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"TASTE MASKED ORAL DISINTEGRATING TABLET DOSAGE FORM OF ARTEMETHER AND LUMEFANTRINE"

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ABSTRACT

The purpose of this research was to mask the intensely bitter taste of Lumefantrine and to formulate oral-disintegrating tablet (ODT) of Artemether&Lumefantrine. Taste masking was done by complexingLumefantrine with amino alkyl methacrylate copolymer (Eudragit E - 100) using solvent deposition method and acetone as a solvent for pH-sensitive polymer and was tested for drug content and in vitro taste in simulated salivary fluid (SSF) of pH 6.8. The complex with drug-polymer ratio of 1: 0.1 that did not release drug in SSF was considered taste-masked and selected for formulation of ODTs.

The properties of tablets such as tensile strength, wetting time, water absorption ratio, in vitro disintegration time, and disintegration in the oral cavity were investigated to elucidate the wetting and disintegration characteristics of tablets. Tablets of batch F4 containing 1.25% of Kyron T-314 showed faster disintegration, within 14 seconds. Good correlation between in vitro disintegration behavior and in oral cavity was recognized. Taste evaluation of ODT in human volunteers revealed considerable taste masking. Thus, results conclusively demonstrated successful masking of taste and rapid disintegration of the formulated tablets in the oral cavity.

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AIM OF WORK

The formulation of an oral disintegrating tablet for a bitter drug is a challenging task for a formulation scientist. Oral Disintegrating Tablets (ODT) were kept on tongue where they rapidly get disintegrate and dispersed in saliva, resulting in a solution or suspension and feel intensely bitter.

Lumefantrine and Artemether are anti-malarial drugs, combination indicated for the treatment of uncomplicated malarial. In general, Mostly Artemether and Lumefantrine are drugs for pediatric as well as geriatric formulation and it is difficult to give drug to the children with a glass of water; hence it is beneficial to administer such drugs as ODTs. Also fast disintegration will reduce

any potential choking hazard and will also make it harder to spit out the dosage form. Lumefantrine is an intensely bitter drug; hence, if it is incorporated directly into an ODT the main objective behind formulation of such a dosage form will definitely get futile. This is because when bitter drugs incorporated in this formulation, it comes in contact with salivary fluids and feels bitter.

The taste and texture of pediatric formulations are critical to facilitate compliance in children since children are more sensitive about the sense of taste than adults. So masking of bitter taste in the formulation is a prerequisite as it improves the compliance of the patient and product value. There are numerous approaches investigated by the researchers to mask the bitter taste of drug. The ideal solution to reduce or inhibit bitterness is to prevent the release of drug in saliva or/and to use artificial sweeteners and flavors.

Many polymer carriers can be used for coating or complexing the drug and thus preventing the drug release in saliva so as to mask the bitter taste of drug. For the present investigation, various percentages of Eudragit E-100 are used.

Thus in the present study, an attempt has been made to mask the taste of Lumefantrine&Artemether and to formulate ODT with good mouth feel so as to prepare a “patient-friendly dosage form.”

Objectives:

- Characterization of drug
- Selection of appropriate polymer for taste masking of lumefantrine
- Preparation and optimization of drug polymer complex
- Characterization of drug polymer complex
- Optimization of super disintegrant ratio in formulation with taste masked drug polymer complex
- Evaluation of oral disintegrating tablet

INTRODUCTION

Orally disintegrating tablets (ODTs) has remarkable disintegration properties; it can rapidly disintegrate without water in the mouth within a few seconds. It offers an advantage for populations who have difficulty in swallowing, more specific with pediatric population. Lumefantrine&Artemether is anti malarial drugs used especially for pediatric and geriatric persons. Lumefantrine is an intensely bitter drug. So, masking of bitter taste in the formulation is a prerequisite as it improves the compliance of the patient and product value. There are numerous approaches investigated by the researchers to mask the bitter taste of drug. The ideal solution to reduce or inhibit bitterness is to prevent the release of drug in saliva or/and to use artificial sweeteners and flavors.

Introduction to taste-masking

There are numerous pharmaceutical and OTC preparations that contain actives, which are bitter in taste. A constant problem in the treatment of patient's especially pediatric and elder patients is their inability or unwillingness to swallow solid dosage forms such as tablets and capsules. To fulfill these requirements, the pharmaceutical industries have developed several other alternatives like syrups, suspensions, emulsions, chewable tablets, dispersible tablets, mouth melt tablets, solutions and inhalers, etc. When bitter tasting drugs incorporated in these formulations, it comes in contact with salivary fluids and feels bitter.

Pharmaceutical companies are investing much time, money and resources in developing palatable, pleasant tasting products because good tasting products not only enhance the patient compliance but also provide a competitive advantage when a therapeutic category is crowded with similar products (e.g. anti-infective). (Gowthamarajan et al.,2004)

MATERIALS AND METHOD

List of materials used

Table No.5. - List of Materials used for project

Sr. No.	MATERIALS	VENDOR'S NAME
1	Artemether	Ipca Laboratories Ltd, Mumbai, India
2	Lumefantrine	Ipca Laboratories Ltd, Mumbai, India
3	Kyron T- 314	Corel Pharma, Ahmedabad, India
4	Eudragit E-100	Degussa Company, New Jersey, USA
5	Acetone	Oswal Chemicals, Pune, India
6	Sancel PH-102	NB Enterprise, Nagpur, India
7	Mannitol	QuingdaoJiucham, China
8	Neotame	Nutrasweet Company, Illinois, USA
9	Flavour Cherry	Firmenich, Geneva, Switzerland
10	Magnesium stearate	Sunshine Organics Pvt. ltd., India
11	Anhydrous Sodium Bicarbonate	Eagle International, Ahmedabad, India
12	Light Magnesium Carbonate	Sunshine Organics Pvt. ltd., India
13	Aerosil	(evonic industries) New Jersey, USA
14	Anhydrous Citric Acid	Alpha Chemika, Mumbai, India
15	Kyron -114	Corel Pharma, Ahmedabad, India
16	Croscarmellose sodium	DMVO international, India

List of equipments used

Table No. 6. – List of Equipments used for project

INSTRUMENTS	VENDOR'S NAME
Digital balance	Citizen scales Pvt ltd., India
Electronic weighing balance	Afcoset ER 200A
Mechanical stirrer	Expo hi-tech, Mumbai, India
HPLC(LC-2010 C_{HT})	Shimadzu, Tokyo, Japan
UV-Visible spectrophotometer	UV-pharmaspec 1700, Shimadzu, Japan
Sonicator	Bransone Ultrasonic Corporation, U.S.A
Digital pH meter	Thermo Orion model 420A+, USA
Hot air oven	Expo hi-tech, Mumbai, India
Rapid mixing granulator	Saral engineering, Vapi, India
Shifter	Saral engineering, Vapi, India
Bulk/Tapped density apparatus	Expo hi-tech, Mumbai, India
Rotary compression machine	Cadmach machinery co. Pvt ltd., India
Thickness tester	Mitutoyo, Japan
Hardness tester	Pfizer hardness tester, Veego Instruments Corporation, India
Friabilator	Electrolab, Mumbai, India
Disintegration test apparatus	Electrolab, Mumbai, India
Dissolution test apparatus	Electrolab TDL-08L, Mumbai, India

Preliminary study

Selection of polymer for taste masking of Lumefantrine

Following polymers were taken initially for selecting the best polymer for taste masking of Lumefantrine.

