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Dissolution Rate Enhancement and Physicochemical Characterization of Artemether and Lumefantrine Solid Dispersions

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Abstract

The current study was conceded out with a vision to enhance solubility and thereby dissolution rate of poorly water soluble Artemether [ARTM] and Lumefantrine [LUM] [BCS-class IV drugs] using Lutrol F127 as carrier surfactant. It's difficult to choose a single carrier which forms solid dispersion [SD] with both the drugs by melt method. For which number of polymers and combination trials were carried out and finally Lutrol F127 was selected for further studies. SD was prepared by melt method using different ratios of drug and Lutrol F127. Saturation solubility study was conducted to evaluate the effect of polymer on aqueous solubility of ARTM and LUM. Solid state characterization was evaluated by fourier transformation infrared spectroscopy, differential scanning calorimetry, x-ray diffraction study and scanning electron microscopy. In vitro dissolution study was performed in phosphate buffer at pH 7.2 [with 1% SLS] and 0.1 N HCl [with 2% Benzalkonium chloride, BKC] for ARTM and LUM respectively. Solid state study showed partial interaction between drug and Lutrol F127. In vitro dissolution rate of ARTM and LUM from SD was significantly higher compared to pure drug. The dissolution rate of SD prepared by melt method was found to be higher than that of pure drugs and their physical mixtures. Thus, SD using melt method can be successfully used for the improvement of the dissolution rate of ARTM and LUM.

Keywords: Artemether, Lumefantrine, Solid dispersion, Melt method, Solubility, Dissolution rate

Introduction

Malaria is one of the oldest infirmities of humans and even today approximately 40% of world's populations are at risk of this disease. Antimalarial drugs have played a mainstream role in management and control of malaria in human host [1]. For decades, malaria chemotherapy has been reliant mostly on relatively small number of chemically related drugs with lack of structural multiplicity. These handful of drugs have their own precincts, of which the acquirement and spread of parasite multidrug resistance has been the most damaging [2]. Artemisinin-based combination therapy [ACT] is increasingly being prescribed as promising treatment. ACT is based on the use of two drugs with different modes of action: an artemisinin-derivative that causes rapid and effective reduction of parasite biomass and gametocyte carriage and a partner drug that has a longer duration of action. ARTM–LUM is an ACT widely used nowadays and consists of a registered fixed dose combination of ARTM [20mg] and LUM [120mg] in tablets [3]. ARTM and LUM both antimalarial drugs that exhibits poor oral bioavailability, owing to its poor aqueous solubility. The rationale is that ARTM will rapidly reduce parasitemia, resulting in symptomatic relief, and LUM will eliminate the remaining parasites. World Health Organization [WHO] recommends this association as first line therapy for falciparum malaria in endemic areas [4]. There is presently no other effective alternative to prevail the ever increasing problem of drug resistance. It is thus essential to focus all efforts on the research and development of novel antimalarial compounds and the effective delivery thereof [5].

SD techniques are also considered useful for improving the dissolution of water-insoluble drugs or controlled release of drugs. Some research groups have demonstrated solubility enhancement of ARTM by SD technique using [PVPK25, MW 25000] and polyethylene glycol [PEG4000, MW 4000] as excipients [6]. Rapid disintegrating taste masked tablet was prepared by Punit Shah and coworkers [7]. Cyclodextrin based host guest system also were reported in the literature [8]. There are various techniques for improving the solubility of poorly water-soluble drugs. Traditional methods for producing particles with

enhanced solubility include the pulverization of large drug particles using a ball or jet mill. Spray drying and freezing methods have been explored for preparing polymer-containing SD particles to enhance the dissolution rate of drugs [9]. The rationale behind the selected melt method is that, it is economic, environmentally friendly and avoids thermal degradation of drug, usage of organic solvent and sophisticated equipment. Also SD powders which are obtained by this method and selected polymers are physico-chemically stable and can be easily formulated [10].

SD is one of the most promising approaches to improve the oral bioavailability of poorly water soluble drugs. By reducing drug particle size to the absolute minimum, and hence improving drug wettability, bioavailability may be significantly improved [11, 12]. They are usually presented as amorphous products, mainly acquired by two chief methods, for example, melting and solvent evaporation [13]. Also SD powders which are obtained by this method and selected surfactant are physico-chemically stable. Recently, surfactants have been included to stabilize the formulations, thus avoiding drug recrystallization and potentiating their solubility [14, 15]. Here first time we have explored potential use of surfactant to make improved SD formulation for ARTM and LUM. Solubility and dissolution rate enhancement of LUM using melt method was not reported earlier as far our knowledge.

Experimental

Materials

ARTM and LUM were obtained as a gift samples from Bajaj Healthcare Pvt. Ltd. Mumbai, India. Lutrol F127 was a kind gift from BASF Chemical Ltd., Germany. All other ingredients were of analytical or pharmaceutical grade. Distilled water was used throughout the study. Sodium hydroxide, sodium chloride, hydrochloric acid, potassium hydrogen phosphate of analytical grades procured from Sd. Fine chemicals, Mumbai.

Preliminary solubility studies

Saturation solubility study

An excess quantity of ARTM and LUM was placed in 20 ml capacity test tubes containing 10 ml of different solutions [distilled water, 0.1 N HCl and phosphate buffer at pH 7.2] separately. The samples were sonicated for 20 min at room temperature and capped glass test tubes were shaken for 48 h at 37±0.1 C, speed 75 rpm using orbital shaking thermo stable incubator [Boekel Scientific, Germany]. The sealed glass test tubes were equilibrated for 48 h at 37 C in the incubator. The solutions in the test tubes were vortexed and kept for centrifugation for 20 min at 10000 rpm. The supernatant solution was then passed through a Whatmann Filter Paper [Grade 1] and the amount of the drug dissolved was analyzed spectrophotometrically [UV-1601PC, Shimadzu, Japan] at 211 nm and 338.6 nm for ARTM and LUM respectively after suitable dilution. All solubility measurements were performed in triplicate. [Fig. 1 & Fig. 2]

Phase solubility study

Phase solubility study was performed according to the method described by Higuchi and Connors [16]. An excess amount of ARTM and LUM was placed in 20 ml test tubes containing in 10 ml of distilled water with different concentrations of Lutrol F127 separately. Lutrol F127 [1%, 2%, 3%, 4% and 5% w/v] was used as hydrophilic polymer. Test tubes were covered with cellophane membrane to avoid solution loss and then shaken [75 agitations/min] in orbital shaking incubator [Boekel Scientific, Germany] for 48 h at 37 C. The solutions in the test tubes were vortexed and kept for centrifugation for 20 min at 10000 rpm. 5 ml of supernatant was withdrawn and filtered through Whatmann Filter Paper [Grade 1]. The filtrates were analyzed using a UV–visible spectrophotometer at 211 nm and 338.6 after suitable dilution. All solubility measurements were performed in triplicate [Fig. 3].

