_{12}H_{12}N_2O_2S$

Mol. Mass: - 248.302 $gmol^{-1}$

Melting point: -175 - 176° C. **[105]**

Boiling point: - 511.7 °C at 760 mmHg. **[106]**

Pharmacology: -

Mechanism of Action:-Dapsone acts against bacteria and protozoa in the same way as sulphonamides, that is by inhibiting the synthesis of dihydrofolic acid through competition with para-amino-benzoate for the active site of dihydropteroatesynthetase. The anti-inflammatory action of the drug is unrelated to its antibacterial action and is still not fully understood. **[107]**

Description: - White to creamy white, crystalline powder. Is odorless and has a bitter taste. **[USP]**

Solubility Profile: -Very slightly soluble in water, freely soluble in alcohol, soluble in acetone and in dilute mineral acid. **[USP][108]**

Solubility Profile: -Freely soluble in ethanol (95%) and in acetone. Very soluble in water. It is soluble in dilute mineral acid. **[IP][109]**

Pharmaceutics: -

Pharmacokinetic data

Bioavailability: - 86 to 104%. **[110]**

Protein binding 70 to 90%

MetabolismHepatic (mostly CYP2E1-mediated)

Half-life 20 to 30 hours

ExcretionRenal. **[104]**

Nature: - Lipophillic.[111]

Log P: -in octane–water is +0.97. **[112]**

PKa**:** -1.3-2.5. **[113]**

Dissolution: -

Dapsone Tablet. [USP][114]

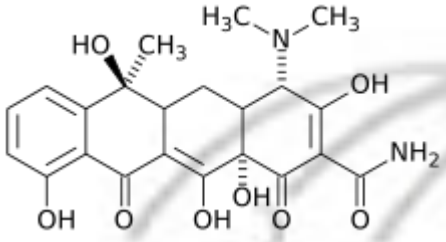
Medium: -Dilute hydrochloric acid. 1000ml

Apparatus: -1

Rpm: - 100 rpm

Time: - 60 minutes.

Tetracycline. [115]



Systematic (IUPAC) name 2-(amino-hydroxy-methylidene)-4-dimethylamino-6,10,11,12a-tetrahydroxy-6-methyl-4,4a,5, 5a-tetrahydrotetracene-1,3,12-trione OR 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro- 3,6,10,12,12a-pentahydroxy-1,11-dioxo-naphthacene-2-carboxamide OR (4*S*,6*S*,12a*S*)-4-(dimethylamino)-3,6,10,12,12a-pentahydroxy- 6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide.

Chemical data

Formula $C_{22}H_{24}N_2O_8$

Mol. mass 444.435 g/mol.

Melting point: -170-173°C. **[116]**

Boiling point: -790.622. **[117]**

Pharmacology: -

Mechanism of Action:-Tetracycline passively diffuses through porin channels in the bacterial membrane and reversibly binds to the 30S ribosomal subunit, preventing binding of tRNA to the mRNA-ribosome complex, and thus interfering with protein synthesis.**[118]**

Description: - Yellow, odorless, crystalline powder. Is stable in air, but exposure to strong sunlight causes it to darken. It loses potency in solution of ph below 2 and is rapidly destroyed by alkali hydroxide solutions. **[USP][119]**

Solubility Profile: -. Very slightly soluble in water, freely soluble in dilute acid and in alkali hydroxide solutions.Sparingly soluble in alcohol, practically insoluble in chloroform and in ether.**[USP]**

Tetracycline Hydrochloride: -

Solubility Profile: -Yellow, odorless, crystalline powder. Is moderately hygroscopic.Is stable in air. But exposure to strong sunlight in moist air causes it to darken. It loses potency in solution at a ph below 2 and is rapidly destroyed by alkali hydroxides and carbonates, slightly soluble in alcohol, practically insoluble in chloroform and in ether.**[USP]**

Tetracycline: -

Solubility Profile: -Soluble in ethanol (95%) and in methanol, sparingly soluble in acetone, slightly soluble in chloroform, very slightly soluble in water, practically insoluble in ether.

