Compatibility study between Artemether Lumefantrine and Excepients polymers used for Solid Unit Dosage Form

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Abstract- The research conducted in this study focused on the use of pure drugs, namely artemether and/or lumefantrine, both individually and in combination with proposed excipients. These excipients included avicel-102 (microcrystalline cellulose), primojel (starch glycolate sodium), aerosil (colloidal silicone dioxide), and magnesium stearate.

The investigation also involved assessing the inactive ingredients, including lubricating agents and diluents, both separately and in combination, to determine their physical and chemical compatibility. Various physicochemical tests were performed, such as measuring diameter, thickness, hardness, disintegration, friability, and percentage purity.

Samples of the formulations were placed under accelerated stability conditions, which included a temperature of 40±2 °C and humidity of 75±5% RH, to assess their stability. Differential scanning calorimetry (DSC), high-performance liquid chromatography (HPLC), and Fourier transform infrared spectroscopy (FTIR) were used to further evaluate chemical compatibility.

The final finding of this study was that the inactive substances utilized in the formulations did not interact in any way, either physically or chemically, with the active medication components.

Index Terms- artemether, differential scanning calorimetry, lumefantrine, primojel,

INTRODUCTION

In the field of pharmaceuticals, compatibility is a critical aspect that ensures the efficacy, safety, and stability of pharmaceutical formulations. This term encompasses a range of physical and chemical techniques that are employed to present therapeutic formulations with confidence [1]. Particularly, when a pharmaceutical dosage form contains multiple active drug molecules within a single formulation, a thorough evaluation of physicochemical compatibility becomes essential. The goal is to ensure that these active drug molecules do not exhibit any form of incompatibility either in their fresh state or throughout the product's shelf life [2].

To achieve specific patterns of pharmaceutical dosage forms, various excipients are used alongside active drug molecules in formulation design [3]. According to the current good manufacturing practice (cGMP) requirements, it is imperative that both the active drugs and excipients used in pharmaceutical preparations are highly compatible in all aspects [4].

In the context of antimalarial regimens, the incorporation of artemisinin derivatives is crucial for reducing mortality rates, suppressing the growth of resistant parasites, enhancing therapeutic value, and improving treatment responses [5].

In light of these considerations, conducting compatibility studies is of utmost importance to ensure the successful development and utilization of pharmaceutical formulations that are both effective and safe. Such studies enable pharmaceutical researchers and manufacturers to identify potential issues and mitigate risks, ultimately leading to the creation of optimal and well-tolerated medications.

Materials and Methods

Artemether and lumefantrine, both active pharmaceutical ingredients (APIs) utilized in this study, were procured from leads pharma Islamabad, Pakistan and were confirmed to have 99.99% purity. The excipients used in tablet formulation included avicel 102 (Microcrystalline cellulose) from Amson Pharma, primojel (Starch Glycolate Sodium) and aerosil (Colloidal Silicone Dioxide) were gifted by Global pharma, pvt, Ltd, Islamabad Pakistan. Various tools and equipment were employed during the testing procedures, including a weighing scale (PS 370/C/1 Made in China) provided by Leads pharma Pvt. Ltd., Islamabad, Pakistan; a ZP-18 Rotary machine (China Zp18 Rotary Tablet press machine) from Rotax Pharma Pvt. Ltd., Islamabad, Pakistan; a stability chamber (Stability Chamber-30/900-Model:Ti-Sc-Thh-08-900) from Global Pharmaceuticals Pvt. Ltd., Islamabad, Pakistan; DSCTA equipment (SDT-Q600 simultaneous TGA/DSC) at Lahore College for Women University, Lahore; FT-IR equipment (Perkin Elmer UATR Two) accessible at the Faculty of Pharmacy, GU DIK, Pakistan; and HPLC equipment (Shimadzu LC-2010CHT HPLC System) supplied by Global pharma pvt ltd, Islamabad, Pakistan. Acetonitrile and phosphate buffer pH 7.2 were the substances used in the studies.

Method

Preparation of Physical Mixtures

To investigate the potential interactions between active pharmaceutical ingredients (APIs) and excipients, prepared

physical mixture. Precise weight measurements of the (APIs) and excipients were performed based on defined concentrations. Each component was individually sieved using a #40 sieve, before being placed in separate containers. This process resulted in the creation of eight samples comprising crushed tablets, physical powders, and mixtures (Table 2). Subsequently, these samples were tested as new entities, following the specified procedure. Furthermore, compressed tablets were stored in sealed containers, while opaque vials were used to preserve them under accelerated conditions for nine months (temperature: 40±2°C, humidity: 75±5%). Prior to the analysis, sample #8 was pulverized using mortar and pestle.

Precise weighing of the active pharmaceutical ingredients (APIs) and the aforementioned excipients is essential before their selection and preparation. All components were thoroughly mixed according to the tablet preparation protocol.

