Vol 5 | Issue 1 | 2015 | 1-5.

e-ISSN 2249 – 7706
print-ISSN 2249– 7714

International Journal of
Advanced Pharmaceutics
www.ijapjournal.com

PHYSIOCHEMICAL CHARACTERIZATIONS OF ARTEMISININ-POLYETHYLENE GLYCOLS (1400, 4000 & 6000) SOLID DISPERSIONS

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ABSTRACT

Artemisinin (ART) is an oral antimalarial agent with poor aqueous solubility and low oral bioavailability. The present study describes the preparation of artemisinin with polyethylene glycol (PEGs 1500, 4000 and 6000) as a solid dispersion to increase the solubility of artemisinin. Solid dispersion of the drug were prepared with PEGs (1500, 4000 and 6000) at these ratios (1: 10 to 8: 10) using melt (fusion) method. The prepared solid dispersions were physiochemically characterized and compared to pure ART. Solubility determination, scanning electron microscopy (SEM) and differential scanning calorimetry (DSC) were used to investigate the physicochemical characteristics of the preparation. The solubility of artemisinin from these preparations increased linearly with increasing the ratio of PEGs to drug. However, the increase in ART solubility was not significant. The data obtained from SEM and DSC studies revealed that the preparations were not capable of increasing the solubility of artemisinin significantly through increasing the percentage of PEGs. These preparations did not result in pure amorphous form but it led to reduce crystallinity of artemisinin.

Keywords: Artemisinin, Solubility, PEG, DSC and SEM.

INTRODUCTION

Artemisinin (ART) is the active principle isolated from the Chinese medicinal herb Artemisia annua [1-2]. ART and its derivatives have gained increasing attention as antimalarial drugs since their low toxicity and high efficacy against malarial parasites, including the cases caused by multidrug resistant and cerebral strains, [3-4]. However, ART has low aqueous solubility, resulting in poor and erratic absorption upon oral administration. This, together with its short half-life and high first pass-metabolism, lead to incomplete clearance of parasites resulting in recrudescence [5]. Many approaches have been used to improve the solubility of the poorly soluble drugs; Wong & Yuen [6] have demonstrated that artemisinin solubility could be increased through inclusion complexation with β-cyclodextrin. Among the other approaches which have been utilized to enhance the drug solubility is solid dispersion. The use of solid dispersion containing water-soluble carriers, to enhance the solubility, the dissolution rate and bioavailability of poorly water-soluble drugs has been demonstrated by a number of investigators [7-14].

The aim of the present study was to enhance the aqueous solubility of artemisinin using solid dispersion technique.

MATERIALS AND METHODS

Chemicals

Artemisinin was obtained from Kuming Pharmaceutical Corporation (Kuming, China). Polyethylene glycol, PEG (1500, 4000, and 6000) from Merck (Schuchardt, Germany). All other chemicals or solvents used were either of analytical or HPLC grades.

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Preparation of artemisinin-PEGS (1500, 4000 and 6000) solid dispersions

Solid dispersions of ART-PEG (1500, 4000 and 6000) at ratios ranging from (1:10 to 8:10) were prepared by heating PEGs-1500, 4000 and 6000 at 45ºC, 55ºC and 65ºC respectively for one hour with constant stirring. ART was added to the melted PEG, gradually. The heater was off for temperature, while the stirrer was kept on during cooling. The capsules were filled at different cooling temperature (65ºC, 45ºC and 35ºC), (55ºC, 45ºC and 30ºC) and (45ºC, 40ºC and 30ºC) for PEGs 6000, 4000 and 1500 respectively. All the capsules were subsequently stored in airtight amber bottle containing silica gel at ambient temperature for 24 hours prior to their characterization.

Determination of artemisinin solubility in artemisinin-PEG solid dispersions

The solubility of ART in prepared ART-PEG solid dispersions was determined according to the method of Higuchi and Connors [16]. An excess amount of pure ART and ART-PEGs solid dispersions were separately added into flasks containing 20ml of water. All the samples were shaken vigorously at 30ºC for 24 hours. 5ml samples were collected for 24 hours and filtered through a membrane filter (0.2µm). The filtrate was then suitably diluted and treated prior to analysis by HPLC using UV detector operated a wave length 260nm. The chromatographic separation was performed using a Gensis C_{18} Column (150 x 4.6 mm). The mobile phase composed of a mixture of acetonitrile and 0.01M disodium hydrogen phosphate adjusted to pH 6.5.