- Kyron T-114 (Methacrylic acid polymer)
- Eudragit E-100 (Polymethacrylate polymer)

Various taste masking technologies were extensively studied and finally ion-exchange, solvent deposition method were tried for taste masking of Lumefantrine with different polymers. (Sharma et al., 2007)

Ion-exchange resins like Kyron T-114, was used for taste masking of Lumefantrine by adsorption mechanism. Resins were allowed to swell in a required quantity of water followed by addition of Lumefantrine and the resultant mass was allowed to dry in a hot air oven and evaluated.

Solvent deposition method was applied for taste masking of Lumefantrine with Eudragit E-100. For this, Eudragit E-100 and Lumefantrine were dissolved in acetone and the resultant solution was deposited onto inert carrier Mannitol with continuous stirring. The wet mass so obtained was allowed to air dry.

Preparation and optimization of Drug-Polymer Complex (DPC)

From preliminary study, Eudragit E-100 was selected as best polymer for taste masking of Lumefantrine. Lumefantrine and Eudragit E-100 complex were prepared using the solvent deposition method. The solutions of Eudragit E-100 and Lumefantrine were prepared in acetone in various ratios and deposited onto inert carrier Mannitol with continuous stirring. The wet mass obtained was allowed to dry completely at room temperature. The dried matrix was sieved through 30# and finally stored in a tightly closed container for further studies.

Characterization of Drug Polymer Complex

Percentage yield determination

After complete drying of DPC, the percentage yield was determined by the formula given below: (Anand et al., 2007)

$$\% \text{ yield} = \frac{\text{weight of dried DPC}}{\text{weight of (Lumefantrine + Eudragit E - 100 + Mannitol)}} \times 100 \quad --(3)$$

Determination of drug entrapment

Drug entrapment was determined by dissolving 100 mg of DPC in 100 ml : Acetonitrile : Ion-pairing Soln. = 65 : 35 ([2.75 gm of NaH_2PO_4 + 1gm of Sod.1-Hexane Sulphonate] in 1000ml Water >> Adjust pH 2.5) mixture in ratio of 65:35 and analyzing appropriate dilution by proposed HPLC method. The% drug entrapment was calculated from linearity curve and the equation below. (Khan et al., 2006)

$$\% \text{ Drug entrapment} = \frac{\text{Actual drug content}}{\text{Theoritical drug content}} \times 100 \quad ----(4)$$

In-vitro taste evaluation

In vitro taste was evaluated by determining drug release in simulated salivary fluid (SSF) (pH 6.8) to predict release in the human saliva. DPC, equivalent to 120 mg of Lumefantrine (equivalent to 120 mg Lumefantrine, i.e., its dose), was placed in 10 ml of SSF and shaken for 60 seconds. The amount of drug released was analyzed by proposed HPLC method. (Khan et al., 2006)

In-vivo taste evaluation

Pure drug (120 mg), DPC (equivalent to 120 mg Lumefantrine) was provided to 11 healthy human volunteers. Subjects scored the intensity of bitterness by placing the given amount of sample on the tongue, taste sensation was felt for one minute, and thoroughly rinsing their mouths with water after each sample evaluation. Each volunteer judged the taste of sample using a bitterness intensity scale involving a five point scale which ranged from 0 to 3.

(0 = no bitterness, 0.5 = threshold bitterness, 1= slight bitterness, 2 = moderate bitterness, 3 = strong bitterness). (Anand et al., 2007)

Optimization of super-disintegrant and Formulation of oral disintegrating tablet

Direct compression method was used for preparing ODTs of Lumefantrine: Eudragit E-100 complex. Different batches of tablets were prepared using different ratio of super-disintegrantto achieve ODTs. DPC of final batch was used for preparing

ODTs. DPC were incorporated on the basis of drug loading so as to give the required dose of 120 mg/tablet. The DPC were blended along with Artemether& the other excipients (super-disintegrant, diluent, sweetener, flavor and lubricants) and the resulting mixture was compressed into tablet of 11.00 mm diameter and weighing 320 mg. The compositions of the tablet prepared with different combinations of super-disintegrant are given in table. (Anand et al., 2007)

Table 7.- Composition of Orally-Disintegrating Tablets

Ingredients, mg	Trial batches				
	F1	F2	F3	F4	F5
DCP	132.0	132.0	132.0	132.0	132.0
Anhydrous sodium bicarbonate	4.0	4.0	4.0	4.0	4.0
Light magnesium carbonate	7.0	7.0	7.0	7.0	7.0
Artemether	20.0	20.0	20.0	20.0	20.0
Mannitol	98.4	97.6	96.8	96.0	95.2
Sancel PH 102	25.0	25.0	25.0	25.0	25.0
Neotame	4.0	4.0	4.0	4.0	4.0
Flavour cherry	3.0	3.0	3.0	3.0	3.0
Aerosil	8.0	8.0	8.0	8.0	8.0
Anhydrous citric acid	7.0	7.0	7.0	7.0	7.0
Kyron T-314	**1.6**	**2.4**	**3.2**	**4.0**	**4.8**
Talc	2.0	2.0	2.0	2.0	2.0
Magnesium stearate	8.0	8.0	8.0	8.0	8.0
Total	320	320	320	320	320

DPC indicates drug polymer complex. Formula for one tablet is shown in the table.
Each tablet contains 120 mg of Lumefantrine& 20 mg of Artemether.

Physical properties of tablet blend

Physical properties such as bulk density, tapped density, compressibility index, and the angle of repose of blend were determined. (Khan et al., 2006)

Angle of repose was measured using fixed base cone method. Tablet blend were allowed to fall freely through a funnel fixed at 1cm above the horizontal flat surface until the apex of the conical pile just touches to the tip of the funnel. The height and diameter of the cone was measured and angle of repose was calculated by using the following formula.

$$\theta = \tan^{-1} h/r - - - - - (\mathbf{5})$$

Where, h=cone height, r = radius of circular base formed by the powder on the ground.

The bulk and tapped densities were measured in a 25ml graduated cylinder as a measure of pack ability of the blends. The sample contained in the measuring cylinder was tapped mechanically by means of constant velocity rotating cam. The initial bulk volume and final tapped volume were noted from which, their respective densities were calculated.