Dosage Form: The physically mixed material for each formulation was crushed using a direct compression method with upper and lower punches (8 mm, round concave). The humidity in the compression chamber was maintained at 40%, and the temperature was maintained at 25°C throughout the process. Bulk excipients (Sample #7) did not contain active substances but had the same mixing ratio, as shown in Table No. 2. Except for Sample #8, which was compressed into tablets, all the other samples were in powder form. The ingredients of the tablet formulation (sample #8) are listed in Table 2.

Physicochemical Analysis: The physical mixes are listed in Table No. 3 were extensively compressed using a single-punch machine (ZP-18, China). The resulting tablets underwent various physicochemical tests, including diameter, weight fluctuation, hardness, and friability measurements. These evaluations were performed thrice, and the data obtained represent the mean values.

Stability Studies: The Prepared tablets were carefully packed into amber-colored, airtight bottles or containers and subjected to accelerated stability conditions to assess their stability. The temperature was maintained at 40±2 degrees, and the humidity was set at 75±5%. At predetermined intervals (three, six, and nine months), the pills were subjected to the same physicochemical analyses. The data from these stability trials, also conducted in triplicate, are reported as mean values.

ATR-FTIR, or Fourier Transform Infrared Spectroscopy:

Following the methodology described by Shah and Mashru in 2008, Fourier transform infrared spectroscopy analysis was conducted using an ATR-FTIR spectrophotometer (UATR TWO, Perkin Elmer, UK). To assess the powdered samples, including physical mixtures of artemether, lumefantrine, avicel-102, primojel, aerosil, magnesium stearate, excipient bulk mixture, and active drug-excipient bulk combination, a diamond crystal was employed to ensure precise attachment and immobilization. Spectra in the 4000-450 cm^{-1} wavenumber region were recorded for two minutes. Each sample underwent three runs, and the results are presented as the average with mean and SD.

DSC: Differential Scanning Calorimetry

To perform thermal analyses of the active pharmaceutical ingredients artemether and lumefantrine, as well as excipients such as avicel-102, primojel, aerosil, and magnesium stearate, either individually or in various combinations, we utilized a TA Instrument for simultaneous endothermic exothermic analysis (SDT-Q600 simultaneous TGA/DSC, USA). Samples weighing 3 mg were created for each component/sample and placed in a platinum pan with a capacity of 100 µL connected to a microbalance. The samples were then heated from 0 °C to 500 °C at a rate of 10 °C/min under a nitrogen gas flow of 5 ml/min. Enthalpy and transition temperature data were recorded for each study. The analysis was performed in triplicate for accuracy, and the results were taken in triplicate and measured the mean [6].

High-performance liquid chromatography (HPLC)

We adapted an HPLC technique based on the work of César et al. in 2008, with slight modifications, to assess the drug concentration in fresh and aged samples for stability evaluation. Our HPLC system consisted of a UV/VIS wavelength detector, an ODS silica column, a degassing device, and total Chrom navigator software (Perkin Elmer 200 Series, USA). The HPLC rheodyne injector, along with an ODS Hypersil C-18 column (4.62 mm) and guard column, were operated at 298 Kelvin.

Before conducting the HPLC analysis, all samples and diluents were appropriately degassed using a sonicator (Elma D 78224, Germany). Phosphate buffer (PBS) was prepared using potassium hydroxide and a pH meter (Inolab series, Germany), with the pH adjusted to 7.2. The mobile phase, consisting of phosphate buffer (PBS) at pH 7.2 and acetonitrile in an 80:20 (v/v) ratio, was filtered and degassed using ultrasonication. Acetonitrile and phosphate buffer served as diluents, and the flow rate was set to 1 ml/min.

During the HPLC analysis, 20 µL of each sample was introduced into the HPLC loop. Artemether and lumefantrine were detected at 216 and 335 nm, respectively. The limits of quantification (LOQ) for artemether and lumefantrine were found to be 5 µg/ml and 0.10 µg/ml, respectively, while the limits of detection (LOD) were 15 µg/ml and 0.5 µg/ml, respectively [7]. These criteria ensured the accurate and sensitive identification of the drug components in the prepared samples.

Result and Discussion

The primary objective of this study was to develop a tablet formulation containing the active pharmaceutical components artemether and lumefantrine, along with excipients such as avicel-102, primojel, aerosil, and magnesium stearate. Extensive compatibility testing was conducted, as detailed in Section 3, to ensure the effectiveness and safety of the formulation. In this

chapter, we present a comprehensive analysis of our findings and discuss the most optimal approach for creating artemether and lumefantrine tablets, thereby ensuring their efficacy in treating malaria.

Physical and Chemical Characteristics

For the tablets (Sample No. 8), several physicochemical characterizations were performed, and the following observations were made.