Gibbs-free energy [ΔG tr]

The ΔG tr value provides information about whether the treatment is favorable or unfavorable for drug solubilization in an aqueous medium. Negative Gibbs-free energy values indicate improved dissolution [17, 18].The ΔG tr values of ARTM and LUM were calculated using the following equation:

$\Delta G\ tr = \{-2.303RTLog\ [S_0/Ss]\}$

Where S0/Ss, is the ratio of the molar solubility of ARTM and LUM before and after treatment with surfactant Lutrol F127. The value of gas constant [R] is 8.31 J $K^{-1}mol^{-1}$ and T is temperature in degree kelvin.

The order of Phase solubility and ΔG tr of ARTM and LUM at different concentrations of Lutrol F127 shown in [Table 1]. Negative values of Gibbs free energy indicates improved dissolution.

Stability indicating HPLC method development [19, 20]

The assay of the SD was evaluated using high-performance liquid chromatography [HPLC] apparatus equipped with Binary HPLC pump, and 2998 Photodiode Array detector [Agilent Corporation, Milford, Massachusetts]. A reverse-phase C18 column [150 4.6 mm; 5 µm particles] was used. The mobile phase was composed of water–acetonitrile [25:75, v/v]. Samples equivalent to 20 mg of ARTM were dissolved in 5 mL of methanol and appropriately diluted and the drug content was determined by HPLC at λ = 211 nm [19].

For LUM acetonitrile–0.1M ammonium acetate buffer adjusted to pH 4.9 [85:15%, v/v] was used as the mobile phases using same apparatus as in case of ARTM. Samples equivalent to 120 mg of LUM were dissolved in 5 mL of methanol and appropriately diluted and the drug content was determined by HPLC at λ = 338.5 nm [20].

Both the methods developed were found to be stable for acid, base, oxidation, reduction, heat degradation studies. Flow rate and injection volume was 1 ml/min and 20µl for both the drugs respectively. Inter- and intraday coefficients of variation for ARTM and LUM were 10%.

Moisture uptake and Stability studies

A weighed amount of prepared SD about 100 mg were placed in crucibles at accelerated condition of temperature and humidity, 40 ±2 C and 75 ± 5% RH respectively in environmental test chamber [Thermo lab, INDIA,]. The changes in weight of samples were determined using Moisture balance MB 50C [CITIZEN, India].

Preparation of SD

SD were prepared with ARTM: Lutrol F127 and LUM: Lutrol F127 in 1:1, 1:2, 1:3, 1:4 and 1:5 weighed ratios by melt method

Melt method

The drug and surfactant were weighed and mixed together in mortar pestle. Then the mixture was taken in a glass beaker and heated on a heating mantle at particular [70 C and 100 C for ARTM and LUM respectively] temperature, while stirred with the help of glass rod to form uniform solid solution. This solid solution was kept at ice cooled temperature and then powdered to obtain SD. This material was then sifted through the sieve #60 to obtain fine powder. Melting of a pure drug occurs at the temperature when the chemical potential of the crystalline drug is equal to the chemical potential of the drug melt. If the melt drug is miscible with a polymer and dissolved in it, the chemical potential of the drug in the solution will be lower than that of the pure drug melt, and this phenomenon leads to melting point depression of drug crystals embedded in the polymer matrix and make it amorphous [21].

Solid state characterization

Infrared spectroscopy [IR]

IR spectroscopy was conducted using an FTIR Spectrophotometer [Spectrum GX-FT-IR, Perkin Elmer, USA]. The spectrum was recorded in the range of 4000–400 cm^{1}. The procedure consisted of dispersing a sample in KBr followed by gentle mixing. The spectrum was scanned at a resolution of 4 cm^{1} and scan speed was 4.0 $scans^{-1}$.

Differential scanning calorimetry [DSC]

Differential scanning calorimeter [DSC-PYRIS-1, Perkin Elmer, USA] was used to study the drug polymer interactions and thermal behavior of drug. The experiments were performed in a dry nitrogen atmosphere. The samples were heated at a rate of 10 C min^{1} from ambient temperature to the melting point. Empty aluminum pan was used as a reference.

X-ray diffraction [XRD]

The crystallinity between two samples was measured using a Miniflex apparatus [Rigaku, Japan] with CuK radiation. Samples were held on quartz frame. Diffraction pattern were obtained at a voltage of 45 kV and at a current of 20mA. The slide was then placed vertically at 0 angle in the X-ray diffractometer so that the X-ray beam fell on it properly. The results were recorded over a range of 0–40 [2θ] using the Cu-target X-ray tube and Xe-filled detector. The operating conditions were: voltage 40 kV; current 20 mA; scanning speed 1/min; temperature of acquisition: room temperature; detector: scintillation counter detector and sample holder: non-rotating holder.

Scanning electron microscopy [SEM]

The surface characteristics of samples were studied by scanning electron microscopy [SEM]. Double sided carbon tape was affixed on aluminum stubs. The powder sample was sprinkled onto the tape. The aluminum stubs were placed in the vacuum chamber of a scanning electron microscope. The samples were observed for morphological characterization using a gaseous secondary electron detector [working pressure: 0.8 Torr, acceleration voltage: 30.00 kV] XL 30. Model JEOL 5400 made in japan was used during analysis.