Compressibility index or Carr's index value of blends was computed according to the following equation:

$$Carr'Index\ (\%) = \frac{\{Tabpped\ Density - Bulk\ Density}{Tapped\ Density} \times 100 - - - -(6)$$

Hausner's ratio of microbeads was determined by comparing the tapped density to the bulk density by using the equation:

$$\text{Hausner's Ration} = \frac{Tapped\ Density}{Bulk\ Density} - - - - - (7)$$

Evaluation of tablet

General appearance, thickness, hardness test

Five tablets from each batch were randomly selected and organoleptic properties such as color, odor, taste, shape were evaluated. The thickness and diameter of tablet was measured using vernier

calipers. Hardness of the tablet was tested by using 'Pfizer' hardness tester. (Khan et al., 2006)

Determination of tablet friability

Tablet friability was reported as the percentage weight loss from twenty tablets after 100 rotations at 25 rpm in a friabilator. Pre weighed samples of tablets were placed in drum, which was when operated for 100 revolutions. The tablets were dedusted and reweighed.

Wetting time and water absorption ratio

Wetting time of the tablets can be measured using a simple procedure.Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10-cm diameter. Ten milliliters of water-soluble dye (eosin) solution is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as the wetting time.

For measuring water absorption ratio the weight of the tablet before keeping in the petridish is noted (W_b). The wetted tablet from the petridish is taken and reweighed (W_a). The water absorption ratio, *R* can be then determined according to the following equation. (Bandari et al., Orodispersible tablets).

$$R = 100\frac{Wa - Wb}{Wb} - - - - - (\mathbf{8})$$

Dispersion test

A qualitative test 'Uniformity of dispersion' was checked according to the specification given in the European Pharmacopoeia for oral disintegrating tablet. Two tablets were placed in 100 ml water (at 25˚C in a beaker). The tablets were allowed to disintegrate and the dispersion was stirred with a glass rod until a smooth dispersion was obtained. The dispersion was passed through a 710 µm sieve (No. 22) and the sieve screen was checked for any material retained. (Anand et al., 2007)

In-vitro disintegration study

In vitro disintegration time for ODTs was determined using USP and modified disintegration apparatus with stimulating salivary fluid (SSF) (pH 6.8) as the disintegrating medium. During this study we made an attempt to develop a more suitable apparatus for ODT (Figure 3.) because many reports indicated the unsuitability of the conventional disintegration test apparatus for RDT. Briefly, the apparatus consisted of a glass beaker of 1000-mL capacity with the wire basket positioned in the beaker with the help of a support in a way that when the beaker contained 900 mL of disintegrating medium, the basket had only 6 mL of it. A magnetic bead was placed at the bottom of the beaker maintained at 37 ± 2°C. Disintegration time was determined at 25 and 50 rpm and compared with results obtained from the USP disintegration test apparatus and the in vivo disintegration test. (Khan et al., 2006)

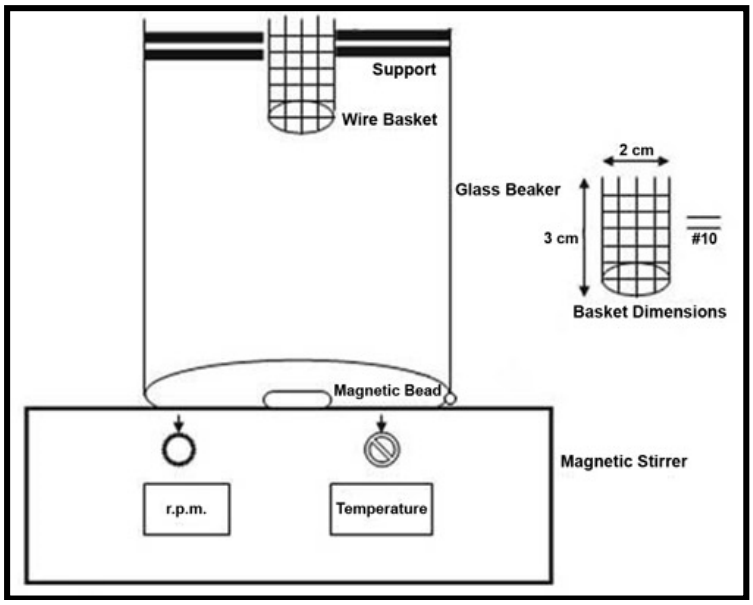


Figure.3- Modified disintegrating apparatus

In-vivo disintegration time

In vivo disintegration was performed on 6 healthy human volunteers, from whom informed consent was first obtained. One tablet was held in the mouth after rinsing and the time required for complete disintegration of the tablet was recorded and then spat out. The mouth was rinsed with water without swallowing the disintegrated material. (Khan et al., 2006)

In-vivo taste and sensory evaluation of roughness

Tablet of selected batch on the basis of disintegration time was used for in-vivo taste and sensory evaluation. Taste evaluation was done using the time intensity method on a panel of 6 healthy human volunteers. One ODT (containing 120 mg of Lumefantrine& 20 mg Artemether) was held in the mouth until complete disintegration and then spat out. Bitterness was recorded immediately and at several intervals for 15 minutes according to the bitterness intensity scale from 0 to 3 where 0, 0.5, 1, 2, and 3 indicate no, threshold, slight, moderate, and strong bitterness respectively. For sensory evaluation, '+' indicates palatability along with the numerical value of bitterness intensity scale. (Khan et al., 2006)

HPLC method for the estimation of artemether&lumefantrine

Chromatographic condition of artementher

Instrument used	:	Shimadzu HPLC with UV-detector
Analytical Column	:	Nucleosil C18, 125x4.6mm, 5µ or Equivalent
Flow rate	:	1.0 ml/minute
Oven temperature	:	Ambient (25^0C)
Wavelength	:	215nm
Injection volume	:	20 µl
Run time	:	7.5 Minute
Retention time	:	Approximately 6.0 minute for Artemether
Mobile phase and diluting solvent	:	Acetonitrile : Water = 65 : 35

Chromatographic condition of lumefantrine

Instrument used	:	Shimadzu HPLC with UV-detector
Analytical Column	:	Nucleosil C18, 125x4.6mm, 5µ or Equivalent
Flow rate	:	1.5 ml/minute
Oven temperature	:	Ambient (25^0C)
Wavelength	:	380nm
Injection volume	:	20 µl
Run time	:	12 Minute
Retention time	:	Approximately 9.0 minute for Artemether
Mobile phase and diluting solvent	:	Acetonitrile: Ion pairing sol. = 65 : 35
([2.75 gm of NaH_2PO_4 + 1gm of Sod.1-Hexane Sulphonate] in 1000ml Water >> Adjust pH 2.5)		

Drug content analysis (Assay)

Assay of Artemether&Lumefantrine ODT of selected batch F4 was determined by the proposed HPLC method.

