RESEARCH ARTICLE

Microemulsion Drug Delivery of Anti-malarial

Jaiswal Nilesh*, Mehta Parulben

School of Pharmacy, LNCT University, Bhopal, Madhya Pradesh, India.

Received: 27th February, 2024; Revised: 28th May, 2024; Accepted: 24th June, 2024; Available Online: 25th September, 2024

ABSTRACT

Malaria affects millions of people every year, especially in our world. The main treatments are oral antibiotics and vaccines. The rise of the malaria parasite, now resistant to most anti-viral drugs, is causing a global crisis. Furthermore, low water solubility and permeability of both new and old antibiotics cause limited oral bioavailability and non-compliance from patients. Lipid formulations are frequently employed to lessen toxicity, boost solubility, and improve effectiveness. The findings of studies on oral-specific lipophilic drug delivery systems, such as self-emulsifying drug delivery systems, are reviewed in this article. (SEDDS). SEDDS increases the absorption of anti-inflammatory drugs by promoting the formation of liquid emulsions that dissolve the drug in the intestine. However, traditionally used SEDDS are usually in liquid form, administered into the oral cavity, and have poor safety. This article discusses a new solidification process that can be easily and economically scaled up by using existing equipment. This strategy might also increase patient compliance and product stability. Oral SEDDS has a substantial potential influence in the fight against malaria.

Keywords: Self-emulsify, Anti-malarials, Lipoidal formulations, Microemulsions, Lymphatic system.

International Journal of Drug Delivery Technology (2024); DOI: 10.25258/ijddt.14.3.03

How to cite this article: Nilesh J, Parulben M. Microemulsion Drug Delivery of Anti-malarial. International Journal of Drug Delivery Technology. 2024;14(3):1261-1268.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Malaria is one of the worst diseases in the world and is most common in tropical and subtropical regions. The World Health Organization's (WHO) Department of Malaria and Tropical Diseases reported in 2021 that there were over 241 million cases of malaria worldwide in 2020, accounting for over 620,000 fatalities. According to the WHO malaria report, 229 million malaria cases are expected to occur worldwide in 2019. According to the WHO, African Region accounts for 94% of all malaria deaths. While the worldwide mortality rate varies between ~0.3 and ~2.2%, mortality statistics in tropical climates vary between ~11 and ~30%.[1,2]

Patients in need have long taken antimalarial drugs, which have advantages and disadvantages of their own. While many of us are aware of the benefits of these medications, the majority are also ignorant of their drawbacks, which are primarily related to their pharmacokinetics, particularly their poor oral absorption. Artemisinin, a powerful antimalarial medication, has been extracted from the traditional Chinese medicinal plant Artemisia annua, according to Klayman DL *et al.* article.[2] *It is a blood schizonticide that acts quickly and has a shortened duration for parasite clearance, which helps to relieve malaria symptoms quickly. Similarly, later in 2015, White NJ et al. underlined in their publication[3] that Qinghaosu, or artemisinin, is a Chinese antimalarial medication. It also works well against Plasmodium falciparum strains that are resistant to drugs, and even people who have cerebral malaria recover quickly from it.* Oral administration of medications such as artemisinin, halofantrine, amodiaquine, and chloroquine results in poor and irregular absorption due to their low water solubility. Low oral bioavailability may result from this, as well as from its short half-life and rapid first-pass metabolism.

The war with the *Plasmodium*: Its Challenges and Way Forward

The *Plasmodium* microorganism, which causes malaria, is often spread by the bite of a female *Anopheles* mosquito. Once in human blood, the virus resembles sporozoites and enters liver cells within 30 minutes of being released into the body. The next stage of development is asexual in erythrocytes, where all Plasmodium species cause erythrocyte rupture. Patients with fevers or body temperatures above 37.5°C and those who have visited or stayed at malaria incident sites are typically considered to be the patient's primary cause of malaria. Hence, for the most part(s), malaria cases are caused by *P. falciparum* and *P. vivax*. In areas where mosquitoes are prone to biting humans and have a long lifespan, the disease is more common.[4] Both direct and indirect effects of malaria include fever, headache, nausea, vomiting, diarrhea, chills, and muscle soreness. Through malarial pregnancy, these illnesses can develop before delivery and result in congenital illnesses,

*Author for Correspondence: nileshjaiswal2@gmail.com

miscarriages, baby and child deaths, and deformities. The danger of various illnesses, is also raised by it. Furthermore, Burkitt lymphoma, nephrotic syndrome, severe intestinal infections, and kidney damage are linked to malaria, and these conditions have an immediate negative impact on quality of life and employment.[5]