Dissolution rate studies

Dissolution rate studies were performed in phosphate buffer [pH 7.2, with 1% SLS] and 0.1 N HCl [pH-1.2 with 2% BKC] at 37±0.5 C using USP Type II rotating basket apparatus, 900 ml and 1000 ml medium in each dissolution vessel [ELECTROLAB, Mumbai, India] at 100 rpm and 75 rpm for ARTM and LUM respectively. Pure ARTM and LUM, all the batches of SDs and Physical mixtures each containing 20 mg of ARTM and 120 mg of LUM were subjected to dissolution. Accurately weighed quantities of samples were filled into hard gelatin capsule shells and were subjected to dissolution. At predetermined intervals of 20, 40, 60, 120 and 180 min., 10 ml of samples were withdrawn with replacement of equal volume of pre-warmed medium into the vessel. These samples were filtered and spectrophotometrically assayed for drug content at 211 nm and 338.6 nm. Each test was performed in triplicate [n=6] [22].

Results

Solubility study

The pH of solution had a significantly effect on the solubility of ARTM as well as LUM. The reason for choosing phosphate buffer [pH 7.2] as the dissolution medium is that ARTM has a low solubility in water and in acidic media. Solubility of ARTM and LUM in different media is given in Table 2.

Phase solubility study

The influence of Lutrol F127 on solubility of ARTM and LUM in distilled water at 37 C is presented in Fig. 3. The phase solubility diagram corresponds to ARTM-LUM type profiles. The stability constant for Lutrol F127 was found to be 51.73 mg ml^{1}. At 5% concentrations of Lutrol F127, the solubility of ARTM and LUM was increased. The enhancement in solubility might be due to the hydrophilic nature of surfactant and surface adsorption of drug on the surfactant.

HPLC Stability studies

The prepared SD kept for stability studies at 37 C at room temperature and 40 C/70 RH [relative humidity]. Samples were withdrawn at 3, 6 months and analyzed for drug content. Percentage drug content was in the range of 99.37 ± 0.81% to 99.15 ± 0.48% in ARTM and LUM formulations respectively. All determinations are mean ± SD [n = 3].

Results of Moisture uptake studies

Moisture uptake study is conducted to check hygroscopic nature of the prepared SD. No significant change in weight was observed after subjecting the sample to accelerated conditions of temperature and humidity. The accelerated stability studies showed that there was no considerable change in drug content during study duration. Drug content was found to be almost same as initial 99%.

Solid state characterization study

FTIR

FTIR spectra of pure ARTM indicated the presence of characteristic peaks of O-H stretching [3393.6 cm^{-1}], C-H stretching [2934.0 cm-1], and C-O-O-C bending vibrations [1157.3 cm^{-1}]. C=O stretching at 1655cm^{-1} and C-H bending at 1373.8 cm^{-1}. The FTIR spectra of physical mixture of ARM- Lutrol F127 showed similar stretching vibrations. FTIR spectra of melt SD of ARM-Lutrol F127 showed O-H stretching [3447.3 cm^{-1}], C-H stretching [2934 cm^{-1}], carbonyl stretching [1648 cm^{-1}] and C-H bending [1344.9-1459.5 cm^{-1}] [Fig. 4].

FTIR spectra of pure LUM indicated the presence of characteristic peaks of O-H stretching [3393.8 cm^{-1}], C-H stretching [2951.0-2854.9 cm^{-1}], and C-O-O-C bending vibrations [1152.5 cm^{-1}]. C=O stretching at 1652.8 cm-1 and C-H bending at 1402.5 cm^{-1}, C-Cl stretching [834.9-894.4 cm^{-1}]. The FTIR spectra of PM's of LUM-Lutrol F127 showed similar stretching vibrations in functional and fingerprint regions [data not shown]. FTIR spectra of melt SDs of LUM-Lutrol F27 showed O-H stretching [3457.8 cm^{-1}], C-H stretching [2872.4 cm^{-1}], carbonyl stretching [1653.9 cm^{-1}] and C-H bending [1344.4-1397.8 cm-1]. The FTIR spectra of pure Lutrol F127 exhibited characteristic signals at 3427 cm^{-1} [O-H stretching], at 2873 cm^{-1} [C-H stretching vibration] [Fig. 5].

Overall there was no chemical interference of functional groups between ARTM and LUM with Lutrol F127 observed.

Interpretation of DSC

The DSC curves obtained for pure ARTM, SD and their corresponding physical mixtures are displayed [Table 3]. ARTM showed a sharp endotherm at 90.84 C corresponding to its melting point. There was a noticeable reduction in endothermic peak height and heat of fusion, in physical mixtures and in SD as compared to pure ARTM [Fig. 6 to Fig. 9]. These suggest that the physical state of ARTM changed from crystalline to amorphous. LUM showed a sharp endotherm at 131.54 C corresponding to its melting point. The melting peak of LUM tends to shift to lower temperatures in the SD powder relates to transformation of its crystalline behavior into amorphous nature [Fig. 10 to Fig. 13]. It has been known that transforming the physical state of the drug to amorphous or partially amorphous state leads to a high-energy state and high disorder, resulting in enhanced solubility and faster dissolution.

XRD

The XRD pattern of pure ARTM, LUM and that of Lutrol F127, SD are obtained. The XRD scan of pure ARTM and LUM showed intense peaks of crystallinity. Whereas the XRD pattern of prepared SD exhibited a reduction in both number and intensity of peaks. It was observed that the plain ARTM and LUM indicating the decrease in crystallinity or partial amorphization of the drug in its SD form [Fig. 14 to Fig. 16].

SEM

SEM micrographs of ARTM, LUM and SDs at different magnifications are obtained. The pure ARTM was characterized by crystals of bigger size and regular shape with an apparently smooth surface. In SDs, ARTM and LUM crystals adhered on the surface of polymer. The reduced crystallinity of ARTM and LUM in SD was further confirmed from the results of XRD and DSC studies [Fig. 17 to Fig. 21].

