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Research Article

Preparation and Characterization of Artemether Solid Dispersion by Spray Drying Technique

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Abstract

Introduction: Artemether, a BCS class IV drug (poorly water soluble and poorly permeable, less bioavailability) but is found to be effective against falciparum malaria. Preparation of water soluble formulation could be the technique to improve bioavailability of such drug. The most ideally used technique to enhance the solubility and dissolution of poorly water soluble drugs is Solid dispersion method.

Method: The objective of the study was to enhance the solubility and dissolution rate of Artemether by preparing solid dispersions using Soluplus, at different ration of 1:1, 1:2, 1:3 and 1:4 using spray drying technology. Prepared Solid dispersions were characterized by Fourier transform infrared spectroscopy and differential scanning calorimetry.

Results: The spray-dried solid dispersions found to be having less crystallinity and showed higher dissolution rates. Solubility study data showed the optimum drug/Soluplus ratio to be 1:3. The dissolution studies of Solid dispersions in 1.2 pH and 6.8 pH buffer showed higher drug release as compared to pure drug.

Conclusion: Thus we conclude that an amorphous solid dispersion of Artemether could be a better option for enhancing the dissolution rate of drug

Keywords: solid dispersion, artemether, soluplus, solubility enhancement.

INTRODUCTION

Amongst various parasitic infections, malaria is the most life threatening disease. Malaria remains one of the most prevalent and deadly infectious diseases across Africa, Asia and America. The tropical countries such as India are more prone to malaria and around two million cases are reported annually.Various treatments have been proposed for the eradication of malaria which includes various drug types such as sulphonamides and cinchona alkaloids. However, the emergence of malarial resistance towards conventional treatments has led to persistent risk of infection. Drugs that target the transmission and stages of mosquito life cycle are important to arrest the infection of other humans, and would benefit an eradication agenda. Artemisinin- based combination therapies (ACTs) are the current standard of care for uncomplicated malaria.[1]

Artemether (ART), anti-malarial drug belongs to the artemisinins family and is an active constituent of Chinese herbs known as qinghao, also termed *Artemesia annua* have shown effectiveness against acute uncomplicated and severe falciparum malaria. It is active against P. vivax as well as chloroquine-sensitive and chloroquine-resistant strains of P. falciparum and is also indicated in the treatment of cerebral malaria. However, the therapeutic potential of ARTM is substantially delayed due to its low oral bioavailability (~40%). The low bioavailability of ARTM shoots from its poor aqueous solubility.[2]

ART is a poorly soluble and poorly permeable BCS class IV drug.[3]The low bioavailability of ART results from its poor aqueous solubility which ultimately results in poor absorption, as undissolved drug unable to reach absorption site. Preparation of water soluble formulation could be the technique to improve bioavailability of such drug.[4]

Different formulation approaches are adopted to overcome the poor aqueous solubility problem of such drugs.[5]The most trusted and successful strategy amongst researchers to enhance the solubility and dissolution of poorly water soluble drugs is Solid dispersion method. [6]The most accepted methods reported to formulate solid dispersions are fusion method, Extrusion, spray drying, Solvent evaporation, precipitation and freeze drying methods.[7,8,9]

Spray drying is well known technique known to prepare amorphous material due to the transition between liquid and solid phases. In this technique the drug and polymer dispersion is atomized and dispersed into hot gas, which leads to evaporation of solvent and formation of amorphous solid particles.[10]

In the present research work, amphiphilic polymer Soluplus (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer) was used. Soluplus shows exceptional solubilizing properties for BCS class II and class IV drugs. The primary objective of this study was to obtain stable solid dispersion of poorly water soluble drug ART with Soluplus by spray drying technique to enhance solubility and dissolution rate.[8]

MATERIALS AND METHODS

MATERIALS

Artemether was obtained from Ajanta Pharma Ltd, Aurangabad India. Soluplus was obtained as a gift sample from BASF (Germany).All other chemicals and solvents used were of pharmaceutical grade and were procured from SD Fine chemicals, Mumbai, India. All the materials were used as received.