Self-micro emulsifying dosages in antimalarials

It is estimated that around ~70% of pharmaceuticals on the market now fall within Class II of the Biopharmaceutics Classification System (BCS). Because of this, about 75% of all medications have high permeability and low solubility, which prevent oral medication absorption and consequent bioavailability. Improving the drug's subsequent solubility and, consequently, bioavailability is a complex task.[6] Thankfully, a wide range of technologies are available to enhance solubility and resolve problems related to bioavailability. Lipid formulations are one of these solubilization strategies that have been widely used in approved pharmaceutical products since 1980.[7] Lipid-based systems, which frequently comprise fatty acid esters, can be as basic as an oil-based medication or considerably more intricate formulations that are intended to emulsify on their own when they meet watery media. The systems indicated below can be developed in a way that is profitable:

Emulsions include nano-emulsions, pickering emulsions, micro-emulsifying drug delivery systems, self-micro-emulsifying drug delivery systems, self-nanoemulsifying drug delivery systems, and self-emulsifying drug delivery systems (SEDDSs).

Liposomes, biosomes, and pharmaco-somes are the components of vesicular systems.

Systems of lipid particulates that include conjugates, solid-lipid particles, solid-lipid microparticles, and lipospheres.[8]

The most well-known of these formulations is SEDDSs, which use spontaneous emulsification. Historically, SEDDSs have been used as oral drug delivery systems in their liquid form or packed into soft or hard gelatin capsules. Various solidification strategies have been explored recently to provide more acceptable delivery systems and enhance the stability of these overly simple systems. These techniques include converting liquid SEDDSs into dispersible powders, pellets, and granules.[8] Furthermore, current studies have demonstrated that SEDDSs can effectively improve drug delivery through a variety of channels, including the vaginal, rectal, ocular, nasal, and topical/transdermal routes of administration.[8] Once a drug is solubilized, the following favorable mechanisms of lipophilic drug uptake occur enhanced membrane fluidity, which facilitates drug absorption transcellular; opening tight junctions, which facilitates drug transport paracellularly; enhanced cytochrome (CYP) P 450 and/or P-glycoprotein intracellular concentration and residence time caused by surfactants; and lipid stimulation of lipoprotein/chylomicron synthesis for lymphatic absorption.[9]

Science behind lymphatic drug delivery via self-emulsifying microemulsions

The lymphatic system presents an intriguing route for medication absorption. This is mostly accessible to lipid-based formulations and can protect a lipophilic medication from enzymatic hydrolysis in the GIT wall and avoid first-pass metabolism, hence improving drug bioavailability.[9] Another benefit of lymphatic transport is that it can help target diseases that appear in the lymph nodes specifically.[9] Given its extensive drainage network throughout the entire body and its closeness to the circulatory system, it performs a unique function in the transportation of medicines to the systemic circulation[9]. Products that have gotten lost into the interstitial space, such as oxygen, carbohydrates, proteins, and lymphocytes, are mostly returned to the systemic circulation by the lymphatic system. The lipoidal formulations that impart self-emulsifying properties in-order to remain micro-emulsion (i.e. retain their globule size less than 100 nm) need to be stable *in-situ* too, especially when the formulation is diluted in the stomach and intestine. This stability of formulation of maintaining the globule size less than 200 nm enables the drug to permeate through the enterocyte, form drug-chylomicrons conjugates and pass through the lymphatic circulating system to deliver the drug. Every micro-emulsion may not be necessary to transport the drug into the lymphatic system directly. Those microemulsions, which are formulated as self-emulsifying in characteristics, will only withstand the digestion and enzymatic stress in the GUT and transport the microemulsion into the enterocytes, where they combine with chylomicrons to transport into the lymphatic circulatory system. Hence its highly essential to understand here that "self-micro emulsifying systems, i.e., O/W type" wherein oil globules are preloaded with lipophilic drugs need to remain in a complete solubilized state within oil globules and the globules should not coalesce to each other in-situ before they are been transported in enterocytes. Drugs with a Log *p-value* of more than 5 and solubility of a drug of more than 50 mg/g in long-chain triglycerides have the only chance to bind with chylomicrons and directly transport to the lymphatic system. Formulation excipients, especially surfactants and co-surfactants in their appropriate ratio, govern the drug solubility in the oil phase and secondly also help in maintaining globule size of less than 100 nm *in-situ*. Compared to conventional "non-self-emulsifying emulsions," the self-emulsifying systems are more resistant to the drastic conditions of the GUT like acid and alkaline pH, enzymes, etc., which in turn breaks the conventional emulsions but do not break the self-emulsifying systems, because of the higher concentrations of surfactants and co-surfactants.