In vitro dissolution study

In vitro dissolution study of SD and physical mixture [PM] prepared using Lutrol F127 with drug release studies in phosphate buffer at pH 7.2 [with 1 % SLS] for 1 h are depicted in [Fig. 22 & Fig. 23]. The pure drug showed a release of 18.2% at the end of 1 h, while SD showed 76.54% drug release in 1 h. While in Fig C in *vitro* drug release studies in buffer at pH 1.2 [0.1N HCl, with 2 % BKC] for 1 h are depicted as pure drug showed a release of 12.77 % at the end of 1 h, while SD showed 56.51 % drug release in 1 h [Fig. 24 & Fig. 25]. The percent drug dissolution increased with an increase in drug to Lutrol F127 ratio. Physical mixtures also showed an improved dissolution rate to a significant extent as compared with pure ARTM. The highest dissolution rate was exhibited by SD of ratio1:5. The enhancement in the dissolution of ARTM and LUM from SD can be ascribed due to several factors, like lack of crystallinity, particle size reduction, reduction in interfacial tension between hydrophobic drug and dissolution medium, increased wettability and effective surface adsorption of drug on hydrophilic carrier [i.e. surface SD is formed]. Lutrol F127 [size of particle-180 um] has a large surface area and can absorb a large amount of drug. During dissolution studies, the immediate sinking of the particles was observed.

The dissolution profile of ARTM/ Lutrol F127 and LUM/ Lutrol F127 SD showed an improved dissolution when compared with the pure drug. The reasons for the augmentation in drug dissolution could be the dispersion of drug in pores of Lutrol F127 and increased wettability. The dissolution rate of the drug

increased up with increment in the quantity of surfactant. This might be due to the intact adsorption of the drug on Lutrol F127, which enhances the dissolution of the drug. Thermal behavior of Lutrol F127 can be responsible for the intact adsorption of the drug. Physical mixtures also showed an improved dissolution rate.

Mechanism of dissolution [23]

The dissolution kinetic studies were carried out and the best suited results obtained in the case of Higuchi equation model. The value of R^2 in Higuchi model is nearer to 0.1 and thus we conclude that dissolution followed Higuchi order kinetics [Table 4].

Discussion

The phase solubility study with water and with Lutrol F127 shows an increase in the solubility of the drug. The values of Gibbs free energy [ΔG tr] associated with the aqueous solubility of ARTM and LUM in the presence of Lutrol F127 were all negative at various concentrations indicating the spontaneous nature of drug solubilization. The values decreased with increasing surfactant concentration, demonstrating that the reaction became more favorable as the concentration of surfactant increased. All SD formulations with various ratios of Lutrol F127 showed higher rate of dissolution than ARTM and LUM pure drug, and to equivalent physical mixtures. The pure drug ARTM and LUM showed up to 18% and 12%dissolution over 60 min, but its SDs prepared by melt method with Lutrol F127 [1:5 ratio] showed dissolution of more than 75% and 60% over 60 min respectively. This enhancement in the dissolution rate of ARTM and LUM from drug carrier systems can be attributed to several aspects such as complete amorphization of drug, increased wettability and dispersibility. FTIR spectroscopy shows no interference amongst characteristics peaks in the spectra of drug and SD prepared, specifying there is no chemical or functional interaction between the drug and the surfactant. The DSC study indicates that the drug is homogenously distributed in the polymer matrix and is of amorphous nature in prepared SD. The XRD study reveals there is change in the crystallinity of pure ARTM and LUM to amorphous state in the SD. SEM studies reveals that the drug particles gets entrapped within the polymer matrix and having smooth morphological surface which also contributed to the enhancement in the permeability.

Conclusion

The present study demonstrated a successful and simple method to prepare ARTM and LUM SD to enhance its aqueous solubility and dissolution rate. Nature and the amount of the carrier used, played an important role in the enhancement of dissolution rate. The solid state studies showed partial interaction of both the drugs with polymer and the decrease in crystallinity. Lutrol F127 is a potential matrix carrier for the delivery of the poorly soluble drugs. The dissolution rate has been increased with the increasing the concentration of polymer Lutrol F 127.

Acknowledgments

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Table 1- Gibbs free energy calculated values of ARTM and LUM

Conc. Of polymer [% w/v]	Concentration of ARTM [µg/ml] with Lutrol F127	ΔG°tr [J/Kmol] of ARTM	Concentration of LUM [µg/ml] with Lutrol F127	ΔG°tr [J/Kmol] of LUM
1	1.713	-762.881	1.167	-2478.33
2	2.008	-1171.73	1.575	-3250.83
3	2.491	-1727.55	2.363	-4295.54
4	2.85	-2074.54	3.183	-5063.89
5	3.2	-2372.99	3.783	-5508.8

Table 2- Solubility of ARTM and LUM in different media

Sr. No.	Medium	Solubility of pure ARTM [µg/ml]	Solubility of pure LUM [µg/ml]
1.	Distilled water	1.18	0.44
2.	0.1 N HCl [pH-1.2]	1.37	1.31
3.	Phosphate buffer [pH-7.2]	2.35	0.68

Table 3- Interpretation of DSC showing peak height, peak area and heat of fusion

Drug & SD / DSC parameters	Lutrol F127	ARTM	ARTM + Lutrol F127 PM (1:1)	ARTM + Lutrol F127 SD (1:1)	LUM	LUM + Lutrol F127 SD (1:1)
System Peak point °C	57.67	90.84	88.03	72.34	131.54	123.96
Peak height (mW)	6.2290	10.9852	0.3162	0.06556	6.4543	0.8541
Peak area (mJ)	154.437	247.369	2.767	2.125	21.480	58.698
Heat of fusion ΔHF (J/g)	38.6092	61.8422	0.6917	0.5313	21.480	14.6745
Peak Onset	53.84	89.02	86.60	67.74	127.55	118.83
Peak Endpoint	59.98	92.37	88.60	75.17	135.76	126.15

Table 4- Dissolution kinetic studies

	Zero order	**First order**	**Higuchi**	**Hickson Crowell**	**Korsemeyer -Peppas**
R^2	0.683	-0.905	0.981	0.623	0.9735
Slope	0.342	-0.005	18.292	19.145	1.295
Intercept	40.58	1.749	20.31	49.625	-0.023