It dissolves in dilute acid and alkaline solutions. **[IP][120]**

Tetracycline Hydrochloride: -

Solubility Profile: -Freely soluble in water, slightly soluble in ethanol (95%), practically insoluble in acetone, in chloroform and in ether. It dissolves in aqueous solutions of alkali hydroxides and carbonates. **[IP]**

Pharmaceutics: -

Pharmacokinetic data

Bioavailability: - 60-80% Oral, while fasting<40% Intramuscular.

Protein binding 69%.**[121]**

Metabolism Not metabolised

Half-life 6-11 hours

ExcretionFecal and Renal.

Nature: - Lipophillic.[122]

Log P: -unmodified **tetracycline log P** =−2.706, and for the ethylated **tetracycline log P** =−2.28. **[123]**

PKa**: -**4.79. **[118]**

Dissolution: -

Tetracycline hydrochloride tablets. [USP][124]

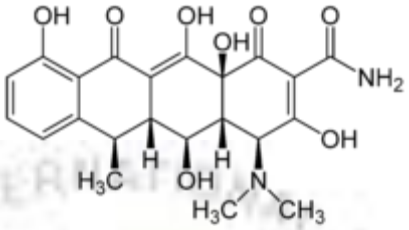
Medium: -Water, 900ml

Apparatus: -2

Rpm: - 75rpm

Time: - 60 minutes.

Doxycycline. [125]



Systematic (IUPAC) name(4*S*,4a*R*,5*S*,5a*R*,6*R*,12a*S*)-4-(dimethylamino)- 3,5,10,12,12a-pentahydroxy- 6-methyl- 1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene- 2-carboxamide.

Chemical data

Formula$C_{22}H_{24}N_2O_8$

Mol. mass 444.435 g/mol.

Melting point: ->300 ºC. **[126]**

Boiling point: -685.2 °C at 760 mmHg. **[127]**

Pharmacology: -

Mechanism of Action:-Doxycycline, like minocycline, is lipophilic and can pass through the lipid bilayer of bacteria. Doxycycline reversibly binds to the 30 S ribosomal subunits and possibly the 50S ribosomal subunit(s), blocking the binding of aminoacyl tRNA to the mRNA and inhibiting bacterial protein synthesis. Doxycycline

prevents the normal function of the apicoplast of Plasmodium falciparum, a malaria causing organism. **[128]**

Description: - Yellow, crystalline powder. Very slightly soluble in water, freely soluble in dilute acid and in alkali hydroxide solutions**.[USP][129]**

Solubility Profile: - sparingly soluble in alcohol, practically insoluble in chloroform and in ether. **[USP]**

Doxycycline Hyclate: -

Solubility Profile: -Yellow, crystalline powder. Soluble in water and in solutions of alkali hydroxides and carbonates.Slightly soluble in alcohol, practically insoluble in chloroform and in ether.**[USP]**

Doxycycline Hydrochloride: -

Solubility Profile: -Freely soluble in water and in methanol, sparingly soluble in ethanol(95%), practically insoluble in chloroform and in ether. It is soluble in solutions of alkali hydroxides and carbonates. **[IP][130]**

Pharmaceutics: -

Pharmacokinetic data

Bioavailability: - 100%

Protein binding>90%.**[128]**

Metabolismhepatic,minimally.

Half-life18-22 hours.

Excretionurine, feces

Nature: - Lipophillic.[131]

Log P: -0,22 (pH=7.4). **[132]**

PKa**:** -3.40, 7.7, and 9.3. **[133]**

Dissolution: -

Doxycycline Hyclate delayed released capsule. [USP][134]

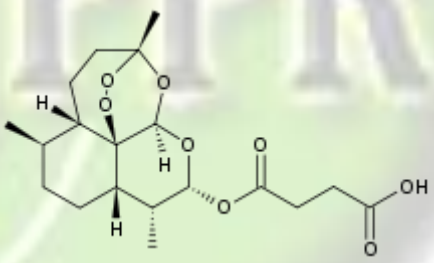
Medium: -0.6 N hydrochloric acid, 900ml

Apparatus: -1

Rpm: - 50rpm

Time: - 20 minutes.