Hence, the current research study focuses primarily on the preparation of 3 different kinds of emulsion each, in four test antimalarial. The basic design and formulation strategy of preparing such formulations is to study the key role of different ratio of surfactants and co-surfactants in each trial and their impact on the self-emulsifying property of each antimalarial drug. With this aim, every antimalarial drug was formulated in four different kinds of dosages with varied concentrations

of surfactants and co-surfactants and simultaneously, they were also compared to conventional drugs in hard gelatin capsules. In the end, all such formulations were subjected to dissolution studies in lipoidal dissolution media and the results were compared to the control formulation of the drug in hard gelatin capsules.

Compared to macro emulsions, the self-emulsifying microemulsions have better advantages wherein they can increase the solubility of the lipophilic compounds by dissolving them in the oil phase and then preparing a O/W type emulsion. In addition to solubility increase, these emulsions are also comparatively more resistant to creaming and have thermodynamically less potential energy.[10]

However, whereas the conventional macro-emulsions are highly dependent on the concentration of bile juices *in-situ*, whereas the micro-emulsions are not at all dependent because they "self" emulsify in the least presence of GUT juices.[11] Above and beyond, there is no fed effect involved wherein the absorption of lipophilic compounds would be dependent on post-prandial conditions.[12]

Surfactants that exhibit higher HLB values (indicative of the presence of polysorbate 80, Propylene glycol, PEG 200, 400 and PEG 600 and likewise) have a tendency to enhance the permeability of the lipophilic formulated microemulsions. This is achieved by opening the tight junctions of the Intestinal endothelial wall.[13]

Emulsification stability is an important parameter that governs the shelf life of the product. Hence it becomes very important to screen the range of surfactants and cosurfactants in different proportions by adding small amounts of long-chain oils and checking for flask inversions view to achieve a homogenous dispersion.[14]

One highly challenging situation that comes over in front of the researchers is the absence of a validated lipoidal *in-vitro* mode that can simulate the exact in-situ conditions to study the drug release of such specialised and versatile microemulsions.[15] In 2024, Patil *et al.* conducted a study in which they examined nine different formulations of liquid self-micro-emulsifying drug delivery systems (L-SMEDDS) intended to administer itraconazole.[16] This study exhibited superior drug release of itraconazole.

In their study, Ravindra *et al.* focused on creating a liquid self-micro emulsifying drug delivery system (L-SMEDDS) for the medication fenofibrate. This was accomplished by developing and utilizing a lyophilization technique to transform the L-SMEDDS into a solid SMEDDS and then producing tablets with improved solubility and dissolution rate. When compared to conventional dosage forms, these self-emulsifying formulations generated remarkably high *in-vitro* results.[17]

MATERIAL AND METHODS

Artemisinin was purchased from M/s Rhyme Organics, Hyderabad. Amodiaquine was purchased from M/s. Sigma Aldrich, Hyderabad, procured Merix Labs, Hyderabad and Halofantrine. Chloroquine was supplied by M/s. Dev-Life Corporations, Mumbai, Maharashtra.

Preparation of the self-emulsifying formulation of artemisinin with different surfactant to a co-surfactant ratio (Sur:Co-Sur::3:1) [18,19]

Procedure

Based on the below composition, Miglyol 810 was heated up to 40°C and to it artemisinin was dispersed until a translucent dispersion was observed. To this dispersion, under high shear mixing (using an ultra stirrer with 6000 rpm speed) labrafac and ethanol were added dropwise slowly until a period of 30 min. Table 1 captures a transparent O/W emulsion.

Preparation of the self-emulsifying formulation of artemisinin with a different surfactant to a co-surfactant ratio (Sur:Co-Sur::2:1) [18,19]

Procedure

Based on the below composition, Miglyol 810 was heated up to 40°C and to it, artemisinin was dispersed until a translucent dispersion was observed. To this dispersion, under high shear mixing (using an ultra stirrer with 6000 rpm speed) labrafac and ethanol were added dropwise slowly until a period of

Table 1: Preparation of self-emulsifying microemulsion of artemisinin (Sur:Co-Sur::~ 3:1)

S. No.	*Lipids Excipients/Drug*	*Function*	*% w/w*
1	Artemisinin	Drug	5
2	Miglyol 810	MCT oil	15
3	Labrafac PG	Lipophilic surfactant	60
4	Ethanol Anhydrous	Hydrophilic co-surfactant	20
	Total		100

Table 2: Preparation of Self-emulsifying microemulsion of artemisinin (Sur:Co-Sur::2:1)