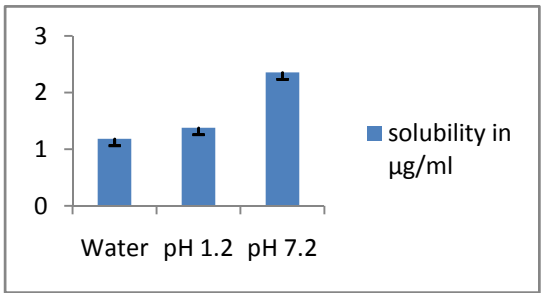

Fig. 1

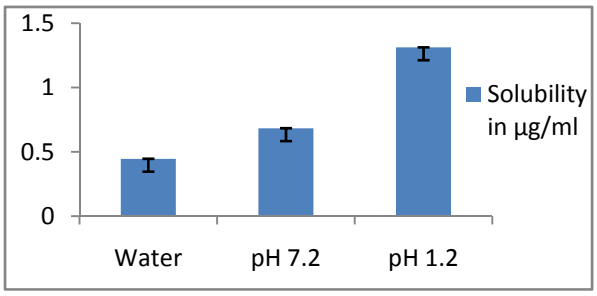

Fig. 2

Fig. 1 & Fig. 2- Saturation solubility of ARTM and LUM in different medium [Each point refers to mean ± SD [n=6]]

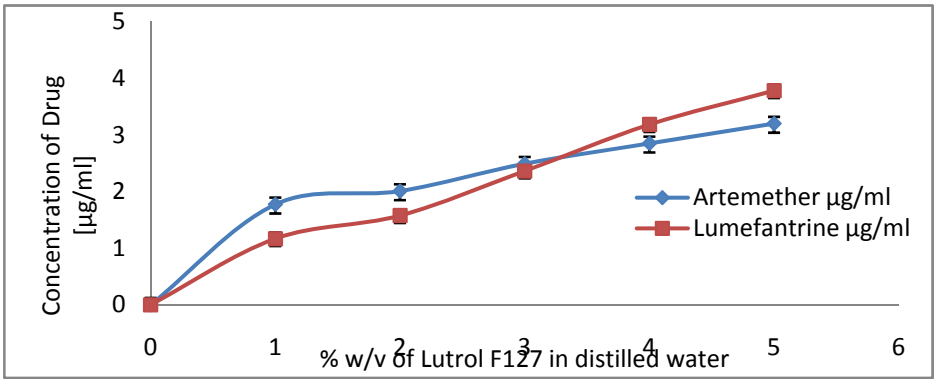

Fig. 3 Phase solubility profile of ARTM and LUM [Each point refers to mean ± SD [n=6]]

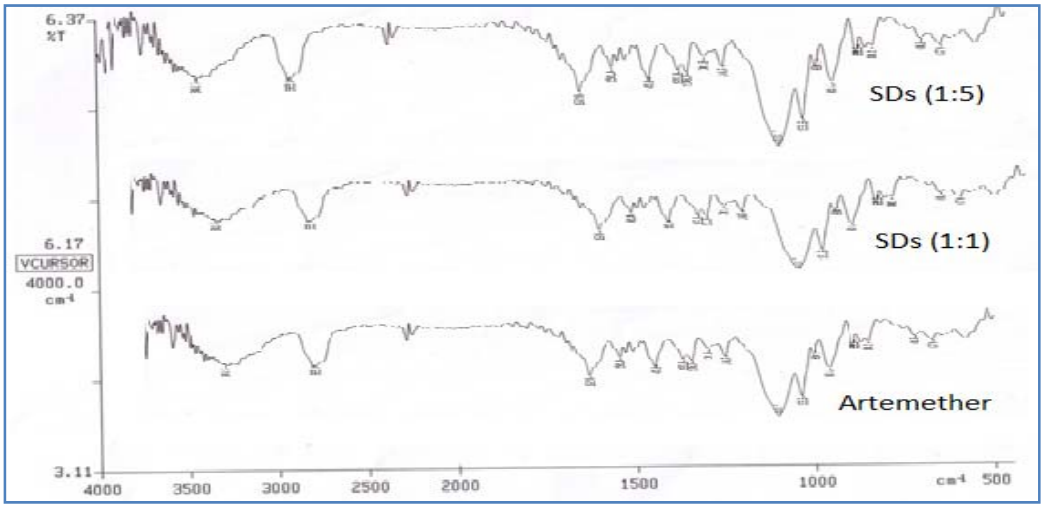

Fig. 4 IR of Plain ARTM, ARTM-Lutrol F127 SD [1:1] and ARTM-Lutrol F127 SD [1:5]

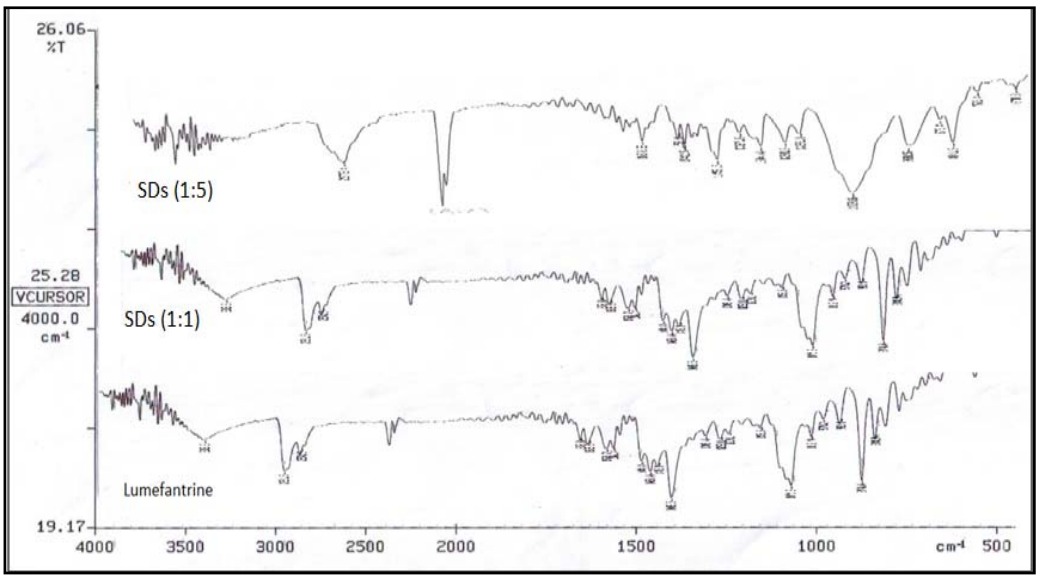

Fig. 5 IR of Plain LUM, LUM-Lutrol F127 SD [1:1] and LUM-Lutrol F127 SD [1:5]