Preparation of standard solution

Preparation of standard solution- Artemether

Accurately weighed20 mgof standard Artemether in a 50ml dried Vol. flastk. Add 35ml Acetonitrile and sonicate for 5 minutes, adjust the volume to 50 ml with the diluting solvent. The resultant solution (400µg/ml) was analyzed by HPLC method.

Preparation of standard solution- Lumefantrine

Standard solution of pure drug was prepared by dissolving to 24 mg Lumefantrine in 100 ml diluting solvent. From stock solution pipette our 5 ml and

dilute it up to 10 ml. The resultant solution (120µg/ml) was analyzed by HPLC.

Preparation of sample solution

Preparation of sample solution- Artemether

Accurately weighed sample equivalent to20 mgof Artemether in a 50ml dried Vol. flastk. Add 35ml Acetonitrile and sonicate for 5 minutes, adjust the volume to 50 ml with the diluting solvent. The resultant solution (400µg/ml) was analyzed by HPLC method and area of samples was compared with those of standard.

Assay of Artemether ODT was determined by following equation:

$$\%\frac{W}{W} = \frac{Area\ of\ sample}{Area\ of\ standard} X \frac{Weight\ of\ standard}{Dilution\ factor\ of\ standard} X \frac{Dilution\ factor\ of\ sample}{Weight\ of\ sample} X \frac{Average\ Weight}{Label\ Claim} X\ Potency$$

-----(9)

Preparation of sample solution- Lumefantrine

Accurately weighed sample equivalent to 12mg Lumefantrine in a 100ml dried Vol. Flask. Add 70 ml Mobile phase and sonicate for 5 minutes, adjust volume up to 100 ml with the mobile phase. The resultant solution (120µg/ml) was analyzed by HPLC method and area of sample was compared with those of standard.

Assay of Lumefantrine ODT was determined by following equation:

$$\%\frac{W}{W} = \frac{Area\ of\ sample}{Area\ of\ standard} X \frac{Weight\ of\ standard}{Dilution\ factor\ of\ standard} X \frac{Dilution\ factor\ of\ sample}{Weight\ of\ sample} X \frac{Average\ Weight}{Label\ Claim} X\ Potency$$

-----(10)

Dissolution study

Preparation of dissolution media

Preparation of dissolution media: Artemether

1.4196 gm Di Sodium Hydrogen Phosphate (Na_2HPO_4) in 1000ml water was taken. Adjust pH=6.8 with Ortho Phosphoric Acid (H_3PO_4). Add 10gm SLS to prepare buffer. (USP-30 NF 25).

Preparation of dissolution media: Lumefantrine

8.5 ml concentrated Hydrochloric acid in 1000ml water was taken. Add 10gm Benzalchonium chloride i.e. 20ml 50% Benzalchonium Chloride solution.

Preparation of dissolution standard solution

Preparation of dissolution standard solution- Artemether

20mg Artemether in 50ml vol. Flask was taken. Made up volume up to 50ml by Acetonitrile. From that stock solution take 5.0ml and dilute up to 100ml with Dissolution media. (120µg/ml)

Preparation of dissolution standard solution- Lumefantrine

24mg Lumefantrine in 100ml vol. Flask was taken. Made up volume up to 100ml by dissolution media. From that stock solution take 5.0ml and dilute up to 100ml with Dissoltion media. (120µg/ml)

Dissolution method

Dissolution method: Artemether

In-vitrorelease study of Artemether was carried out in USP dissolution apparatus II (Paddle apparatus) (Electrolab Dissolution Tester TDL-08L, USP) at 100 rpm in 1000 ml 1% w/v SLS in Sodium Phosphate buffer, pH=6.8 at 37±0.5°C (US FDA guidelines). Aliquots of 5 ml were withdrawn at specified time interval of 5, 10, 15, 20, 30, 45 and 60 minutes and replaced with fresh media. The samples were analyzed in HPLC for the dissolved drug and the %drug dissolved was determined by the following equation.

$$\%\frac{W}{W} = \frac{Area\ of\ sample}{Area\ of\ standard} X \frac{Weight\ of\ standard}{Dilution\ factor\ of\ standard} X \frac{Dilution\ factor\ of\ sample}{Weight\ of\ sample} X \frac{Average\ Weight}{Label\ Claim} X\ Potency$$

-----(11)

Dissolution method: Lumefantrine

In-vitrorelease study of Lumefantrine was carried out in USP dissolution apparatus II (Paddle apparatus) (Electrolab Dissolution Tester TDL-08L, USP) at 100 rpm in 1000 ml 0.1N HCl containing 10gm of Benzalchonium Chloride, at 37±0.5°C (US FDA guidelines). Aliquots of 5 ml were withdrawn at specified time interval of 5, 10, 15, 20, 30, 45

and 60 minutes and replaced with fresh media. The samples were analyzed in HPLC for the dissolved drug and the %drug dissolved was determined by the following equation.

$$\%\frac{W}{W} = \frac{Area\ of\ sample}{Area\ of\ standard} X \frac{Weight\ of\ standard}{Dilution\ factor\ of\ standard} X \frac{Dilution\ factor\ of\ sample}{Weight\ of\ sample} X \frac{Average\ Weight}{Label\ Claim} X\ Potency$$

-----(12

RESULT AND DISCUSSION

Selection of polymer for taste masking of Lumefantrine

From the following table, the best polymer for taste masking of Lumefantrine was selected on the basis of in-vitro studies like percentage yield, % drug entrapment and % drug release in simulated salivary fluid (SSF).

Table 8.-Selection of polymer for taste masking of Lumefantrine

Polymer	Drug: Polymer ratio	Percentage yield	% Drug entrapment	% Drug release in SSF
Kyron T-114	1:0.1	65.28 ± 0.58	80.37 ± 0.49	3.02 ± 0.28
Eudragit E-100	1:0.1	89.28 ± 0.30	99.18 ± 0.56	ND

Results are the mean of 3 observations ± SD.

ND indicates not detectable (no drug release)

From the above table, it was observed that complex with Eudragit E-100 gives 89.28 % yield, 99.18 % drug entrapment and show no drug release in a SSF (pH-6.8) while complex with Kyron T-114 polymers showed somewhat less percentage yield, less drug entrapment and/or more drug release in SSF. Drug release in SSF indicates improper or incomplete masking of bitter taste. So, it was concluded that Eudragit E-100 is the best polymer for taste masking of Lumefantrine.

But from the above studies, it was also observed that formulating DPC with Eudragit E-100 in the ratio 1:0.1 gave difficulty in the processing, DPC became so hard, lumps was formed and it was very difficult to sieve. So, concentration of Eudragit E-100 was reduced to half and DPC was prepared with drug polymer ratio of 1:0.1 which indicates the proper and complete taste masking. Hence, Eudragit E-100 was selected for the taste-masking of Lumefantrine. After selection, concentration of Eudragit E-100 was further reduced to get minimum optimal concentration.