Artesunate. [135]



Systematic (IUPAC) name: - ArtesunateC19H28O8;Artemisinin monosuccinate;ArtesunicAcid;Butanedioic Acid Mono(3R,5aS,6R,8aS,9R,10R,12R,12aR)-decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10-yl] Ester;Arteannuinum;Arteannuinum succinate;(3R,5aS,6R,8aS,9R,10S,12R,12aR)-Decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano(4,3-j)-1,2-benzodioxepin-10-ol hydrogen

succinate;vARTESUNATE;(3R,5aα,8aα,12aR)-Decahydro-10α-(3-carboxypropionyloxy)-3,6α,9β-trimethyl-3β,12α-epoxypyrano[4,3-j]-1,2-benzodioxepin;Succinic acid 1-[(3R,12aR)-3,6α,9β-trimethyl-3β,12α-epoxy-3,4,5,5aα,6,7,8,8aα,9,10-decahydropyrano[4,3-j]-1,2-benzodioxepin-10α-yl] ester;WR-256283.**[136]**

Chemical data

Formula$C_{19}H_{28}O_8$

Mol. mass 384.421 g/mol.

Melting point: - 132 - 135 C. **[137].**

Boiling point: - 502.1 °C at 760 mmHg. **[138].**

Pharmacology: -

Mechanism of Action:-Artemisinin is a rapid parasiticidal of the asexual stages; it is anti-gametocyte and blocks sporogony (heppner and Ballou 1998). It produces ultra-structural changes to the growing trophozoite parasite. A whorl is produced in the food vacuole and the parasite's mitochondria proliferated. This reduces parasite's survival (Hien and White 1993). Endoperoxidebridge is essential for its anti-malarial activity. The compound is activated by the intra-parasitic haem to irreversibly decompose, generating free radicals that alkylate and oxidises proteins and lipids. The membrane of the parasite is damaged by lipid peroxidation and channel proteins' inactivation. (Ridley & Hudson 1998). Parasites clearance times are shorter than with chloroquine and also symtomatic response. **[139]** .

Description: - white crystalline powder odorless and almost tasteless. **[140]**

Solubility: - Slightly soluble. **[137]**

Pharmaceutics: -

Pharmacokinetic data

Bioavailability: - Rapid. **[142]**

Protein binding59%..**[141]**

Metabolismplasma. . **[142]**

Half-life 0.33 h.**[143]**

Nature: - good' – 'polar'. 'poor'-**lipophilic**. **[144]**

Log P: ≤0.05.**[145]**

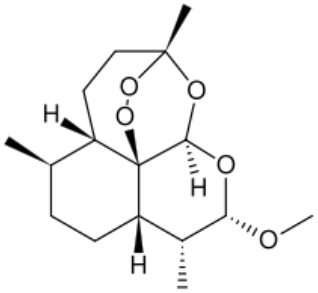
PKa**:** -4.6. **[146]**

Dissolution: -

Artesunate tablet[147]

Medium: -Water, 900ml.

Apparatus: -1
Rpm: - 100 rpm
Time: - 30 minutes.
Artemether.[148]



Systematic (IUPAC) name: - 3,12-epoxy-12h-pyrano(4,3-j)-1,2-benzodioxepin,decahydro-10-methoxy-3,6,9-trim;5a-beta,6-beta,8a-beta,9-alpha,12-beta,12ar)-(3-alph(+)-ethyl;artemisininelactolmethylether;cgp56696;dihydroartemisininmethylether;dihydroquinghaosumethylether;methyl-dihydroartemisinine;[3r-(3r,5as,6s,8as,9r,10r,12s,12ar**)]-decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12h-pyrano[4,3-j]-1,2-benzodioxepin;ARTEMETHER;ARTHEMETER;Artimether;ArtemetherC16H26O5;ARTEMTHER;[3R-(3R,5aS,6S,8aS,9R,10R,12S,12aR**)]-Decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin;(3R,5aS,6R,8aS,9R,10S,12R,12aR)-Decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin;dihydroqinghaosu methyl ether;3,12-Epoxy-12H-pyrano(4,3-j)-1,2-benzodioxepin, decahydro-10-methoxy-3,6,9-trimethyl-, (3-alpha,5a-beta,6-beta,8a-beta,9-alpha,12-beta,12aR)-, (+);(3R,5aα,8aα,12aR)-Decahydro-10β-methoxy-3,6α,9β-trimethyl-3,12α-epoxypyrano[4,3-j]-1,2-benzodioxepin;(3R,5aα,8aα,12aR)-Decahydro-10β-methoxy-3,6α,9β-trimethyl-3β,12α-epoxypyrano[4,3-j]-1,2-benzodioxepin;Dihydroartemisin methyl ether. **[149]**

Chemical data

Formula $C_{16}H_{26}O_5$.