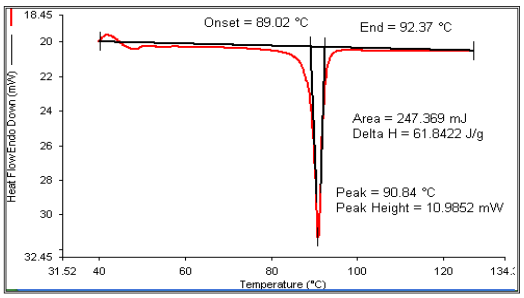

Fig. 6 DSC of pure ARTM

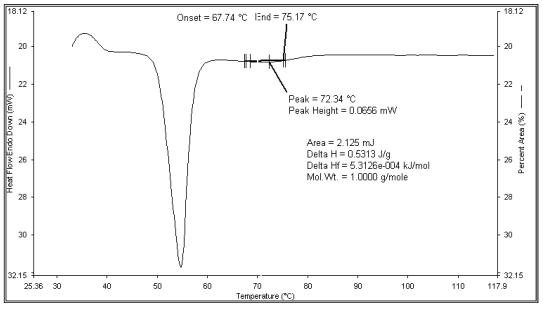

Fig. 7 DSC of ARTM-Lutrol F127 SD [1:1]

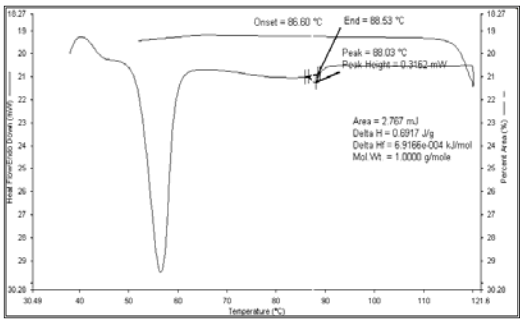

Fig. 8 DSC of ARTM-Lutrol F127 PM [1:1]

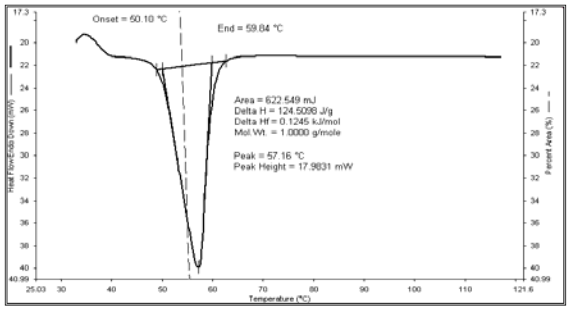

Fig. 9 DSC of ARTM-Lutrol F127 SD [1:5]

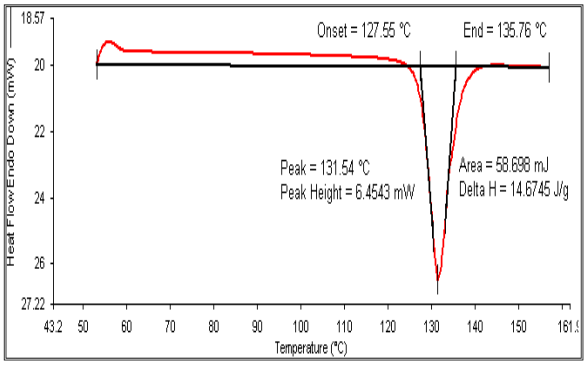

Fig. 10 DSC of pure drug LUM

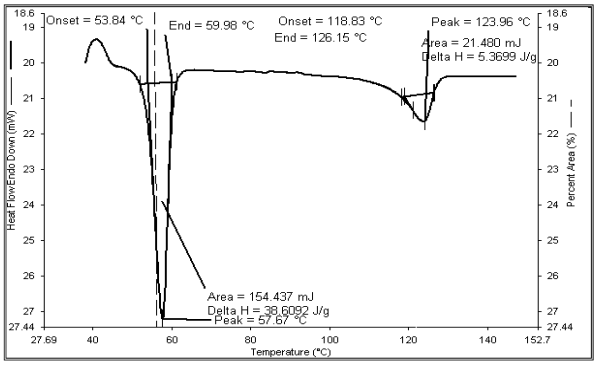

Fig. 11 DSC of LUM-Lutrol F127 SD [1:1]

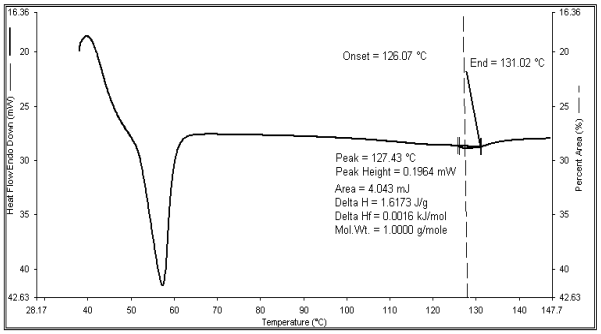

Fig. 12 DSC of LUM-Lutrol F127 PM [1:1]

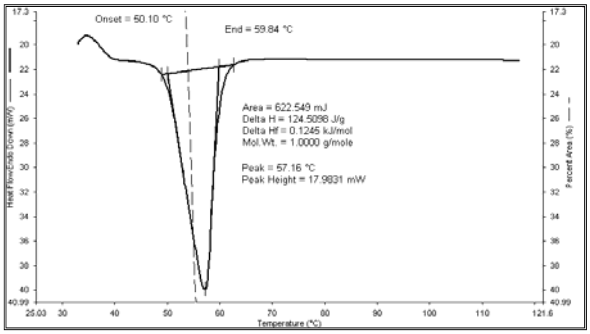

Fig. 13 DSC of LUM-Lutrol F127 SD [1:5]