- **Friability:** The friability ranged from 0.22±0.09 to 0.40±0.06, indicating that the tablets remained intact during handling and transportation, with minimal fragmentation.
- **Dissolution Time:** The dissolution time ranged from 2.29±0.32 to 3.5±0.54, demonstrating the ability of the tablets to dissolve within the desired timeframe.
- **Weight Variation**: The weight variation ranged from 263.50±5.4 to 264.00±8.4, indicating uniformity in tablet weight among different batches.
- **Hardness:** The hardness ranged from 5.3±1.4 to 5.6±0.98, indicating that the tablets had sufficient mechanical strength to withstand compression and handling.
- **Diameter**: The diameter ranged from 8.05±0.02 to 8.10±0.07, indicating consistency in tablet size.
- **Thickness:** The thickness ranged from 3.08±0.01 to 3.10±0.04, indicating uniformity in tablet thickness.

Based on the physicochemical characteristics evaluated for both fresh and aged tablets, it was evident that the compressed tablets maintained stability and compatibility, yielding uniform and consistent results. These findings support the robustness of tablet formulations and align with those of previous research [6].

Analyzing ATR-FTIR (Fourier Transform Infrared Spectroscopy)

A comprehensive examination using Fourier transform infrared spectroscopy (FTIR) was conducted on various substances, including artemether, lumefantrine, avicel-102, primojel, aerosil, and magnesium stearate, as well as their mixtures (Figure 1).

Distinctive peaks in the FTIR spectra of artemether were observed at 1030.8 cm^{-1}, 1122.4 cm^{-1}, and 1191.7 cm^{-1}, indicating O-C stretching in C-O-C bonds. Additionally, peaks at 2850.4 cm^{-1} (C-O-CH3 stretching) and 2943 cm^{-1} (C-H stretching in CH3) were identified (Figure 1) [9].

For lumefantrine, peaks were seen at 874.61 cm^{-1} (C-Cl stretching), 1070.6 cm^{-1} (C-O stretching), 1389.8 cm^{-1} (C-N stretching), 2949 cm^{-1} (C-H stretching), and 3410.3 cm^{-1} (O-H stretching) (Figure 1).

Avicel-102 exhibited distinct peaks at 536.4 cm^{-1} (stretching of cellulose bond in C-O-C group), 1030.6 cm^{-1} (stretching of C-O bond in C-OH group), 1149.6 cm^{-1} (stretching of C-O bond in C-OH group), 290.7 cm^{-1} (stretching of C-H bond in CH2), and 340.6 cm^{-1} (O-H stretching in the presence of hydrogen bonding) (See Figure 1).

Similarly, primojel displayed peaks at 551 cm^{-1} (starch skeleton vibrating), 1005.8 cm^{-1} (C-O stretching in C-O-C group), 1141 cm^{-1} (C-O stretching in C-OH group), 2920.4 cm^{-1} (C-H stretching in CH2), and 3280 cm^{-1} (O-H stretching in the presence of hydrogen bonding) (Figure 1).

Magnesium stearate exhibited peaks at 1470.6 cm-1 and 1540.09 cm^{-1} (vibrations of aliphatic chains), and 2860.45 cm^{-1} and 2920.32 cm^{-1} (stretching of COO bonds) (Figure 1) [12].

The ATR-FTIR spectra demonstrated the purity and absence of adulteration in the constituent components, which is in agreement with the literature. Moreover, the spectra showed minimal variation when combined with active medicinal components, indicating a high level of compatibility and stability in the formulation. The results of the accelerated stability investigation further support these findings (See Figure 2).

Analyzing using DSC (Differential Scanning Calorimetry)

Differential scanning calorimetry (DSC) was used to investigate the compatibility of the medicines and excipients.

Artemether displays an endothermic peak at approximately 83°C, corresponding to its melting point, and an exothermic peak at approximately 160°C. The sample mass decreased by approximately 80% during the second heat event, indicating decomposition of the medication (Figure 3).

In the DSC analysis, lumefantrine exhibited an endothermic peak at 125°C, indicating its melting point, followed by a significant exothermic peak at 250°C, suggesting thermal degradation, with a sample weight loss of approximately 70% (Figure 3). The endothermic peak at 250°C indicated thermal disintegration of the sample, accompanied by an estimated 80% mass loss, while a broad thermal shift in enthalpy within a temperature range of 120–140°C indicated a glass transition (Figure 3). Remarkably, in the DSC thermogram (Figure 3), the same thermal event is observed as an exothermic peak.

The thermogram of Aerosil displayed enthalpic variations over a temperature range up to 300°C, indicating the removal of adsorbed water, air, or molecular packing (Figure 4).

Primojel exhibited an endotherm at 80°C, suggesting a composite reaction comprising melting and dehydration. Although the latter caused a slight deviation in the TGA profile, the former was evident by a weight reduction of approximately 10%. Thermal degradation of the sample was observed at 320°C, indicating a weight loss. Additionally, the DSC profile revealed a wide endotherm over the temperature range of 320-400°C (Figure 4)

DSC analysis of the formulation components, including artemether, lumefantrine, avicel-102, primojel, aerosil, magnesium stearate, inactive substances, and their mixtures, indicated that all components were thermally stable. The absence of endothermic peaks suggested no major molecular interactions and confirmed the effectiveness of the formulation technique in retaining the active medications artemether and lumefantrine. The thermogram of each component demonstrates its unique thermal stability (Figure 4) [16, 17].