Mol. mass298.374 g/mol.

Melting point: - 86 - 90 C. **[150]**

Boling point: - 358 °C. **[151]**

Pharmacology: -

Mechanism of Action:-The specific mechanism of action of artemisinin is not well understood, and there is ongoing research directed at elucidating it. When the parasite that causes malaria infects a red blood cell, it consumes haemoglobin and liberates free haeme, an iron-porphyrin complex. The iron reduces the peroxide bond in artemisinin generating high-valent iron-oxo species, resulting in a cascade of reactions that produce reactive oxygen radicals which damage the parasite leading to its death. **[152]**

Description: - White crystalline **powder**. **[153]**

Solubility Profile: -Very soluble in dichloromethane and acetone. Freely soluble in ethylacetate and practically insoluble in water.**[IP][154]**

Pharmaceutics: -

Pharmacokinetic data

Bioavailability: - (95% C). **[155]**

Protein binding50%.**[156]**

Metabolism biliary.**[157]**

Half-life2 hours **...[158]**

Nature: - lipophilic nature. [159]

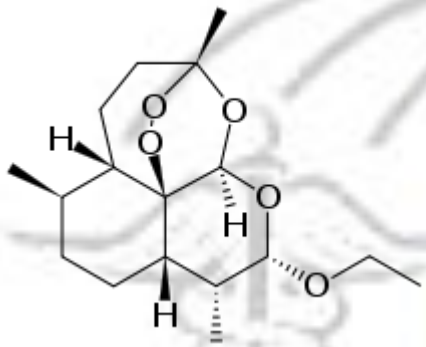
Log P: 2.6. **[160]**

PKa**:** -Not available.

Dissolution: -

Not available.

Artemotil[161]



IUPAC Name: - (3*R*, ä*S*,6*R*, 8a*S*,9*R*,10*S*,12*R*, 12a*R*) - decahydro 10-ethoxy-3,6,9-trimethyl-3,12-epoxy 12*H*- pyrano [4,3*j*] - 1,2-benzodioxepin.**[162]**

Chemical data

Formula $C_{17}H_{28}O_5$

Mol. mass312.401 g/mol.

Melting point: - 80-820 °C. **[163]**

Boiling Point: 372.4 °C at 760 mmHg. **[164]**

Pharmacology: -

Mechanism of Action:-Their mode of action is still not completely understood, although different theories have been proposed. The lipid-soluble artemether and artemotil are released slowly when administered intramuscularly because of the 'depot' effect related to the oil formulation. Understanding the pharmacokinetic profile of these 2 drugs helps us to explain the characteristics of the toxicity and neurotoxicity. The water-soluble artesunate is rapidly converted to artenimol at rates that vary with the route of administration, but the processes need to be characterised further, including the relative contribution of pH and enzymes in tissues, blood and liver. This paper intends to summarise contemporary knowledge of the pharmacokinetics of this class of compounds and highlight areas that need further research. **[165]**

Description: -A white or almost white, crystalline powder. **[166]**

Solubility Profile: -Soluble in acetone, dichloromethane, ethyl acetate, ketone and methanol. **[IP][167].**

Pharmacokinetic parameters: -

Metabolism Hepatic

Half-life20 hours

Protein binding98 to 99%.**[168]**

Nature: - Highly **lipophilic.** [169]

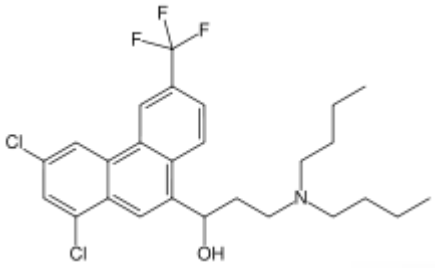
Log P: 0.0408.**[170]**

PKa**: -**4.6. **[171]**

Dissolution: -

Not available.