METHOD

Preparation of ART solid dispersions:

Solid dispersion for artemether was prepared by spray drying method. Each solution for spray drying was prepared by adding different ratios of drug (ART) and polymer (soluplus) 1:1, 1:2, 1:3 and 1:4 by using ethanol (200ml) as a solvent. The total solid content of spray solution was (2%, 3%, 4% and 5%) and was sonicated for 10 min. The spray drying was carried out using the instrument Spray dryer model LU-222 advanced (Labultima, Mumbai, India). The liquid atomization was performed with a pneumatic spray nozzle. The dried products were collected and thoroughly characterized for process yield, solubility and total ART content. The SDs were prepared using a spray dryer with the following conditions: inlet temperature of 70-75 °C, feed rate of 3 ml/min, outlet temperature of 45-50 °C, and aspirator set to at 40 -60 m^3/h; the spray dryer had a nozzle diameter of 0.7 mm.

EVALUATION OF SOLID DISPERSION

Product yield

The solid dispersion yield was determined by the ratio of the weight of solid dispersion collected at dryer exit and the initial weight of raw materials taken for spray drying. The results were calculated as the percentage ratio of the final mass of solid dispersion to the initial mass of raw material (dry basis; %w/w) using the following definition

Product yield (%) = (mass of solid dispersion / mass of raw material) x 100

Determination of Solubility

Solubility study was carried out for ART and ART solid dispersions in 20 ml of distilled water, 0.1N HCL, phosphate buffer-pH 6.8 to check out the maximum solubility in respective dissolution media after 48 hrs. An excess amount of ART, and ART SD's were placed in glass bottles containing 20ml of solvent. After sonification the bottles were shaken for 48 hrs at 37 ± 0.5 °C. The supernatant was then diluted with respective dissolution medium and analysed at 213 nm on UV-spectrophotometer (UV-2501 PC, Shimadzu, Japan).All solubility measurements were performed in triplicates.

Determination of drug content

The drug content was determined by using HPLC analysis. A stainless steel column 25 cm x 4.0 mm packed with octadecylsilane bonded to porous silica (5µm) was used. A mixture of 62 volumes of acetonitrile, 38 volumes of water at flow rate 1.5 ml per minute on 213 nm was taken. The volume of injection of sample was 20 µl.[11]

Fourier transformation infrared analysis (FTIR)

FTIR spectra of the ART and SD samples were obtained on a brooker Eco- ATR machine i.e. attenuated total reflectance spectroscopy. The samples were premixed with KBr using mortar and pestle, and KBr disks were prepared by means of a hydraulic press. The scanning range was 3600–400 cm^{-1}

Differential scanning calorimetry (DSC)

DSC analysis was performed to check the physical state of SDs with respect to plain ART using Shimadzu TA-60. Samples were heated in an open aluminium pan at a rate of 10°C/min conducted over a temperature range of 25 to 300°C under a nitrogen flow of 50ml/min.

Surface morphology:

The morphological characteristics of the solid dispersion were observed by scanning electron microscopy (SEM) using a JSM 6390 microscope (JEOL, Japan). The powder samples were coated with gold by ion sputtering using autofine coater JSC 1600 (JEOL, Japan). Photomicrographs were taken at an acceleration voltage of 20.0 kV.

In Vitro Dissolution study

A dissolution study of ART and SDs was performed using USP basket method by dissolution apparatus (Lab India Disso 2000) at 37 ± 0.2 °C. Samples equivalent to 20 mg of ART solid dispersions were filled in hard gelatine capsules and placed in 900 ml of dissolution media containing phosphate buffer of pH 6.8 and hydrochloric acid (0.1N).The solutions were stirred with a rotating basket at 50 rpm. Samples (5 ml) were withdrawn from each vessel at the interval of 10 minutes and same volume of fresh medium was added to dissolution media to maintain the sink conditions. The withdrawn sample was analysed at 213 nm by UV spectrophotometer.

RESULTS AND CONCLUSION

Process yield

The process yield for different batches was found to be in range of 43.66-48.66%w/w. These results were satisfactory for a lab-scale spray apparatus.

Determination of Solubility

As presented in Table 1, it can be observed that, the solubility study of SDs made by spray drying showed an increase in the drug solubility with an increase in the ratio of Soluplus as shown in table 1. The solubility of pure ART in distilled water was found to be 0.011 ± 0.6 µg/mL, indicating its poor solubility. SD's prepared in 1:3 ratio showed significant increase in solubility than the other ratios. The increase in solubility in the entire medium could be due to hydrophilic environment created by the polymer around the drug resulting in a decrease in particle size of SDs and increased wettability of ART.