High-performance liquid chromatography (HPLC) was used to measure the stability of medications over specific time intervals. The proposed HPLC method effectively identified lumefantrine and artemether with retention durations of 2.42 min and 8.04 min, respectively, with minor modifications.

During the accelerated stability study, three assessments were conducted: at three months, six months, and nine months. The percentage assay of the pharmaceutical dosage form remained within acceptable limits during the first evaluation at three months, indicating no incompatibility between the excipients and the active medication. The second assessment at six months also showed that the product sample percentage assay was within permissible ranges, consistent with the three-month results. Detailed findings are provided in Tables 4 and 5, which demonstrate the sustained compatibility of the dosage form over this period.

The third evaluation at nine months of accelerated stability testing showed no significant changes in the % assay of the product preparation (Tables 7 and 8).

Distinct peaks were observed at predetermined wavelengths (216 nm and 335 nm) during the HPLC analysis of the samples, indicating the stability of the active substances, LF and ART. In conclusion, the HPLC results confirmed the compatibility and stability of the formulated dosage form containing artemether and lumefantrine with the chosen excipients during the 3-, 6-, and 9-month intervals of the accelerated stability study (Figure 5, 6 and 7). This observation suggests that there were no interactions, drug degradation, or deterioration during these intervals. The formulation was suitable for longer storage, ensuring its efficacy and therapeutic value in the treatment of malaria, with no significant changes in the percentage assay or the presence of sharp peaks at the designated wavelengths.

Conclusion

In conclusion, this study aimed to assess the compatibility and stability of artemether, lumefantrine, and various excipients in formulating solid tablet dosage forms. Multiple analytical methods, including differential scanning calorimetry (DSC), high-performance liquid chromatography (HPLC), and Fourier transform infrared spectroscopy (FT-IR), have been employed to investigate the potential interactions between the components. In addition, stability experiments were conducted during and after an accelerated stability period to evaluate the long-term effectiveness of the formulation.

The results of the analytical investigations provided strong evidence that there were no observable interactions between the formulation components. The HPLC, FTIR, and DSC spectra of each component support this conclusion, ensuring the stability and integrity of the pharmaceutical formulation. This finding indicates that the selected excipients are well suited for artemether and lumefantrine.

Furthermore, this research sheds light on the chemical characteristics of anti-malarial medications such as lumefantrine and artemether, confirming that these medications retain their chemical properties throughout the shelf life of the formulation.

Summary

In summary, this study provides valuable insights into the compatibility and stability of a formulated dosage form containing artemether and lumefantrine. It also raises important considerations regarding the potential efficacy of treatment, especially in regions where drug-resistant strains of malaria are prevalent. Further research and monitoring are warranted to address these concerns and ensure the continued effectiveness of this medication in combating malaria.

Appendix

Appendixes, if needed, appear before the acknowledgment.

Acknowledgment

The preferred spelling of the word "acknowledgment" in American English is without an "e" after the "g." Use the singular heading even if you have many acknowledgments.

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Table No. 1 Sample combinations of the active pharmaceutical ingredients and excipients as per proposed formulations

S.No	Components
1	Artemether
2	Lumefantrine
3	Avicel 102 (microcrystalline cellulose)
4	Primojel (starch glycolate sodium)
5	Aerosil (colloidal silicone dioxide)
6	Magnesium stearate
7	Avicel 102 (microcrystalline cellulose), primojel (starch glycolate sodium), aerosil (colloidal silicone dioxide) and magnesium stearate.
8	Artemethar, lumefantrine, the other excipients including avicel 102 (microcrystalline cellulose), primojel (starch glycolate sodium), aerosil (colloidal silicone dioxide) and magnesium

Table No. 2 Composition ratio of Active Pharmaceutical Ingredients and Excipients in compressed tablet (sample#8)

S.No	Ingredients	Quantity Per Tab (mg/tab)	QuantityPer Bulk(gm/700 tablets)
1	Artemether	20.85	14.595
2	Lumefantrine	124.00	86.80
3	Avicel-102	101.90	71.33
4	Primojel	11.90	8.33
5	Aerosil	1.90	1.33
6	Magnesium stearate	2.450	1.715
		263mg/tab	184.10gm/700tablets

Table No. 3 Parameters of tablets

Test name	Fresh	After 3 month	After 6 month	After 9 month
Friability (%)	0.32±0.02	0.40±0.06	0.35±0.12	0.22±0.09
DT(min)	3.18±0.12	2.29±0.32	2.55±0.32	3.5±0.54
Weight variation	263.50±5.4	264.00±8.4	264.04±6.5	263.90±8.32
Hardness (kg/cm^2)	5.5±0.54	5.3±1.4	5.6±0.98	5.45±0.65
Diameter (mm)	8.07±0.12	8.07±0.04	8.10±0.07	8.05±0.02
Thickness (mm)	3.10±0.01	3.08±0.01	3.09±0.06	3.10±0.04