In-vivo taste evaluation

The 10 healthy human volunteers held the drug polymer complex in the mouth for 30 seconds and the taste sensation felt was recorded. Volunteer's opinion for bitterness levels were recorded by giving different score values i.e.

- **0:** no bitterness,
- **0.5:** threshold bitterness,
- **1:** slight bitterness,
- **2:** moderate bitterness,
- **3:** strong bitterness.

Table 9. Taste panel score for taste assessment of Lumefantrine-Eudragit E100 complex.

Volunteer code	Drug (pure)	Complex (D:P) ratio
		1:0.1
A	3	0
B	3	0
C	3	0
D	3	0.5
E	3	0
F	3	0
G	3	0

H	3	0
I	3	0
J	3	0
K	3	0

Selection of the super disintegrant ratio and formulation of ODT

Tablets containing superdisintegrantsKyron T- 314 with different percentage – 0.50%, 0.75%, 1.00%, 1.25%, 1.50% of total tablet weight. Kyron T-314 is effective at both 1.25% as well as 1.50% as compared to other concentration of superdisintegrant. But, I have selected minimum desired effective concentration for formulation is 1.25% of Kyron T-314.

Physical properties of tablet blend

Physical properties of tablet blends prepared with different combinations of superdisintegrants and other required ingredients were studied for flow ability and compressibility and the results were given in the table 10.

Table 10.- Physical properties of tablet blend

Property	Formulation trial batches				
	F1	**F2**	**F3**	**F4**	**F5**
Angle of repose, degrees	28.23± 0.51	28.35±0.32	27.98±0.12	27.65±0.56	27.69±0.21
Bulk density, g/cm^3	0.45±0.19	0.45±0.61	0.45±0.28	0.44±0.23	0.45±0.19
Tapped density, g/cm^3	0.54±0.23	0.54±0.36	0.54±0.29	0.53±0.89	0.54±0.12
%Compressibility	16.67±0.38	16.23±0.19	16.16±0.42	16.12±0.41	15.54±0.19
Hausner's ratio	1.16±0.08	1.16±0.17	1.17±0.23	1.16±0.18	1.16±0.21

Values shown in table are the mean of 3 determinations ± SD.

Perusal to above table, the tablet blends of all the batches showed good flowability (angle of repose <30^0) and compressibility.

Evaluation of ODTs

Physical parameters of ODT

Tablets prepared from the DPCs withdifferent percentage of super disintegrants were evaluated with regards to various parameters and the results are given in the table 11.Properties like general appearance, thickness, hardness, weight variation and dispersion test of all the prepared batches were found to be within acceptable limit. The final composition of the formulation was decided on the basis of disintegration time of tablets. Accordingly, the final batch was prepared and evaluated for comparative taste, dissolution and stability studies.

Table 11.-Physical parameters of ODT

Parameters	Formulation trial batches				
	F1	**F2**	**F3**	**F4**	**F5**
In-vitro disintegration time, second	30.0	26.0	19.0	14.0	14.0
% Friability	0.25±0.23	0.32±0.31	0.21±0.52	0.23±0.13	0.24±0.07
Wetting time, second	28.26±0.29	23.43±0.61	15.16±0.18	11.33±0.09	12.21±0.48
Water absorption ratio	220±0.32	223±0.18	232±0.26	238±0.39	243±0.25

Results are the mean of 3 determinations ± SD.

In-vitro and in-vivo disintegration time of ODT

In-vitro disintegration time for ODTs was determined using USP as well as modified disintegration apparatus with SSF (pH 6.8) as the disintegrating medium. Also in-vivo disintegration time in saliva (mouth) was determined on 6 healthy human volunteers and the results are compared with the in-vitro disintegration time.

Table 12. Comparison of disintegration time of ODT

Formulation trial batches	Disintegration time, second			
	USP Apparatus	Modified Apparatus (50 rpm)	Modified Apparatus (25 rpm)	In vivo Disintegration
F1	24	26	30	29
F2	23	24	28	26
F3	11	12	15	15
F4	13	14	15	13
F5	13	13	14	14

Between the 2 stirrer speeds, 25 rpm was found to provide more comparable results with the in-vivo test. Disintegration times of tablets from all the batches at 25 rpm were found nearly same as in-vivo disintegration time. Thus, test apparatus with a stirring speed of 25 rpm was considered the most suitable.

In-vivo taste and sensory evaluation

From the all above studies, batch F4 was selected on the basis of disintegration time of tablets as final formulation that containing 1.25% of superdisintegrant and it was further studied for comparative in-vivo taste and sensory evaluation. Taste evaluation was done using the time intensity method on a panel of 6 healthy human volunteers from whom informed consent was first obtained. Bitterness was recorded immediately and at several intervals for 15 minutes according to the bitterness intensity scale from 0 to 3 where 0, 0.5, 1, 2, and 3 indicate no, threshold, slight, moderate, and strong bitterness. For sensory evaluation, '+' indicates palatability along with the numerical value of bitterness intensity scale.

Table 13. Comparative Taste and Sensory Evaluation

Form of Lumefantrine	Degree of Bitterness After Time					
	10 s	1 min	2 min	5 min	10 min	15 min
Pure drug	3	3	3	3	3	3
DPC	0	0	0.5	0	0	0
Unflavored tablet of DPC	0	0	0	0	0	0
Flavored tablet of DPC	0+	0+	0+	0+	0+	0+

*Results are the mean of 10 observations.

+ indicates palatability; DPC, drug-polymer complex.

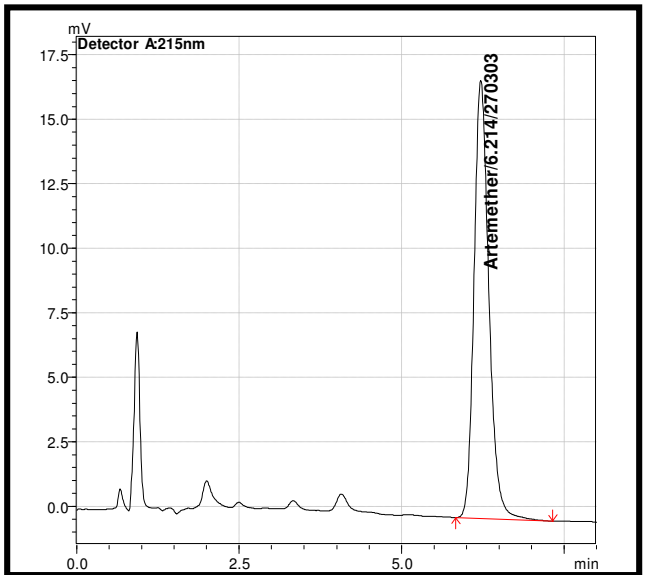
The time intensity study for taste in human volunteers of both the DPC and RDT revealed considerable masking of the bitter taste of Lumefantrine with degree of bitterness below the threshold value (0.5) ultimately reaching to 0 within 15 minutes. Sensory evaluation of the optimized tablet proved good palatability.