S. No.	*Lipids excipients/Drug*	*Function*	*% w/w*
1	Artemisinin	Drug	5
2	Miglyol 810	MCT oil	5
3	Labrafac PG	Lipophilic surfactant	60
4	Ethanol anhydrous	Hydrophilic co-surfactant	30
	Total		100

Table 3: Preparation of Self-emulsifying microemulsion of Artemisinin (Sur:Co-Sur::1:1)

S. No.	*Lipids Excipients/Drug*	*Function*	*% w/w*
1	Artemisinin	Drug	5
2	Miglyol 810	MCT oil	15
3	Labrafac PG	Lipophilic surfactant	40
4	Ethanol anhydrous	Hydrophilic co-surfactant	40
	Total		100

30 min. Table 2 captures transparent O/W emulsion and nomenclature as artemisinin (2:1).

Preparation of the self-emulsifying formulation of artemisinin with different surfactants to the co-surfactant ratio (Sur:Co-Sur::1:1) [18,19]

Procedure

Based on the below composition, Miglyol 810 was heated up to 40°C and to it, artemisinin was dispersed until a translucent dispersion was observed. To this dispersion, under high shear mixing (using ultra stirrer with 6000 rpm speed) labrafac and ethanol were added dropwise slowly until a period of 30 minutes. Table 3 explains the preparation of a transparent O/W emulsion, nomenclature as artemisinin (2:1).

Preparation of the self-emulsifying formulation of halofantrine with different surfactant to co-surfactant ratio (Sur:Co-Sur::3:1)

Procedure

Based on the below composition, Miglyol 810 was heated up to 40°C and to it halofantrine was dispersed until a translucent dispersion was observed. To this dispersion, under high shear mixing (using ultra stirrer with 6000 rpm speed) Cremophor RH 40 and Transcutol P^{20} was added drop wise slowly until a period of 30 minutes. Table 4 explains preparation of a transparent O/W emulsion, nomenclated as halofantrine (3:1).

Preparation of the self-emulsifying formulation of halofantrine with a different surfactant to a co-surfactant ratio (Sur:Co-Sur::2:1)

Procedure

Based on the below composition, Miglyol 810 was heated up to 40°C and to it halofantrine was dispersed until a translucent dispersion was observed. To this dispersion, under high shear mixing (using ultra stirrer with 6000 rpm speed) Cremophor RH 40 and Transcutol P^{20} was added dropwise slowly until a period of 30 minutes. Table 5 explains preparation of a transparent O/W emulsion, nomenclated as halofantrine (2:1).

Preparation of the self-emulsifying formulation of halofantrine with different surfactant to a co-surfactant ratio (Sur:Co-Sur::1:1)

Procedure

Based on the below composition, Miglyol 810 was heated up to 40°C and to it halofantrine was dispersed until a translucent dispersion was observed. To this dispersion, under high shear mixing (using ultra stirrer with 6000 rpm speed) Cremophor RH 40 and Transcutol P^{20} was added dropwise slowly until a period of 30 min. Table 6 explains preparation of a transparent O/W emulsion, nomenclated as halofantrine (1:1).

Preparation of the self-emulsifying formulation of amodiaquine with different surfactant to a co-surfactant ratio (Sur:Co-Sur::3:1)

Procedure

Based on the below composition, Miglyol 810 was heated up to 40°C and to it amodiaquine was dispersed until a cloudy dispersion was observed. To this dispersion, under high shear mixing (using ultra stirrer with 6000 rpm speed) lauroglycol-90[21] and Propylene Glycol was added dropwise slowly until a period of 30 min. Table 7 captures the preparation of a transparent O/W emulsion and nomenclated as amodiaquine (3:1).

Preparation of the self-emulsifying formulation of amodiaquine with different surfactant to co-surfactant ratio (Sur : Co-Sur :: 2:1)

Procedure

Based on the below composition, Miglyol 810 was heated up to 40°C and to it amodiaquine was dispersed until a

Table 4: Preparation of Self-emulsifying microemulsion of Halofantrine (Sur:Co-Sur::~ 3:1)

S. No.	*Lipids Excipients/Drug*	*Function*	*% w/w*
1	Halofantrine	Drug	5
2	Miglyol 810	MCT oil	15
3	Cremophor RH 40	Surfactant	60
4	Transcutol P	Solubilizer	20
	Total		100

Table 5: Preparation of Self-emulsifying microemulsion of Halofantrine (Sur:Co-Sur::2:1)