HPLC assessment after three month

Table No. 4 %age assay of sample 1

%age assay of Artemether	100.09%
%age assay of Lumefantrine	98.95%
%age assay of (AL) sum	98.98%

Table No. 5 %age assay of sample 2

%age assay of Artemether	100.00 %
%age assay of Lumefantrine	99.84 %
%age assay of (AL) sum	99.86 %

HPLC assessment after six month

Table No. 6 %age assay of sample 1 of 2nd assessment

%age assay of Artemether	98.61%
%age assay of Lumefantrine	99.33%
%age assay of (AL) sum	99.32%

Table No. 7 %age assay of sample 2

%age assay of Artemether	100.2 %
%age assay of Lumefantrine	99.44 %
%age assay of (AL) sum	99.45 %

HPLC assessment after nine month

Table No. 8 %age assay of sample 1

%age assay of Artemether	98.26 %
%age assay of Lumefantrine	99.81 %
%age assay of (AL) sum	99.80 %

Table No. 9 %age assay of sample 2

%sage assay of Artemether	98.38 %
%age assay of Lumefantrine	99.51 %
%age assay of (AL) sum	99.50 %

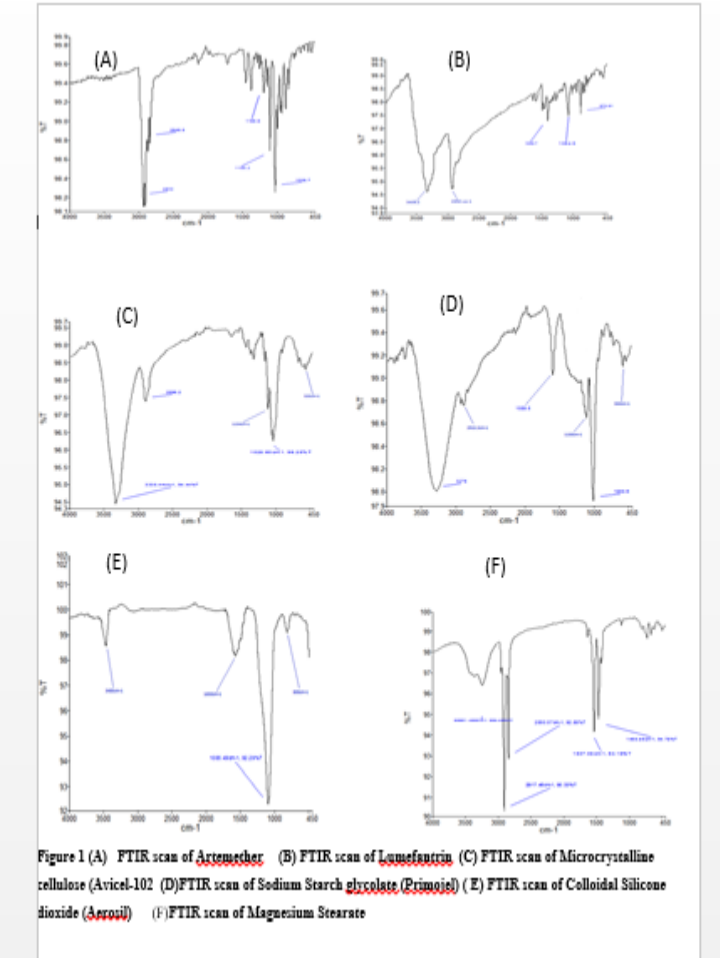

Figure 1 (A) FTIR scan of Artemether (B) FTIR scan of Lumefantrin (C) FTIR scan of Microcrystalline cellulose (Avicel-102 (D)FTIR scan of Sodium Starch glycolate (Primojel) (E) FTIR scan of Colloidal Silicone dioxide (Aerosil) (F)FTIR scan of Magnesium Stearate

Figure 1 (A) FTIR scan of Artemether (B) FTIR scan of Lumefantrin (C) FTIR scan of Microcrystalline cellulose (Avicel-102 (D)FTIR scan of Sodium Starch glycolate (Primojel) (E) FTIR scan of Colloidal Silicone dioxide (Aerosil) (F) **FTIR scan of active and excipients bulk**