Table 1: Solubility of ART and SD's

Medium	Solubility mg/ml				
	Pure drug	SD 1:1	SD 1:2	SD 1:3	SD 1:4
Water	0.011 ± 0.6	2.047	2.414	2.657	2.514
Buffer pH 6.8	0.0129	2.933	3.266	3.552	3.69
0.1N HCl	0.013	2.361	2.600	3.123	3.1

Total drug content

The drug content was determined by using HPLC analysis.

Table 2: Total drug content in drug: polymer solid dispersion

Sample	Retention time	Area	% drug present
Pure drug 20 ppm	6.011	117869	100
Solid dispersion 20 ppm	6.013	29607	25.11 ± 0.03

FTIR

The FTIR spectra of artemether and soluplus and solid dispersion were recorded to check interaction between drug and polymer. The characteristic peaks of artemether appeared in the spectrum of solid dispersion without any significant change in the position. It indicates that there was no interaction between artemether and soluplus.

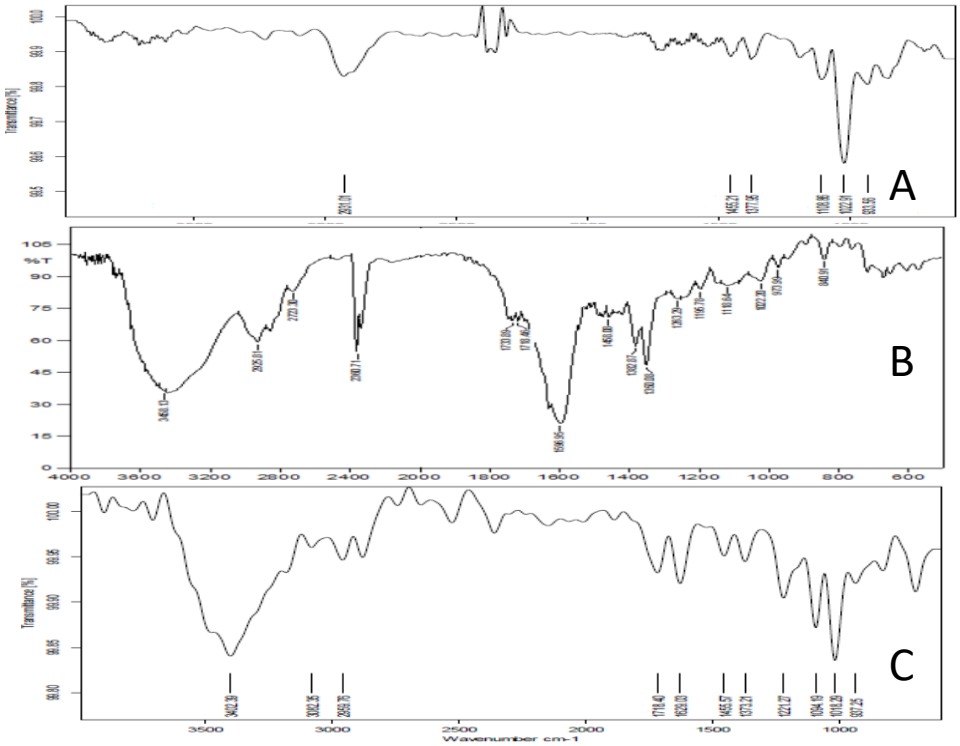

Figure 1: FTIR spectra of Artemether (A), soluplus (B) and Solid dispersion

DSC

Thermal behaviour of pure drug and corresponding drug dispersion system are depicted in the fig. the pure artemether shows a sharp endothermic peak at 88.08°C, followed by exothermic peak at 183.04°C. The characteristic endothermic peak corresponding to melting peak of artemether was shifted towards lower temperature, with reduced intensity in solid dispersions. This could be attributed to higher polymer concentration and uniform distribution of artemether in the crust of polymer, resulting in complete miscibility of molten drug in polymer. Moreover, the data also indicate there seems to be no interaction between the components of the binary system. No significant difference in DSC pattern of solid dispersion and suggests that interaction could not induce at molecular level even in the spray drying process.