S. No.	*Lipids Excipients/Drug*	*Function*	*% w/w*
1	Halofantrine	Drug	5
2	Miglyol 810	MCT oil	5
3	Cremophor RH 40	Surfactant	60
4	Transcutol P	Solubilizer	30
	Total		100

Table 6: Preparation of self-emulsifying microemulsion of halofantrine (Sur:Co-Sur::1:1)

S. No.	*Lipids Excipients/Drug*	*Function*	*% w/w*
1	Halofantrine	Drug	5
2	Miglyol 810	MCT oil	15
3	Cremophor RH 40	Surfactant	40
4	Transcutol P	Solubilizer	40
	Total		100

Table 7: Preparation of Self-emulsifying microemulsion of Amodiaquine (Sur : Co-Sur ::~ 3:1)

S. No.	*Lipids Excipients / Drug*	*Function*	*% w/w*
1	Amodiaquine	Drug	5
2	Miglyol 810	MCT oil	15
3	Lauroglycol-90	Lipophilic surfactant	60
4	Propylene Glycol	Co-surfactant	20
	Total		100

Table 8: Preparation of self-emulsifying microemulsion of amodiaquine (Sur : Co-Sur ::~ 2:1)

S. No.	*Lipids Excipients / Drug*	*Function*	*% w/w*
1	Amodiaquine	Drug	5
2	Miglyol 810	MCT oil	5
3	Lauroglycol-90	Lipophilic surfactant	60
4	Propylene Glycol	Co-surfactant	30
	Total		100

Table 9: Preparation of self-emulsifying microemulsion of Amodiaquine (Sur:Co-Sur::~ 1:1)

S. No.	*Lipids Excipients/Drug*	*Function*	*% w/w*
1	Amodiaquine	Drug	5
2	Miglyol 810	MCT oil	15
3	Lauroglycol-90	Lipophilic surfactant	40
4	Propylene Glycol	Co-surfactant	40
	Total		100

cloudy dispersion was observed. To this dispersion, under high shear mixing (using ultra stirrer with 6000 rpm speed) lauroglycol-90[21] and Propylene Glycol were added dropwise slowly until a period of 30 minutes. Table 8 explains the preparation of a transparent O/W emulsion, nomenclated as amodiaquine (2:1).

Preparation of the self-emulsifying formulation of amodiaquine with different surfactant to co-surfactant ratio (Sur : Co-Sur :: 1:1)

Procedure

Based on the below composition, Miglyol 810 was heated up to 40°C and to it amodiaquine was dispersed until a cloudy dispersion was observed. To this dispersion, under high shear mixing (using ultra stirrer with 6000 rpm speed) lauroglycol-90[21] and Propylene Glycol was added dropwise slowly until a period of 30 min. Table 9 explains the preparation of a transparent O/W emulsion, nomenclature as amodiaquine (1:1)

Preparation of the self-emulsifying formulation of chloroquine with different surfactant to co-surfactant ratio (Sur : Co-Sur :: 3:1)

Procedure

Based on the below composition, Miglyol 810 was heated up to 40°C and chloroquine was dispersed until a cloudy dispersion was observed. To this dispersion, under high shear mixing (using ultra stirrer with 6000 rpm speed) Capryol-90 and a mixture of Cremophor RH-40 and PEG-400,[22] was added dropwise slowly until a period of 30 min. Table 10 explains the preparation of a transparent O/W emulsion, nomenclature as chloroquine (3:1).

Table 10: Preparation of Self-emulsifying microemulsion of Chloroquine (Sur:Co-Sur ::~ 3:1)

S. No.	*Lipids Excipients / Drug*	*Function*	*% w/w*
1	Chloroquine	Drug	5
2	Miglyol 810	MCT oil	15
3	Capryol-90	Lipophilic surfactant	60
4	Cremophor RH-40 – PEG 400 (1:1)	Co-surfactant	20
	Total		100

Table 11: Preparation of self-emulsifying microemulsion of chloroquine (Sur:Co-Sur::~ 2:1)

S. No.	*Lipids Excipients/Drug*	*Function*	*% w/w*
1	Chloroquine	Drug	5
2	Miglyol 810	MCT oil	5
3	Capryol-90	Lipophilic surfactant	60
4	Cremophor RH-40 – PEG 400 (1:1)	Co-surfactant	30
	Total		100

Table 12: Preparation of Self-emulsifying microemulsion of Chloroquine (Sur:Co-Sur::~ 1:1)

S. No.	*Lipids Excipients / Drug*	*Function*	*% w/w*
1	Chloroquine	Drug	5
2	Miglyol 810	MCT oil	15
3	Capryol-90	Lipophilic surfactant	40
4	Cremophor RH-40 – PEG 400 (1:1)	Co-surfactant	40
	Total		100

Preparation of the self-emulsifying formulation of chloroquine with different surfactant to co-surfactant ratio (Sur : Co-Sur :: 2:1)

Procedure

Based on the below composition, Miglyol 810 was heated up to 40°C and to it chloroquine was dispersed until a cloudy dispersion was observed. To this dispersion, under high shear mixing (using ultra stirrer with 6000 rpm speed) Capryol-90 and a mixture of Cremophor RH-40 and PEG-400[22] was added dropwise slowly until a period of 30 minutes. Table 11, explains the preparation of a transparent O/W emulsion, nomenclature as chloroquine (2:1).