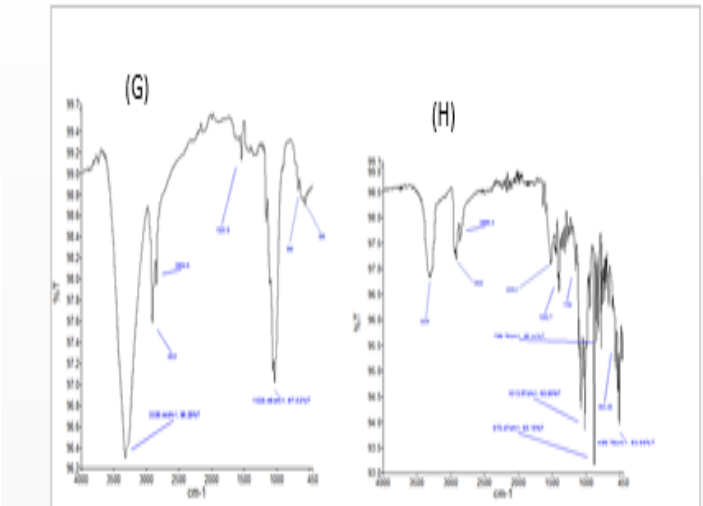

Figure2 (G) FTIR scan of excipients bulk (H) FTIR scan of active and excipients bulk

Figure 2.(G) FTIR scan of excepients bulk (H) FTIR scan of active and excepients bulk

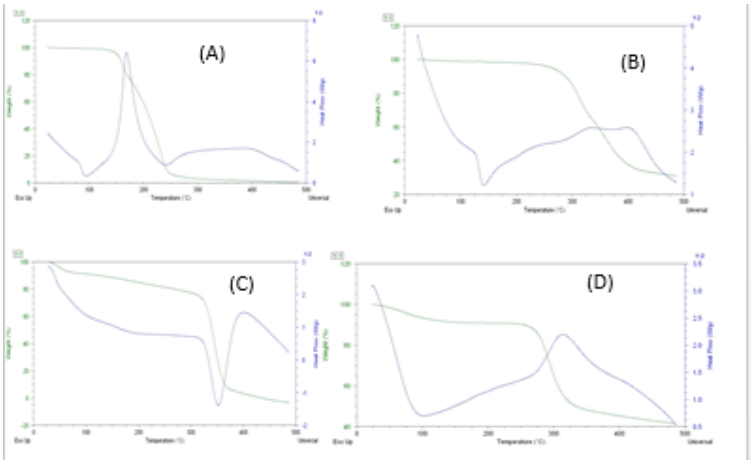

Figure 3 (A) DSC analysis of Artemethe (B) DSC of Lumefantrine (C) DSC of Microcrystalline cellulose (Avicel-102) (D) DSC of Sodium Starch glycolate (Primojel)

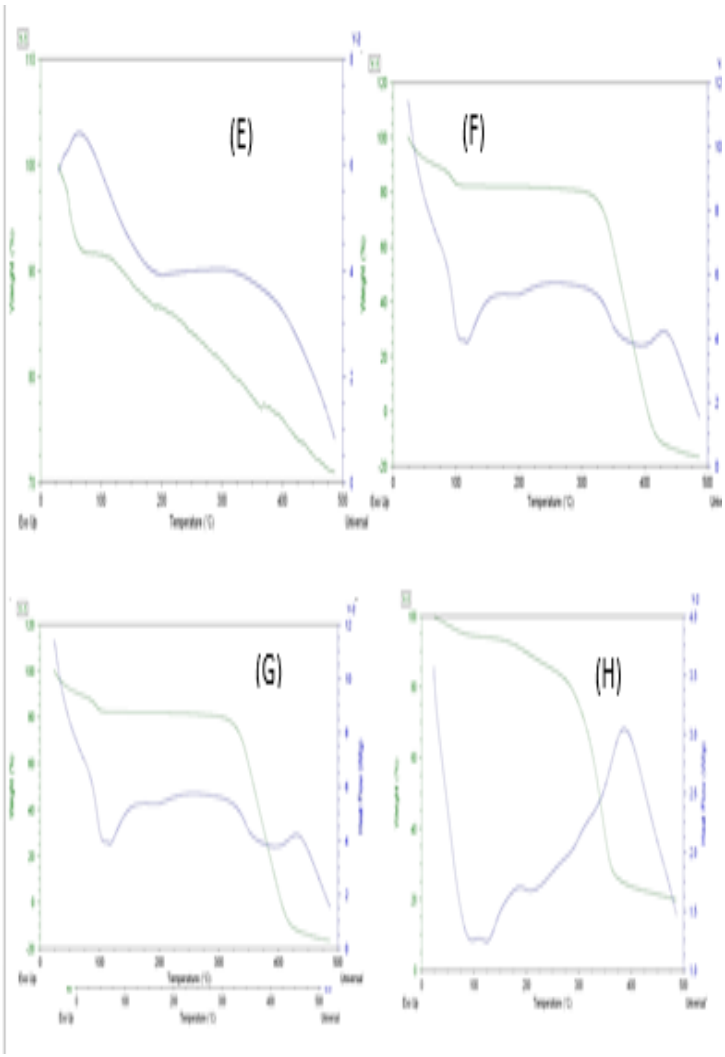

Figure 4. (E) DSC of Colloidal Sillicone dioxide (Aerosil) (F) DSC of Magnesium Stearate (G) DSC of Inactive ingredients/Excipients bulk (H) DSC of Active and Inactive ingredients/ Excipients