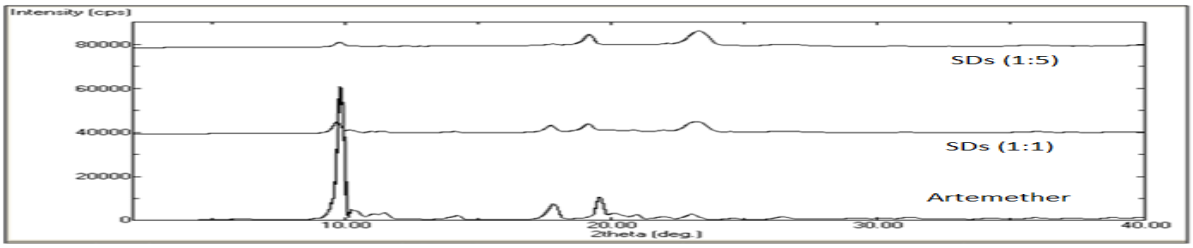

Fig. 14 X-ray diffraction patterns of plain drug ARTM and its SD with Lutrol F127 in ratio [1:1] and [1:5] from bottom to top respectively

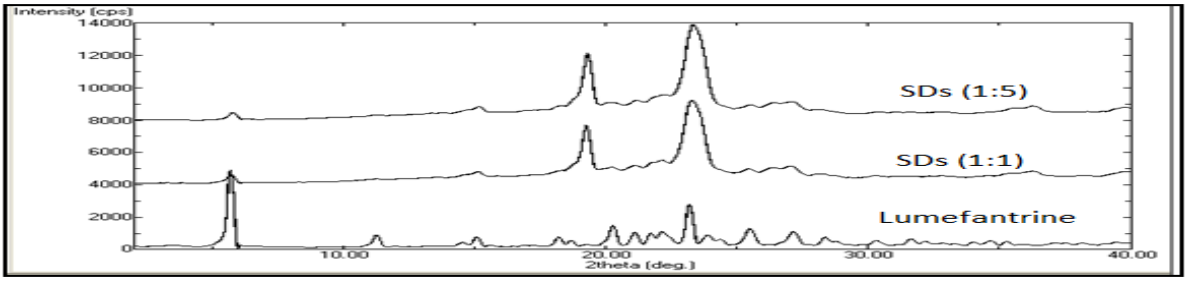

Fig. 15 Shows X-ray diffraction patterns of plain drug LUM and its SD with Lutrol F127 in ratio [1:1] and [1:5] from bottom to top respectively

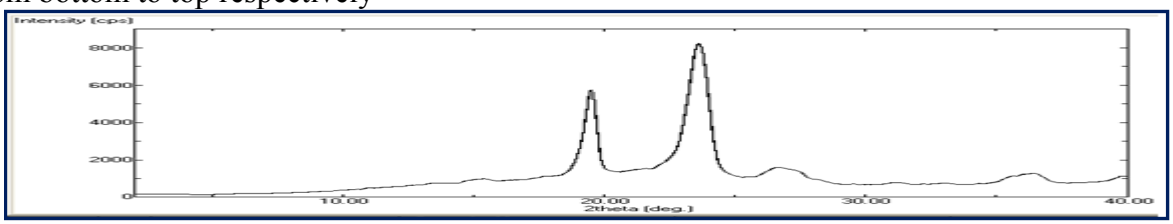

Fig. 16 Shows X-ray diffraction patterns of polymer Lutrol F127

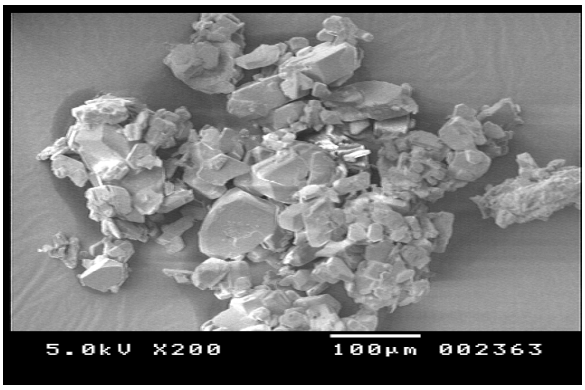

Fig. 17 SEM image of Pure ARTM

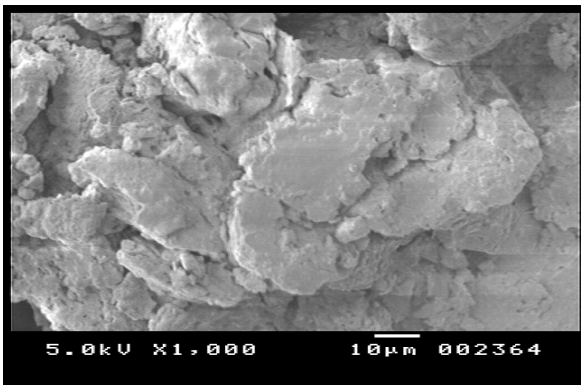

Fig. 18 SEM image of ARTM-Lutrol F127 SD [1:5]

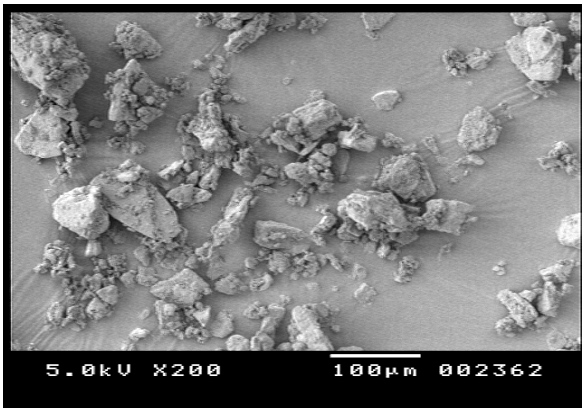

Fig. 19 SEM image of Pure LUM

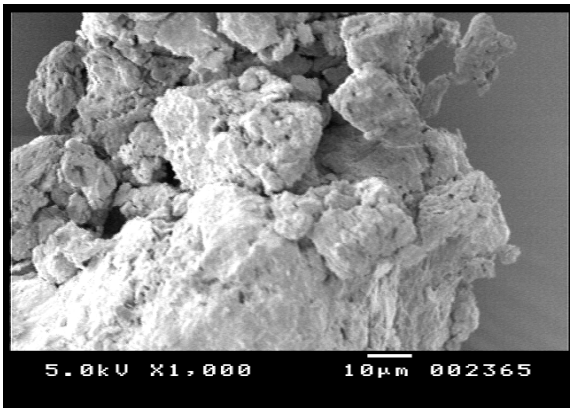

Fig. 20 SEM image of LUM-Lutrol F127 SD [1:5]