Differential Scanning Colorimetric (DSC) Studies

The thermal studies were performed for the prepared solid dispersions, plain PEGs and drug with TA Instrument DSC 210 (De, USA). Each sample (of approximately 10 mg of powder in aluminum pan) were heated at a rate of 10ºC / min and scanned between 25ºC and 200ºC. The data were analyzed using the Universal Analysis Software (TA Instrument, USA).

Microscopic studies

A sample of 5mg of each ART-PEGs solid dispersions ratio was examined under light microscopy. Each sample was mixed with one drop of mineral oil to make the micrograph clearer. The magnification used was 400X.

RESULTS AND DISCUSSION

Figure 1 shows the phase solubility diagram of ART alone or in solid dispersions with PEGs (1500, 4000 and 6000) at different ratios. It can be observed that the aqueous solubility of ART is increased slightly with increasing the ratio of the carrier. It was also observed that the solubility of ART was not synergistically increased with increase in the molecular weight of PEGs from 1500 to 4000, while there was a marginal increase in the solubility of ART when PEG 6000 was used compared with PEG 4000. This result is consistent with result of Geneidi and others, that the dissolution rate and solubility of glibenclamide was independent of PEG molecular weight [17].

Figure 2 A, B and C shows typical scan of ART melts with PEGs 1500, 4000 and 6000 respectively using different cooling rates. As evident from these thermograms, there was a small shift observed in the heat of fusion of different PEGs at the higher cooling rate. There was an appreciable change in the heat of fusion, which was reduced as the rate of cooling was increased (Table 1), indicating a reduction in the degree of crystallinity. Similar finding has been reported by Craig and Newton [18].

From these results obtained, the cooling rate at 30ºC was selected for the cooling of different ratios of ART-PEGs solid dispersions.

Table 1 showed that the heat of fusion and temperature of PEGs (1500, 4000 and 6000) alone, their physical mixture and solid dispersions with artemisinin at different ratios using cooling temperature of 30ºC. It can be observed that, there was no change in the heat of fusion, in the physical mixtures, while the solid dispersions ratios showed a margin change in the enthalpy of melting from 37 to 42.75 (J/G) with increasing the ratio of PEG 1500. On the other hand, it has been found that the enthalpy of melting decreased gradually from 40.25 to 43.43 (J/G) and from the 34.5 to 44.75 (J/G) with increasing the ratio of PEG 4000 or PEG 6000 respectively.

Figure 3 shows the micrograph of ART and ART-PEGs solid dispersions, long and tabular laminar crystalline particles are clearly visible for artemisinin (A), while for the solid dispersions, it is obvious that, the solid dispersion at ratio of (1:10) showed the smallest drug crystal compared to the other ratios. The smallest crystal size of the drug was seen when PEG 6000 is incorporated. It was also observed that the size of the crystals increased slightly as the molecular weight is decreased. It can be concluded that, compared with artemisinin crystals, all the solid dispersion showed much smaller drug crystals which are increased as the drug ratio is in increased. This can be attributed to the influence of supersaturation [19].

Table 1. Heat of fusion of polyethylene glycols and its solid dispersions with artemisinin at different cooling rate (X Y and Z º C)

Preparations	Heat of fusion (J/g)		
	PEG 1500	PEG 4000	PEG 6000
PEGs	42.70	43.00	45.00

ART-PEG at X ºC*	39.75	42.50	42.85
ART-PEG at Y ºC**	38.30	41.35	41.72
ART-PEG at Z ºC***	37.00	40.25	34.50

*XºC (PEG 6000 = 60ºC, PEG 4000 = 55ºC, Peg 1500 = 45ºC)
**YºC (PEG 6000 = 45ºC, PEG 4000 = 45ºC, Peg 1500 = 40ºC)
***ZºC (30ºC)