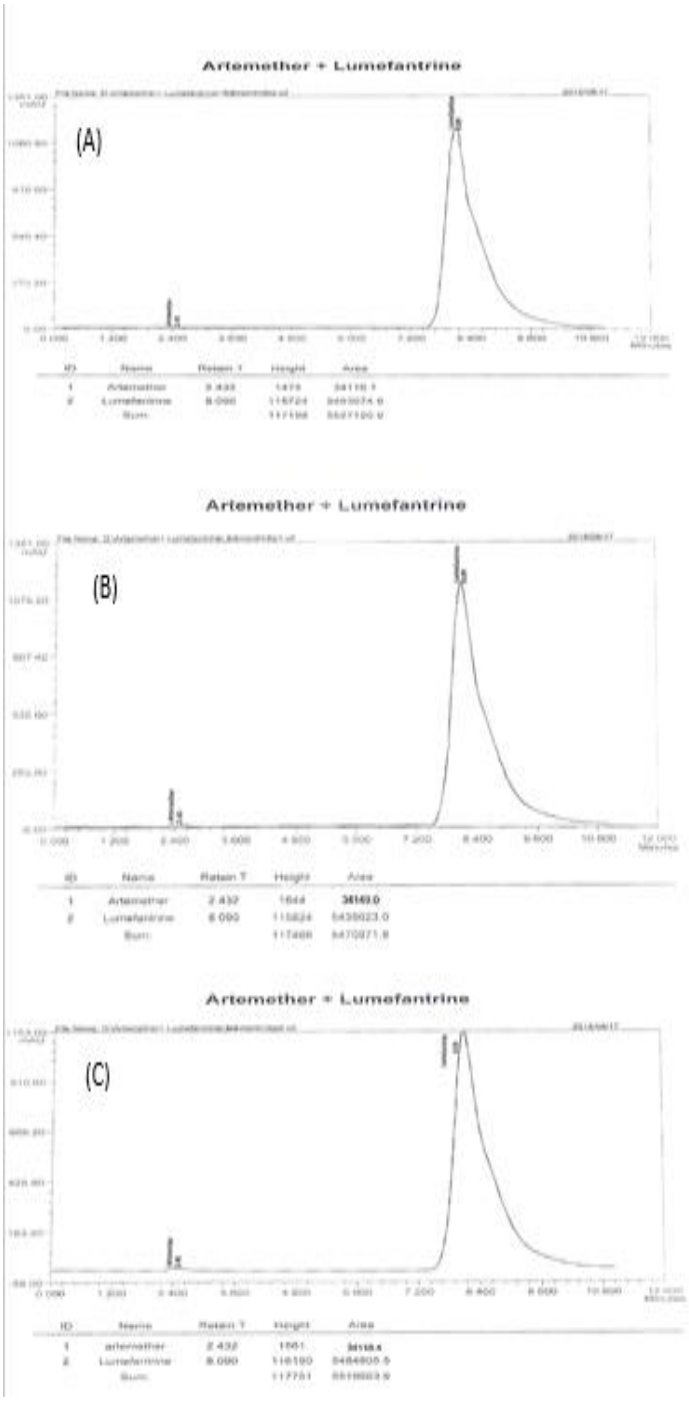

Figure 5 (A) Standard chromatogram of 1st assessment (B) Sample 1 chromatogram of 1st assessment (C)Sample 2 chromatogram of 1st assessment