Preparation of the self-emulsifying formulation of chloroquine with different surfactants to a co-surfactant ratio (Sur:Co-Sur::1:1)

Procedure

Based on the below composition, Miglyol 810 was heated up to 40°C and to it chloroquine was dispersed until a cloudy dispersion was observed. To this dispersion, under high shear mixing (using ultra stirrer with 6000 rpm speed) Capryol-90

Table 13: Results of percent average drug release of micro-emulsions with varied concentrations of surfactant to co-surfactant

S. No.	*Artemisinin*				*Halofantrine*				*Amodiaquine*				*Chloroquine*			
Profile in min	*Drug in cap*	*3:1 ratio*	*2:1 ratio*	*1:1 ratio*	*Drug in cap*	*3:1 ratio*	*2:1 ratio*	*1:1 ratio*	*Drug in cap*	*3:1 ratio*	*2:1 ratio*	*1:1 ratio*	*Drug in cap*	*3:1 ratio*	*2:1 ratio*	*1:1 ratio*
15	ND	33	28	12	ND	22	16	8	ND	38	30	18	ND	42	34	19
20	ND	45	38	16	ND	36	29	16	ND	49	41	22	ND	62	55	29
30	ND	78	68	22	ND	65	56	26	ND	77	67	36	3	78	62	36
45	3	92	77	32	ND	82	75	20	ND	89	79	42	5	91	79	45
60	6	98	80	36	2	97	81	28	3	99	82	56	6	100	83	59

ND: not detected.

and a mixture of Cremophor RH-40 and PEG-400[22] was added dropwise slowly until a period of 30 min. Table 12 explains the preparation of a transparent O/W emulsion, nomenclature as chloroquine (1:1).

In addition to the below microemulsion prepared, the same antimalarial drugs were individually also filled in empty hard gelatin capsules at a concentration of 5% w/w and subjected to drug release studies in simulated lipoidal digestive dissolution media.(as control arm, for comparison purposes)

Estimation of (%)percent drug release of varied 12-micro emulsions in simulated lipid digestive media

The dissolution apparatus was set at the following parameters:
RPM: 100 rpm
Apparatus type: basket
Volume: 900 mL
Media: Simulated lipolytic-digestive fluids/media.
Total drug release time: 60 minutes
Temperature: 37°C.
The results of the *in-vitro* drug release of different emulsion systems are tabulated in Table 13.

RESULTS AND DISCUSSIONS

Table 13 observations depict those formulations that comprise surfactants:co-surfactants ratio of ~3:1 and are most ideal concentrations for enhanced drug release in simulated lipid digestive media.

Hence, because of this reason, the percent drug release of all four drugs with a ration of 3:1 demonstrated complete drug release at 60 minutes; however the other ratio could not succeed in extracting the drug in the dissolution media. On the same grounds similar observation trend was also seen in all formulations of 1:1 ratio wherein the extent and rate were least among all too. There also has been a uniform trend seen of percent drug release and ratio (from 3:1, 2:1 and 1:1) wherein the drug extent was maximum in 3:1 and least in 1:1. One more very important observation was regarding the drug release of drug powder filled in empty hard gelatin capsules. All capsules filled with only drug powder demonstrated the least drug release from the extent and rate point of view. This also indicates that antimalarial drugs like artemisinin, Halofantrine, amodiaquine and chloroquine, when formulated into conventional capsules, will face a lot of challenges from oral bioavailability point of view. However, when emulsions of the same drugs are prepared, the possibility of their oral bioavailability may also be overcome, which is indicated by the above results from tablet 13.

Anjana *et al.,* in a research study in the year 2017, studied numerous natural ingredients and formulated in a unique liquid carrier system called "phytosome," which demonstrated several folds increases in oral bioavailability.[23]

Rao YS *et al.,* in their review paper, also expressed that research on drug delivery *via* microemulsions is a promising field that holds very high potential for regulated release, enables medication targeting to different body locations and with improved bioavailability.[24]

CONCLUSION

Antimalarial drugs are well known for limited oral bioavailability and most of these exhibit limited bioavailability because of poor absorption due to very less aqueous solubility and higher C Log *p-value*(s).