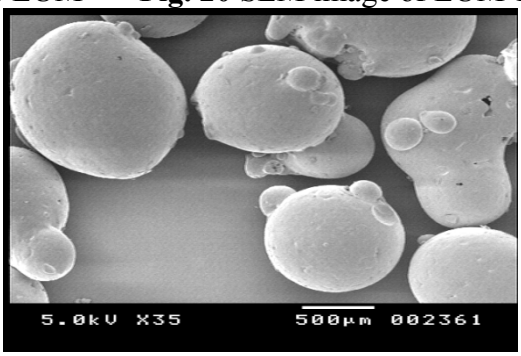

Fig. 21 SEM image of surfactant Lutrol F127

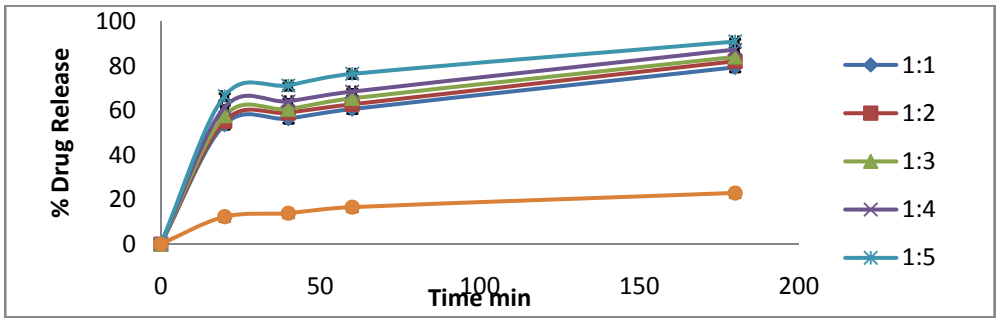

Fig. 22 Comparative Dissolution profile of ARTM-Lutrol F127 SD formulation and pure drug ARTM [Each point refers to mean ± SD [n=6]]

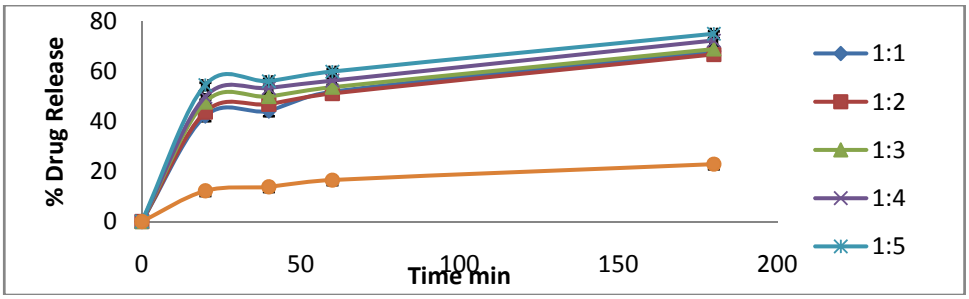

Fig. 23 Comparative Dissolution profile of ARTM-Lutrol F127 physical mixture formulation and pure drug ARTM [Each point refers to mean ± SD [n=6]]

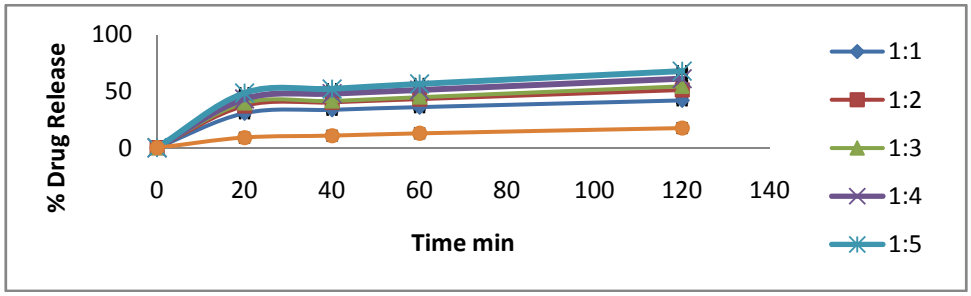

Fig. 24 Comparative Dissolution profile of LUM-Lutrol F127 SD formulation and pure drug LUM [Each point refers to mean ± SD [n=6]]

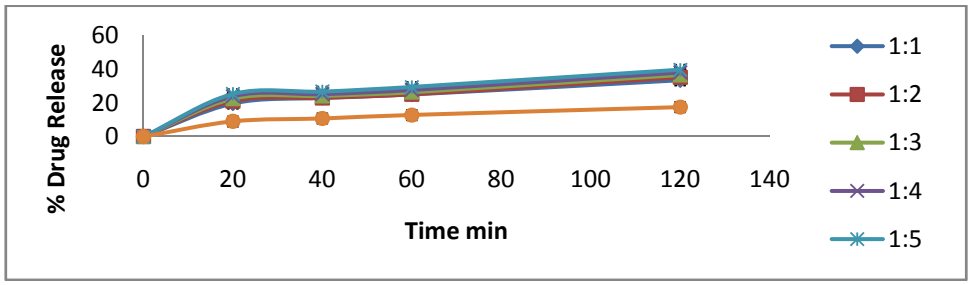

Fig. 25 Comparative Dissolution profile of LUM-Lutrol F127 physical mixture formulation and pure drug LUM [Each point refers to mean ± SD [n=6]]