Figure 1. Solubility of artemisinin in PEG solid dispersions

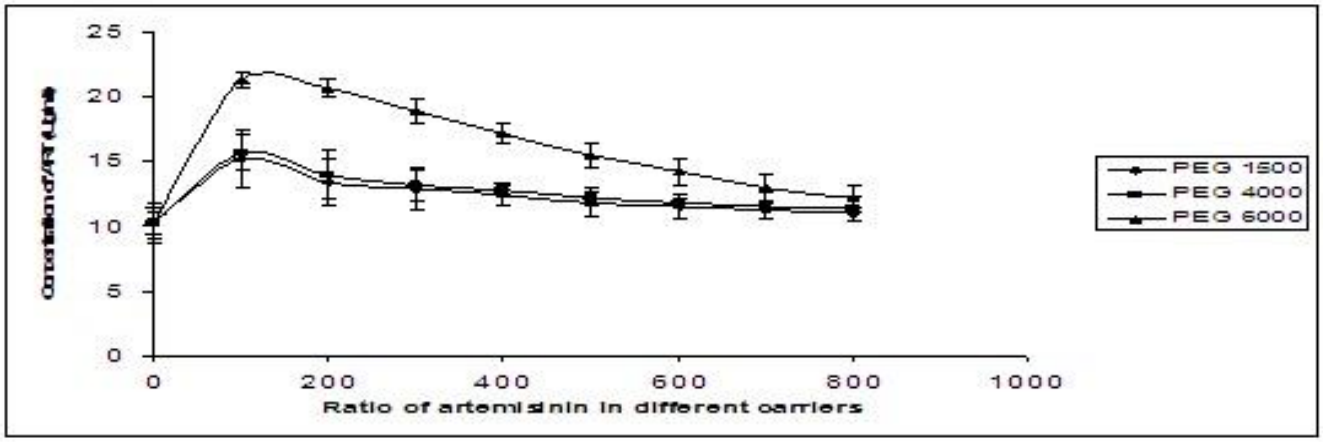
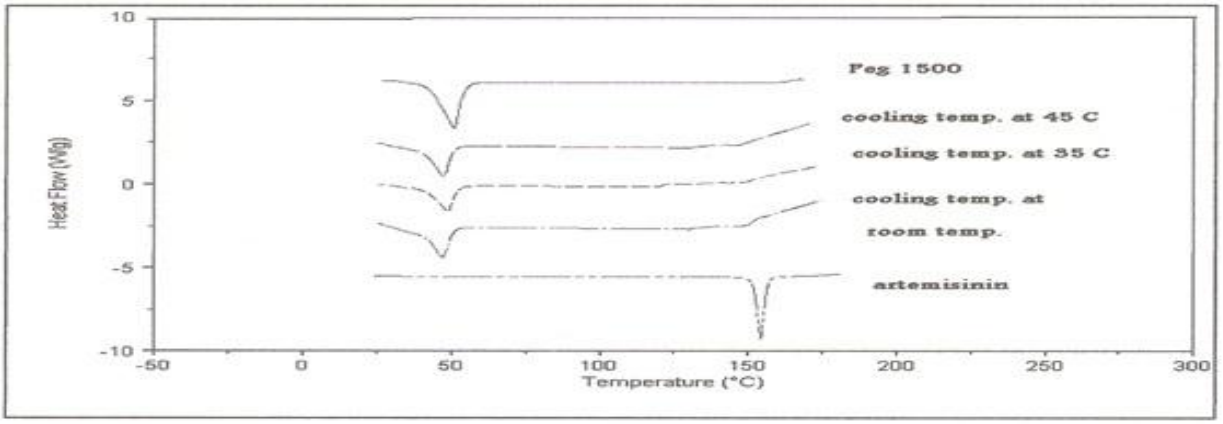
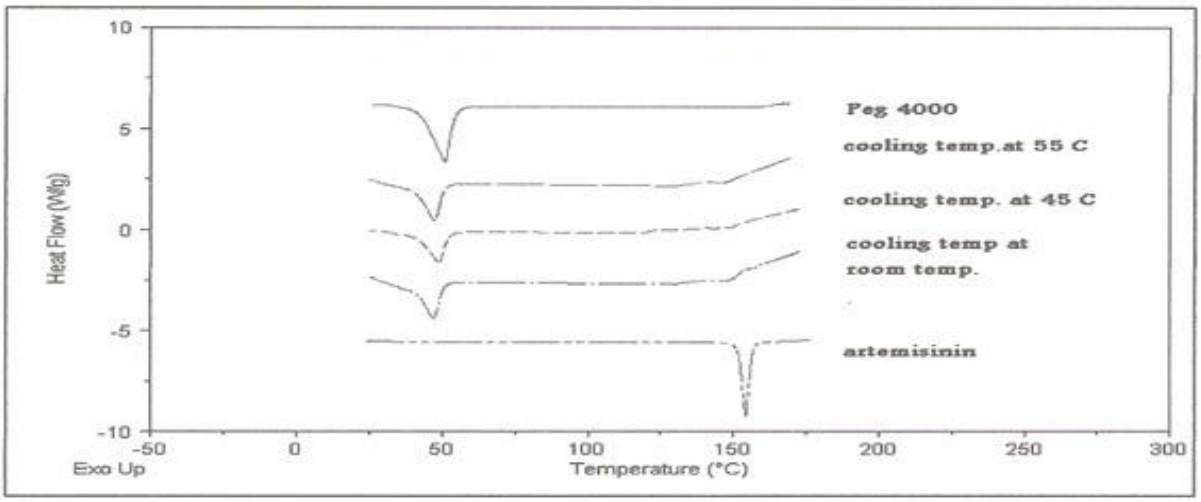