Artemisinin, halofantrine, amodiaquine and chloroquine area also among those antimalarials, which exhibit similar limited oral bioavailability. Microemulsions formed by varied concentrations of surfactant and co-surfactants in this study demonstrated that as the concentration ratio of surfactant to co-surfactant increases, the drug release from the oil droplets also increases. And since these oil droplets that contain the drug are in size of 250 nm in size, the surface area being very high is primarily responsible for higher (rate and extent) drug release in dissolution media when compared to formulation wherein drug powder was filled in empty hard gelatin capsules. This indicates that such microemulsions, when formulated, is anticipated to demonstrate more oral bioavailability compared to conventional solid oral tablets and capsules. The reason for enhanced oral bioavailability is because of the reason that such higher concentrations of surfactants and co-surfactants in emulsions impart a self-emulsifying property depicted by higher thermodynamic stability, more resistance to acid and alkali of GUT, resistance against proteolytic enzymes and all the harsh peristaltic movement of GUT. Even though with all such harsh GUT environmental conditions, these self-emulsifying microemulsions retain their O/W emulsion (droplet size) nature and the oil droplets migrate through the enterocytes of the intestinal wall and form "Drug-Chylomicrons Conjugates," which later transports through "lacteals" (i.e. lymphatic vessels") present in the intestinal

villi. Drug-chylomicron conjugates enter lacteals through these open, button-like junctions between lymphatic endothelial cells. There are two reasons for why the drug-chylomicrons conjugates don't enter the blood circulation and enter only the lymphatic vessels. The first reason is; that the drug-chylomicron conjugates are so big in size that their uptake from the wall of blood capillaries is not possible and secondly, they lack the desired lipophilic and hydrophilic balance which is needed for absorption via blood capillaries exclusively. However, the drug-chylomicron conjugates exocytosis to permeate through lymphatic vessels easily. Once drug-chylomicrons are poured in the lymphatic system, they finally drain into the central systemic circulatory system after bypassing metabolism in the liver. Self-emulsifying microemulsions are advantageous over conventional emulsions and formulations because they have the extra edge of being highly thermodynamically stable *in-situ* and withstand all the GUT stress to remain in sub-microns size, wherein they provide the highest surface area for the drug to get solubilized *in-situ* and absorbs through the lymphatic circulatory system. The microemulsion of four test antimalarial, i.e., artemisinin, halofantrine, amodiaquine and chloroquine, exhibited self-emulsifying characteristics, too.