Halofantrine. [172]



Systematic (IUPAC) name3-dibutylamino-1-[1,3-dichloro-6-(trifluoromethyl) phenanthren-9-yl]-propan-1-ol.

Chemical data

Formula$C_{26}H_{30}Cl_2F_3NO$

Mol. mass 500.423 g/mol

Melting point: - 136-138. **[173]**

Boiling Point: 596.2 °C. **[174]**

Pharmacology: -

Mechanism of Action:-The mechanism of action of Halofantrine may be similar to that of chloroquine, quinine, and mefloquine; by forming toxic complexes with ferritoporphyrin IX that damage the membrane of the parasite. **[175]**

Water solubility: - Aqueous **solubility**is extremely low. **[176]**

Pharmacokinetic data

Protein binding 60 to 70%

Metabolism Hepatic (CYP3A4-mediated)

Half-life 6 to 10 days.

Nature: - Highly**lipophilic.** [177]

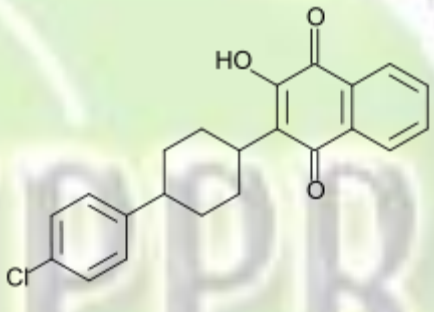
Log P: 8.5.**[178]**

PKa**:** -9.7.**[179]**

Dissolution: -

Not available.

Atovaquone. [180]



Systematic (IUPAC) name*trans*-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthalenedione.

Chemical data

Formula$C_{22}H_{19}ClO_3$

Mol. mass 366.837 g/mol.

Melting point: -216-219. **[181]**

Boiling Point: 542.2 °C at 760 mmHg**. [182]**

Pharmacology: -

Mechanism of Action:-Atovaquone is a hydroxy- 1, 4- naphthoquinone, an analog of ubiquinone, with antipneumocystis activity. The mechanism of action against

Pneumocystis carinii has not been fully elucidated. In Plasmodium species, the site of action appears to be the cytochrome bc1 complex (Complex III). Several metabolic enzymes are linked to the mitochondrial electron transport chain via ubiquinone. Inhibition of electron transport by atovaquone will result in indirect inhibition of these enzymes. The ultimate metabolic effects of such blockade may include inhibition of nucleic acid and ATP synthesis. Atovaquone also has been shown to have good *in vitro* activity against *Toxoplasma gondii*. **[183]**

Description: - Yellow powder. Freely soluble in N-metyl-2-pyrrolidone and in tetrahydrofuran, soluble in chloroform.**[184]**

Solubility Profile: -sparingly soluble in acetone, in di-n-butyl adipate, in dimethyl sulfoxide and in polyethylene glycol 400, slightly soluble in alcohol, in 1,3 outanediol, in ethyl acetate, in glycerin, in octanol and in polyethylene glycol 200, very slightly soluble in 0.1 N sodium hydroxide, insoluble in water. **[USP] [184]**

Pharmacokinetic data

Half-life 2.2 to 3.2 days.

Protein binding: - 99.9%. **[185]**

Biotransformation: - Some evidence suggests limited metabolism (although no metabolites have been identified). **[183]**

Route of elimination: - The half-life of atovaquone is long due to presumed enterohepatic cycling and eventual fecal elimination. There was little or no excretion of atovaquone in the urine (less than 0.6%). **[183]**

Absorption: - The bioavailability of atovaquone is low and variable and is highly dependent on formulation and diet. Bioavailability of the suspension increases two-fold when administered with meals. When administered with food, bioavailability is approximately 47%. Without food, the bioavailability is 23%. **[183]**

Toxicity: - The median lethal dose is higher than the maximum oral dose tested in mice and rats (1825 mg/kg per day). Overdoses up to 31,500 mg of atovaquone have been reported. In one such patient who also took an unspecified dose of dapsone, methemoglobinemia occurred. Rash has also been reported after overdose. **[183]**

Nature: - Highly**lipophilic.** [186]

Log P: 4.0034 and. 4.1402. **[187]**

PKa**: -**9. **[188]**

Oral suspension is available in market.

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