Figure 2. Thermogram of artemisinin-PEG (A-1500, B-4000 and C-6000) ratio (1:10)

A



B



C

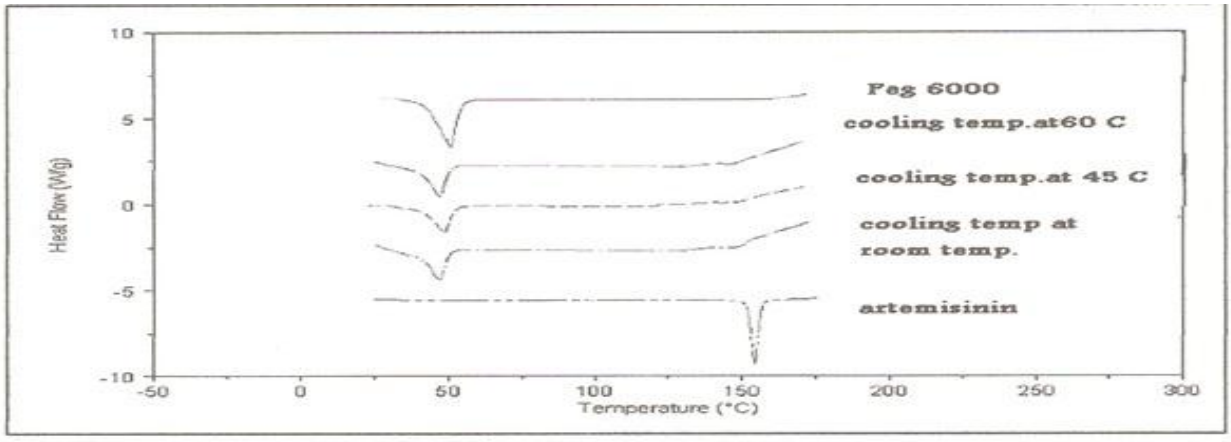
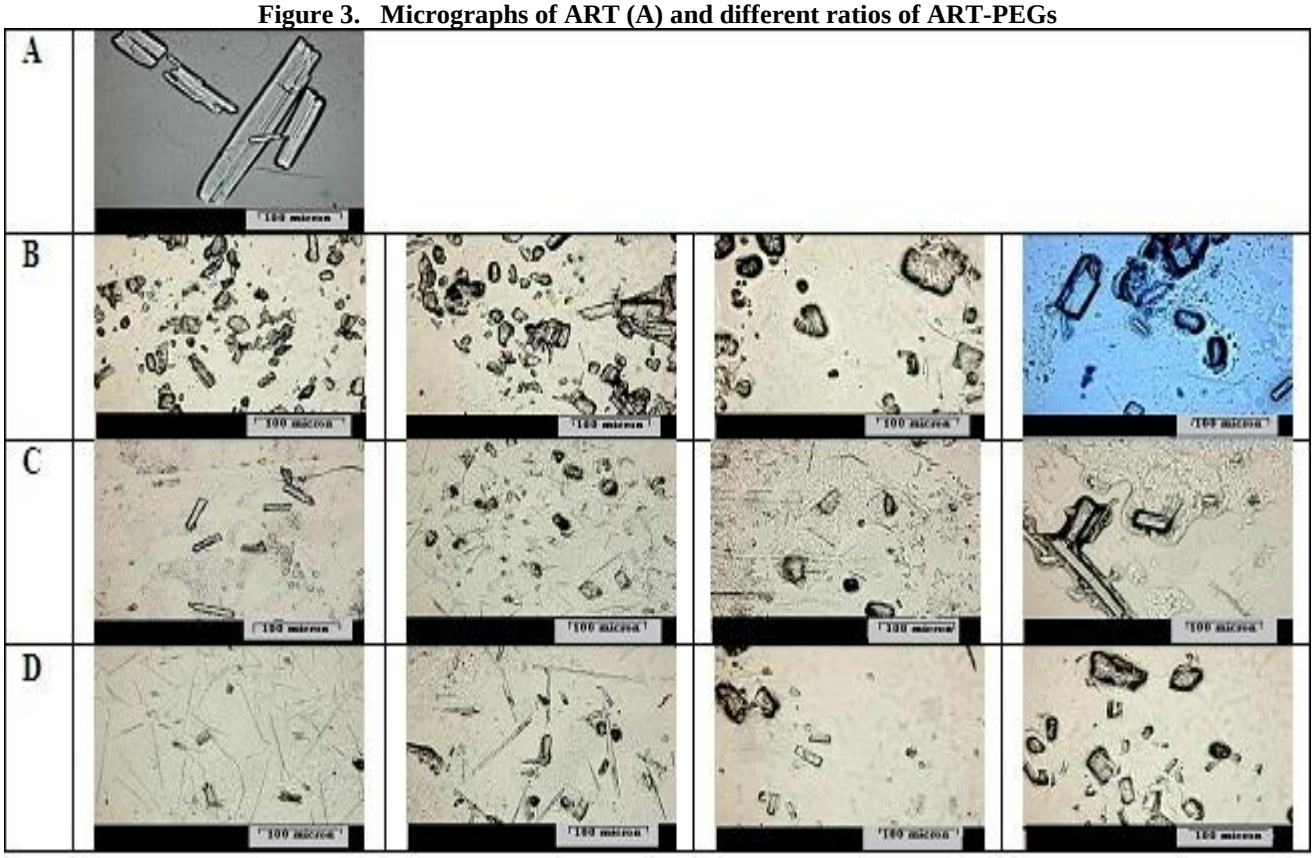


Figure 3. Micrographs of ART (A) and different ratios of ART-PEGs



(B= 1500, C = 4000 and D = 6000). In figures B, C and D left to right indicates 1:10, 2:10, 4:10 and 8:10 of ART: PEG respectively.

CONCLUSION

From the results of the in vitro evaluation of artemisinin PEGs (1500, 4000 and 6000) solid dispersions, it can be concluded that this method was not capable of increasing the solubility of ART significantly. DSC studies indicated that the presence of the drug had a margin effect on the melting profile of the carrier, indicating limited miscibility between the two components.

So this preparation may lead to reduction in the crystallinity of RT rather than forming a pure amorphous phase, this finding was supported by the microscopic studies.

ACKNOWLEDGEMENT

I would like to acknowledge, Prof. Dr. Yuen Kah Hay and Dr. Wong Jia Woei of Department of Pharmaceutical Technology, School of Pharmaceutical Science. Universiti Sains Malaysia. Penang –Malaysia for their endless optimism and positive way of guidance thinking during my work.

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