REFERENCES

1. WHO's World Malaria report. World Health Organization. 2024 Jan p. 322.
2. Klayman DL. Qinghaosu (artemisinin): An antimalarial drug from China. Science. 1985;228(4703):1049–1055. Available from: doi.org/10.1126/ science.3887571
3. White NJ, Hien TT, Nosten FH. A Brief History of Qinghaosu. Trends Parasitology. 2015;31(12):607-610. Available from: doi.org/10.1016/j.pt.2015.10.010
4. Li J, Zhou B. Biological actions of artemisinin: Insights from medicinal chemistry studies. Molecules. 2010;15(3):1378-1397. Available from: doi.org/10.3390/molecules15031378
5. Sugathan A, Rao S, Kumar NA, Chatterjee PK. Malaria and Malignancies-A review. Global Biosecurity. 2024;6(1). Available from: doi.org/10.31646/gbio.249
6. Tan SLJ, Billa N. Improved Bioavailability of Poorly Soluble Drugs through Gastrointestinal Muco-Adhesion of Lipid Nanoparticles. Pharmaceutics. 2021; 13(11):1817. Available from: doi.org/10.3390/ pharmaceutics13111817
7. Gupta S, Kesarla R, Omri A. Formulation strategies to improve the bioavailability of poorly absorbed drugs with special emphasis on self-emulsifying systems. ISRN Pharmaceutics. 2013; 1(1): 1-16. Available from: doi.org/10.1155/2013/848043
8. Mukherjee S, Ray S, Thakur RS. Solid lipid nanoparticles: A modern formulation approach in drug delivery system. Indian Journal of Pharmaceutical Sciences. 2009; 71(4): 349-358. Available from: doi.org/10.4103/0250-474X.57282
9. Peterson B, Weyers M, Steenkamp JH, Steyn JD, Gouws C, Hamman JH. Drug Bioavailability Enhancing Agents of Natural Origin (Bioenhancers) that Modulate Drug Membrane Permeation and Pre-Systemic Metabolism. Pharmaceutics. 2019 ;11(1): 33. Available from: doi.org/ 10.3390/pharmaceutics11010033
10. Taha E, Ghorab D, Zaghloul AA. Bioavailability assessment of vitamin a self-nano emulsified drug delivery systems in rats: a comparative study. Medical Principles and Practice. 2007 ;16(5) :355-359. Available from: doi.org/10.1159/000104808
11. Chen ZQ, Liu Y, Zhao JH. Improved oral bioavailability of poorly water-soluble indirubin by a super saturable self microemulsifying drug delivery system. International Journal of Nanomedicine. 2012; 7:1115-1125. Available from: doi.org/10.2147/IJN.S28761
12. Lawrence MJ, Rees GD. Micro-emulsion-based media as novel drug delivery systems. Advanced Drug Delivery Reviews. 2000;45(1): 89-121. Available from: doi.org/10.1016/S0169-409X(00)001034
13. Tang B, Cheng G, Gu JC, Xu CH. Development of solid self-emulsifying drug delivery system; preparation techniques and dosage forms. Drug Discovery Today. 2008; 13:606-612. Available from: doi.org/10.1016/j.drudis.2008.04.006
14. Zhang P, Liu Y, Xu J. Preparation and evaluation of self-emulsifying drug delivery system of oridonin. International Journal of Pharmaceutics. 2008; 355:269-276. Available from: doi.org/ 10.1016/j. ijpharm.2007.12.026
15. Tang TT, Hu XB, Liao DH, Liu XY, Xiang DX. Mechanisms of microemulsion enhancing the oral bioavailability of puerarin: comparison between oil-in-water and water-in-oil microemulsions using the single-pass intestinal perfusion method and a chylomicron flow blocking approach. International Journal of Nanomedicine. 2013; 8:4415-4426. Available from: doi.org/10.2147/IJN.S51469
16. Patil R, Kshirsagar SK. Formulation, Optimization and Evaluation of Solid SMEDDS of Itraconazole in Effervescent Granules Form. International Journal of Pharmaceutical Quality Assurance. 2024;15(1):273-287. Available from: doi.org/10.25258/ijpqa.15.1.42
17. Arti N, Ravindra K. Formulation and Evaluation of Fenofibrate Dry Emulsion Tablets by Freeze Drying Method. International Journal of Pharmaceutical Quality Assurance. 2022;13(4):369-376. Available from: doi.org/10.25258/ijpqa.13.4.05
18. Ellen KG, Mhangoa B, Benjamin R, Bergthora S, Gizurarson S. Incompatibility of antimalarial drugs: challenges in formulating combination products for malaria. Drug Delivery. 2024; 31 (1) :1-10. Available from: doi.org/10.1080/10717544.2023.2299594
19. Utami1 D, Meliana Y, Budianto E. In-Vitro Dissolution and Characterization of Self-Emulsifying Drug Delivery System of Artemisinin for Oral Delivery. Journal of Physics: Conference Series. 2021; 1811: 1-8. Available from: doi.org/10.1088/1742-6596/1811/1/012133
20. Babu AM, Rao PB, Sudhakar P. Formulation and evaluation of self-microemulsion drug delivery system of low solubility drug "simvastatin" for improved solubility and bioavailability. International Journal of Pharmacy & Therapeutics. 2012: 3(2) :189-197. Available from: doi.org/10.21276/ijpt.
21. Brinkmann J, Exner J, Luebbert C, Sadowski G. In-Silico Screening of Lipid-Based Drug Delivery Systems. Pharmaceutical Research. 2020; 37: 1-12. Available from: doi.org/10.1007/s11095-020-02955-0
22. Ngawhirunpat T, Worachun N, Opanasopit P, Rojanarata T, Panomsuk S. Cremophor RH40-PEG 400 microemulsions as transdermal drug delivery carrier for ketoprofen. Pharmaceutical Development and Technology. 2021; 18 (4): 798–803. Available

from: doi.org/10.3109/10837450.2011.627871
23. Anjana R, Sunil K, Sharma H, Khar RK. Phytosome Drug Delivery of Natural Products: A Promising Technique for Enhancing Bioavailability. International Journal of Drug Delivery Technology. 2017; 7(3) :157-165. Available from: doi.org/10.25258/ijddt.v7i03.9559
24. Rao YS, Deepthi KS, Chowdary KPR. Microemulsions: a novel drug carrier system. International Journal of Drug Delivery Technology. 2009; 1(2): 39-41. Available from: doi.org/10.25258/IJDDT.V1I2.8838