HPLC method for estimation of Artemether&Lumefantrine

Chromatogram of standard solution of Artemether

Standard solution (400µg/ml)for Artemether WS was prepared and analyzed in HPLC. Chromatogram obtained for Artemether standard is shown figure 4.

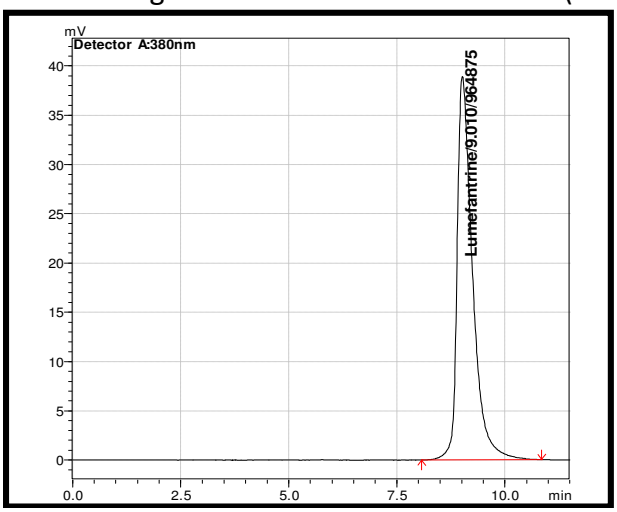
Figure 4. Chromatogram of Artemether standard (400µg/ml)



Chromatogram of standard solution of Lumefantrine

Standard solution (120µg/ml) for Lumefantrine WS was prepared and analyzed in HPLC. Chromatogram obtained for Lumefantrine standard is shown figure 5.

Figure 5. Chromatogram of Lumefantrine standard (120µg/ml)



Assay of Artemether&Lumefantrine ODT

Assay of Artemether

Assay of Artemether of selected batch F4 was determined by the proposed HPLC method. The solutions (400µg/ml) of standard and sample were subjected to analysis by HPLC method and area of sample was compared with those of standards. Chromatogram of sample and standard are shown below:

Figure 6. Chromatogram of Artemether standard (400µg/ml)

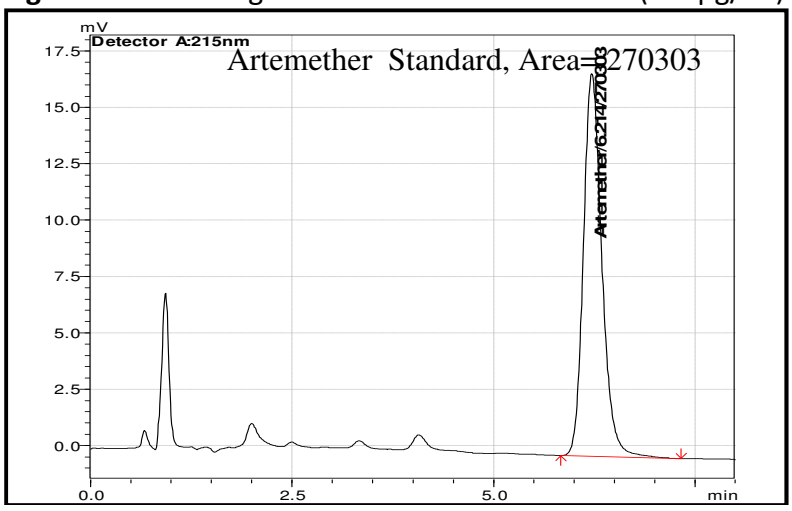
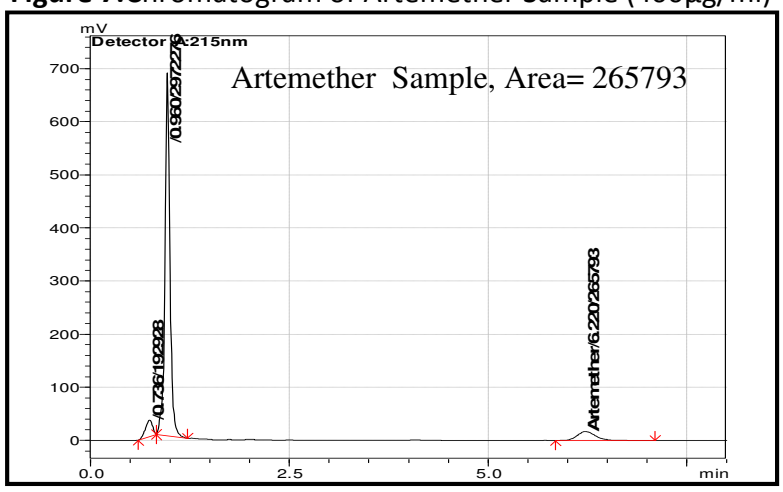


Figure 7. Chromatogram of Artemether Sample (400µg/ml)



From the above chromatogram and calculation, Assay was found to be 98.50% and thus passed the limits (Limit: 90.0-110.0%w/w)

Assay of Lumefantrine

Assay of Lumefantrine of selected batch F4 was determined by the proposed HPLC method. The solutions (120µg/ml) of standard and sample were subjected to analysis by HPLC method and area of sample was compared with those of standards. Chromatogram of sample and standard are shown below:

Figure 8.. Chromatogram of Lumefantrine standard (120µg/ml)

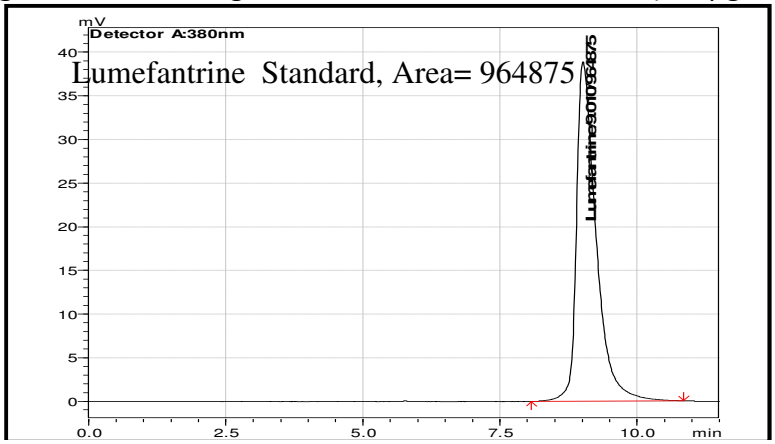
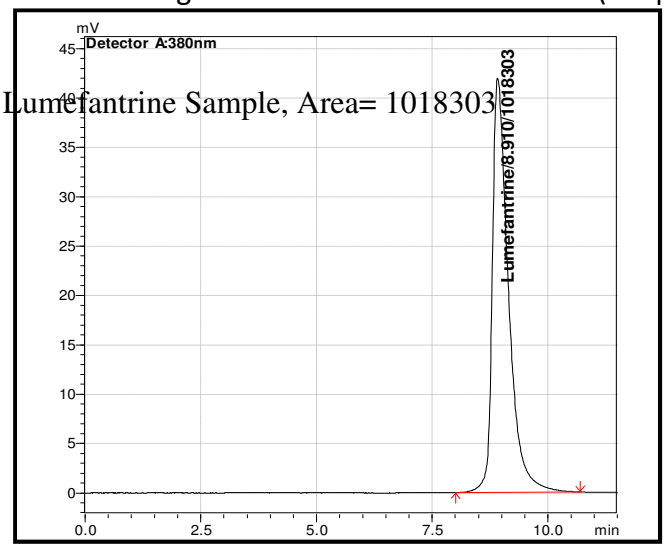