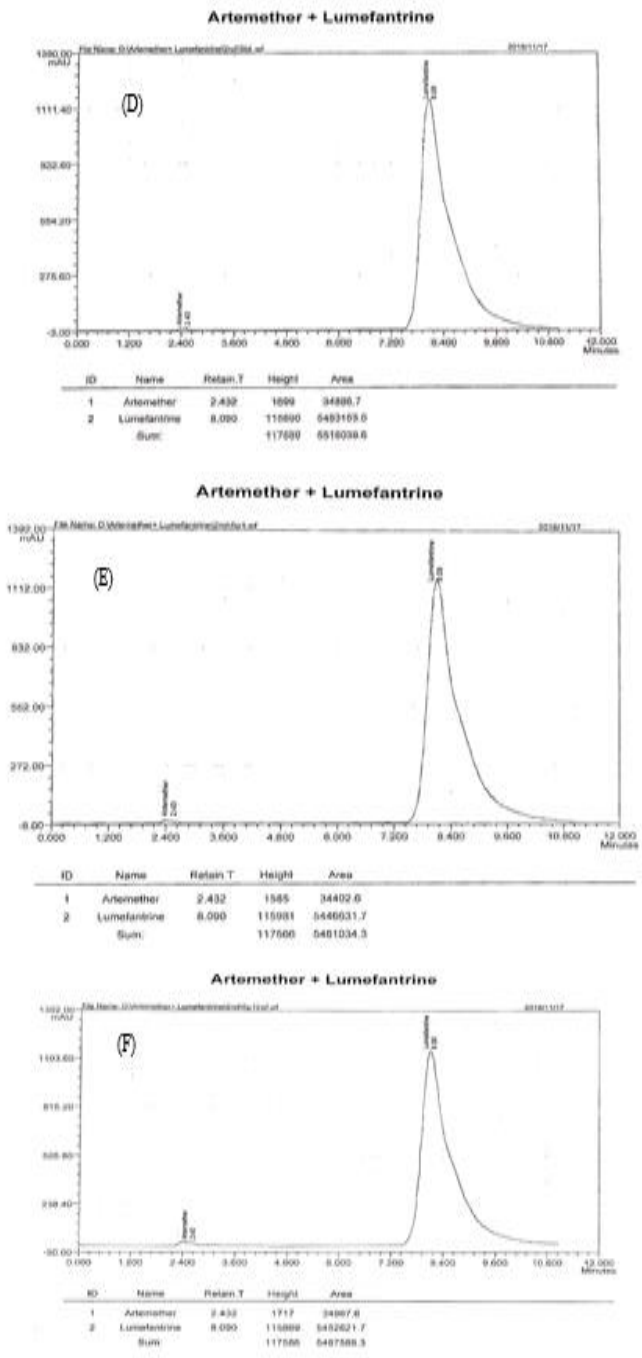

Figure 6 (D) Standard Chromatogram of (E) assessment Sample 1 chromatogram of 2nd assessment (F) Sample 2 chromatogram of 2nd assessment

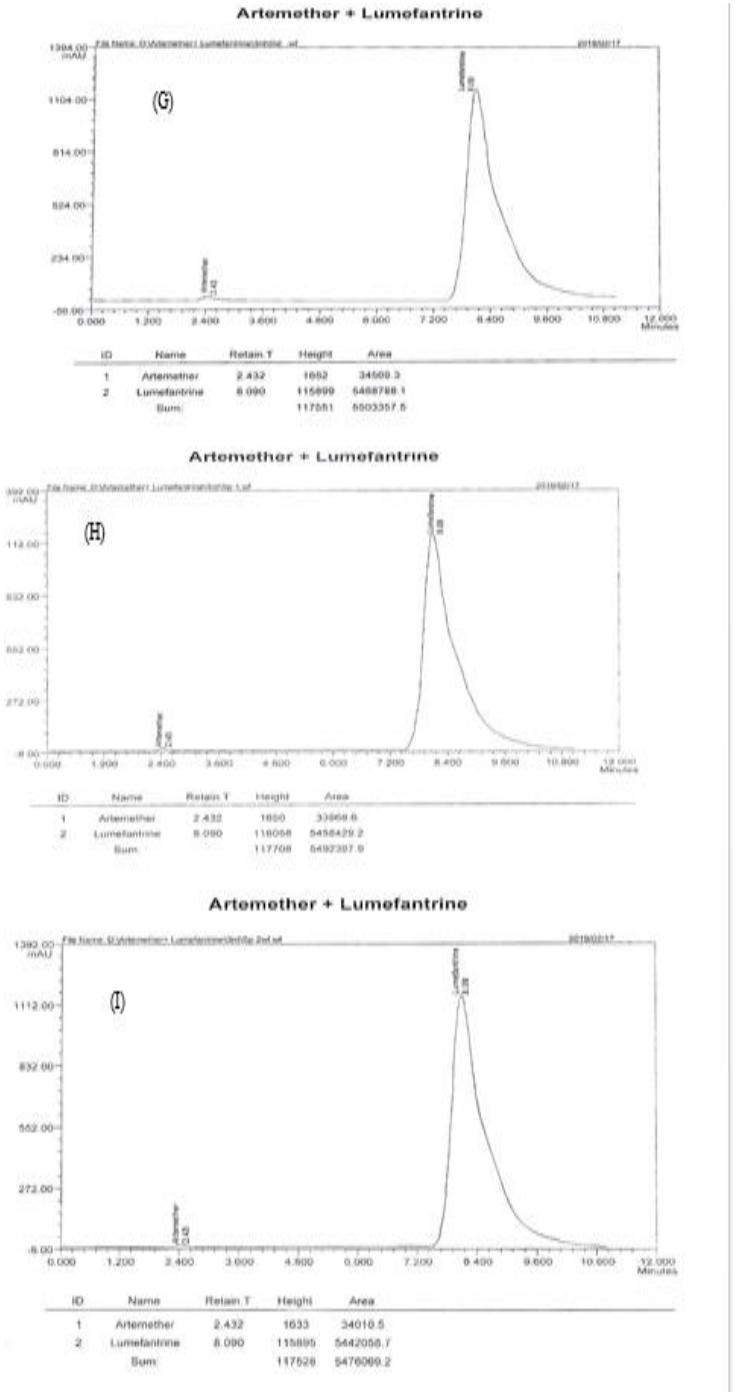

Figure 7 (G) Standard chromatogram of 3rd assessment (H) chromatogram of 3rd assessment (I)Sample 2 chromatogram of 3rd assessment