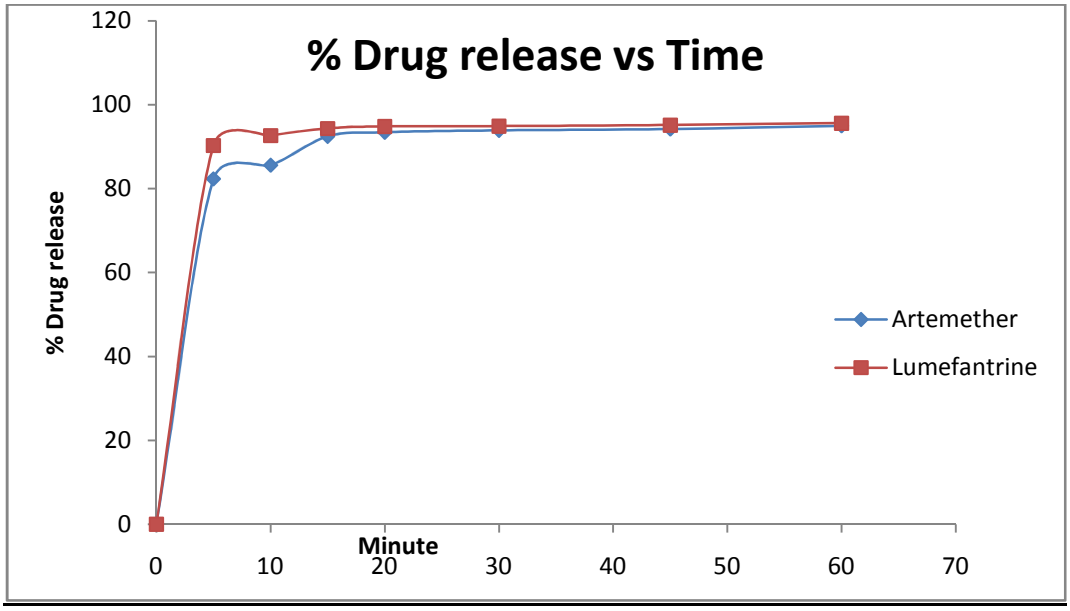
Figure 9. Chromatogram of Lumefantrine standard (120µg/ml)



From the above chromatogram and calculation, Assay was found to be 99.10% and thus passed the limits (Limit: 90.0-110.0%w/w)

Dissolution studies

	% Drug release						
	5 min	**10 min**	**15 min**	**20 min**	**30 min**	**45 min**	**60 min**
Artemether	82.32	85.56	92.45	93.45	93.89	94.20	94.96
Lumefantrine	90.29	92.65	94.32	94.83	94.90	95.15	95.60



Dissolution of Artemether in Phosphate buffer pH 6.8 with 1% SLS

Dissolution of Artemether in selected media was determined by proposed dissolution method. The solutions (20µg/ml) of dissolution standard and sample were subjected to analysis by HPLC method and area of sample was compared with those of standards. % drug release was found to be 92.45% in 15 minutes. Chromatogram of sample and standard are shown below:

Figure 10. Chromatogram of Artemether dissolution standard

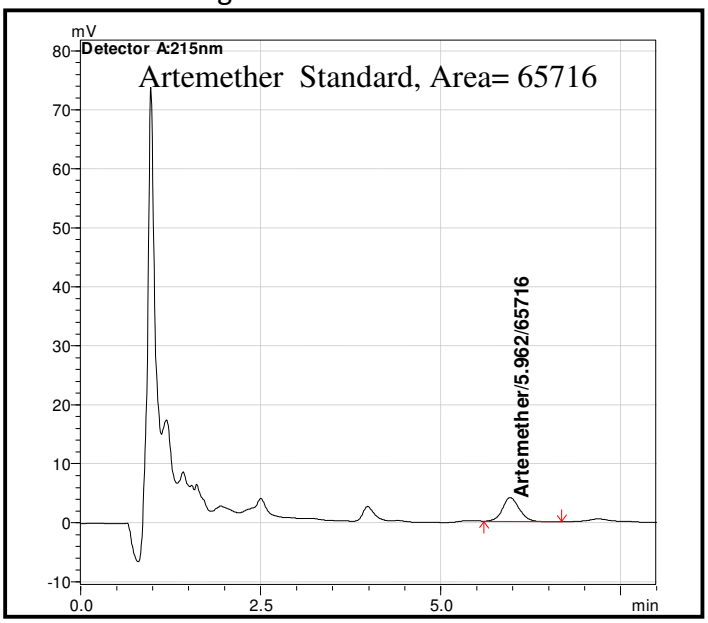
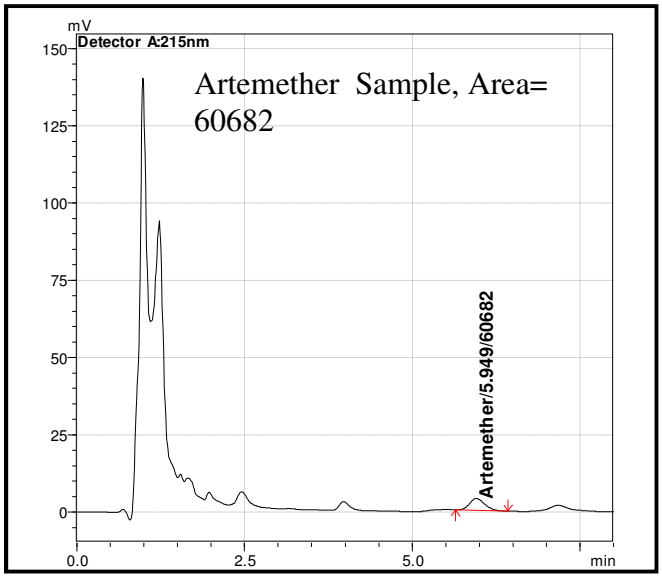


Figure 11. Chromatogram of Artemether dissolution Sample



Dissolution of Lumefantrine in 0.1N HCl with 1%Benzalchonium Chloride

Dissolution of Lumefantrine in selected media was determined by proposed dissolution method. The solutions (120µg/ml) of dissolution standard and sample were subjected to analysis by HPLC method and area of sample was compared with those of standards. % drug release was found to be 94.32% in 15 minutes. Chromatogram of sample and standard are shown below:

Figure 12. Chromatogram of Lumefantrine dissolution Standard

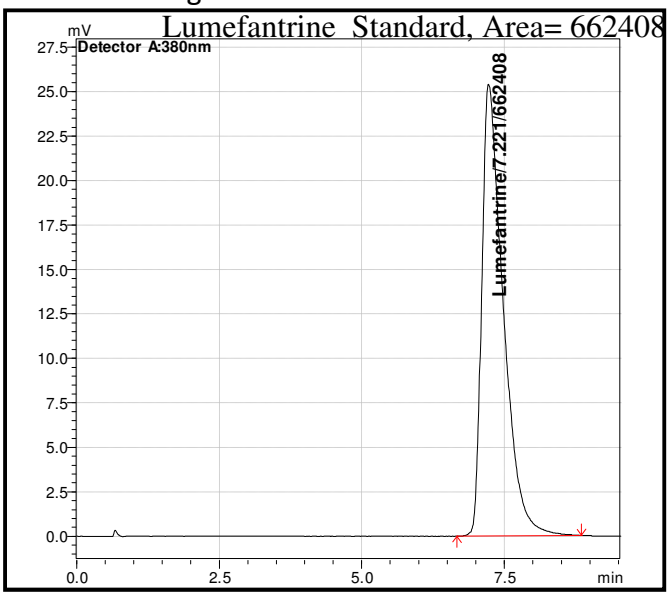
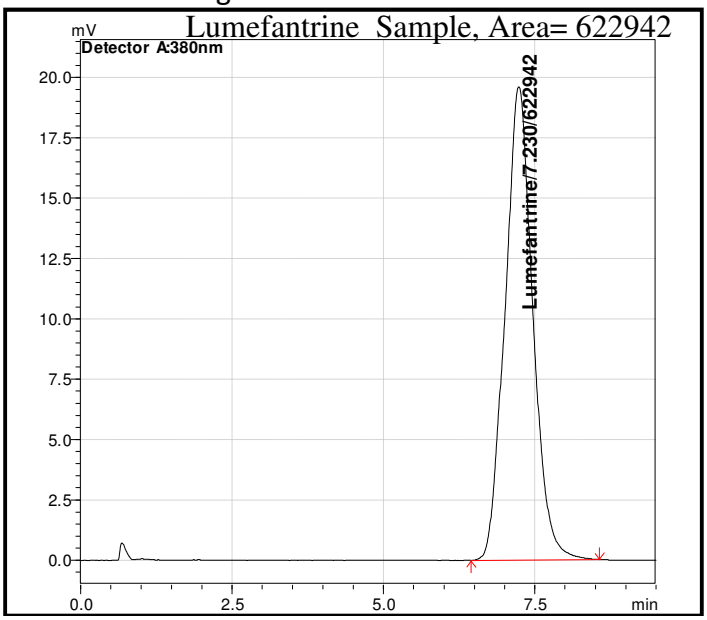


Figure 13. Chromatogram of Lumefantrine dissolution Sample



CONCLUSION

The study conclusively demonstrated that Eudragit E-100 can be successfully used to mask the bitter taste of Lumefantrine by forming a drug-polymer complex and it was easily prepared by the use of solvent deposition methodology. It gave satisfactory results in terms of in-vitro and in-vivo taste evaluation. In-vitro study showed that the release of drug was retarded in simulated salivary fluid (pH 6.8) and therefore, the drug is not expected to be release in saliva after oral administration. In-vivo taste evaluation of drug-polymer complex confirmed this.

ODTs containing taste-masked complex, Superdisintegrants, sweetener, flavor and other excipients were prepared by direct compression method. Characterization of the ODTs confirmed that adequate taste masking and faster disintegration could be achieved for Lumefantrine and Artementher. ODTs containing 1.25% Kyron T-314 showed quick disintegration time among other trials.

Taste masking and rapid disintegration of tablets formulated in this investigation would be helpful in increasing the drug compliance for administration of Lumefantrine and Artemether in children as well as in geriatric patients.

Thus, the "patient-friendly dosage form" of bitter drugs, especially for pediatric, geriatric, bedridden, and non cooperative patients, can be successfully formulated using this technology.

SUMMARY

INTRODUCTION

Orally disintegrating tablets (ODTs) has remarkable disintegration properties; it can rapidly disintegrate without water in the mouth within a few seconds. It offers an advantage for populations who have difficulty in swallowing, more specific with pediatric population. Lumefantrine&Artemether is anti malarial drugs used especially for pediatric and geriatric persons. Lumefantrine is an intensely bitter drug. So, masking of bitter taste in the formulation is a prerequisite as it improves the compliance of the patient and product value. There are numerous approaches investigated by the researchers to mask the bitter taste of drug. The ideal solution to reduce or inhibit bitterness is to prevent the release of drug in saliva or/and to use artificial sweeteners and flavors.

AIMS OF OBJECTIVE

The purpose of this research was to mask the intensely bitter taste of Lumefantrine&Artemether and to formulate oral-disintegrating tablet (ODT) of the taste-masked drug.

MATERIALS AND METHODS

Polymer was selected among Kyron T-114 (Methacrylic acid polymer) and Eudragit E-100 on the basis of percentage drug release in stimulated salivary fluid and drug entrapment. Polymers were used for complexing the drug and the prepared drug-polymer complexes were characterized for percentage yield, percentage drug entrapment, in-vitro and in-vivo taste evaluation. Finally prepared drug-polymer complex was used for further formulation of Oral-disintegrating tablet. Kyron T-314 used as Superdisintegrant, and its optimized percentage in formulation was determined on the basis of Disintegration time. Various evaluation parameters were studied for Oral-disintegrating tablet and final batch was selected on the basis of disintegration time. The dissolution profiles of final batch ODT were studied.

RESULT AND DISCUSSION

The results obtained shows that the drug-polymer complex prepared with Eudragit E-100 in drug:polymer ratio 1:0.1 gave complete taste masking with satisfactory results obtained in terms of in-vitro and in-vivo taste evaluation and these were further used for formulation into ODTs. Tablets of batch F4 containing 1.25% Kyron T-314 having faster disintegration, within 14 seconds. Good correlation between in vitro disintegration behavior and in oral cavity was recognized. Taste evaluation of ODT in human volunteers revealed considerable taste masking.

CONCLUSION

Effective taste-masking was achieved for Lumefantrine&Artemether with Eudragit E-100 by using solvent deposition method. ODTs of acceptable characteristics were obtained by disintegrant addition and direct compression. Thus, it was conclude that the "patient-friendly dosage form" of bitter drugs, especially for pediatric as well as geriatric patients, can be successfully formulated according to the present study.

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