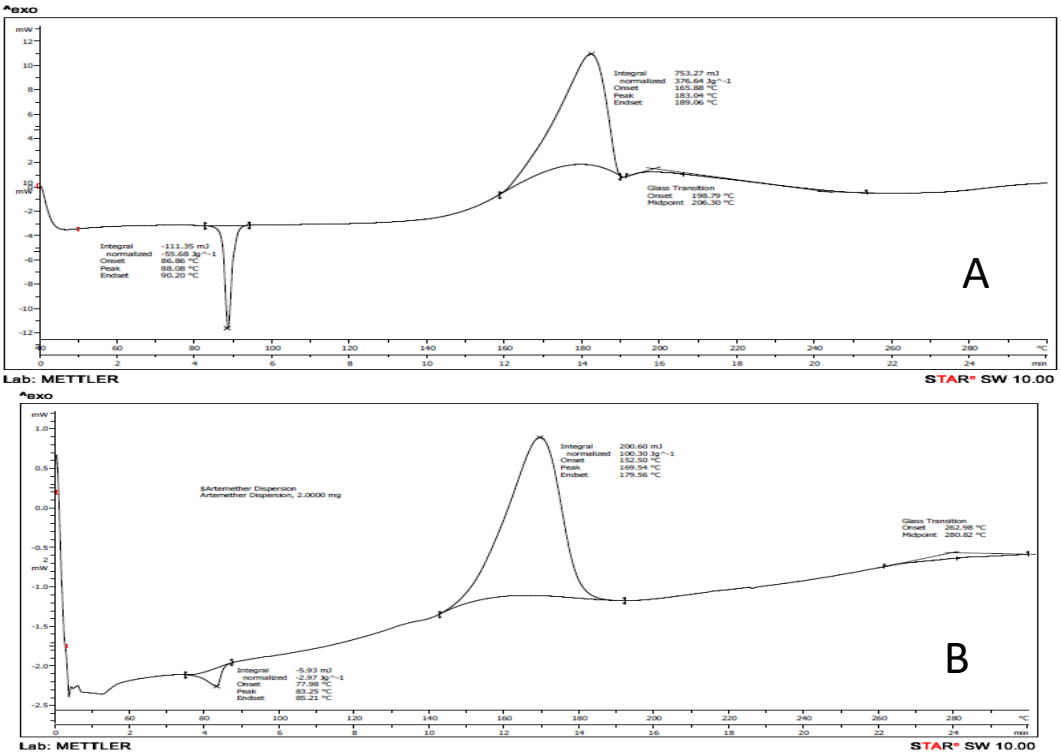

Figure 2: DSC curve of Artemether (A) and Solid dispersion (B)

Surface morphology

SEM used for the determination of surface morphology of pure drug and optimized solid dispersion. The pure artemether was characterized by crystals of bigger size and irregular shape with an apparently smooth surface. In solid dispersion, artemether crystals adhered on the surface of polymer. This reduced crystallinity of artemether ad it became more amorphous.

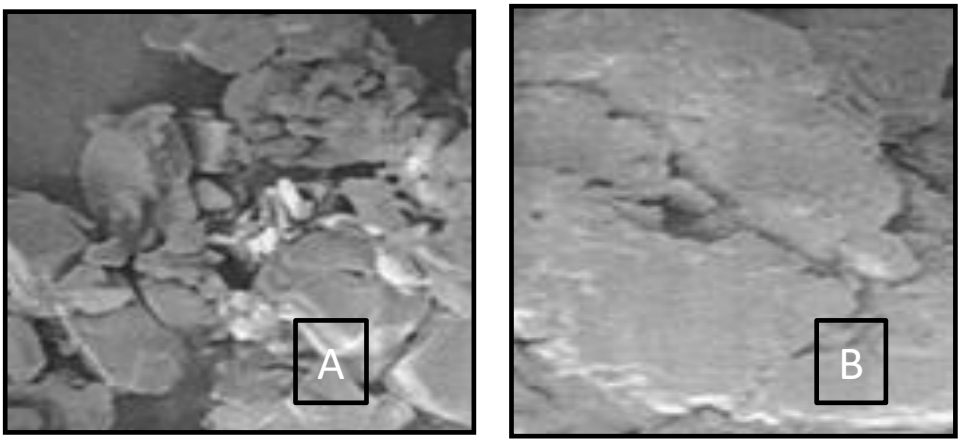

Figure 3: SEM image of Artemether (A) and Solid dispersion (B)

Dissolution studies

The Release of ART from solid dispersion in 0.1N HCl and pH 6.8 buffer shown in figure4 and 5 respectively. There was almost 95% of drug release occurred within 120 minutes. According to dissolution study it was found that drug release was increased only up to 1:3 ratios. In case of 1:4 ratios drug release was also increased but it was negligible than 1:3 ratio. So it was concluded that 1:3 ratio is optimized ratio for the preparation of solid dispersion and above this ratio drug release was not found to be increased much.

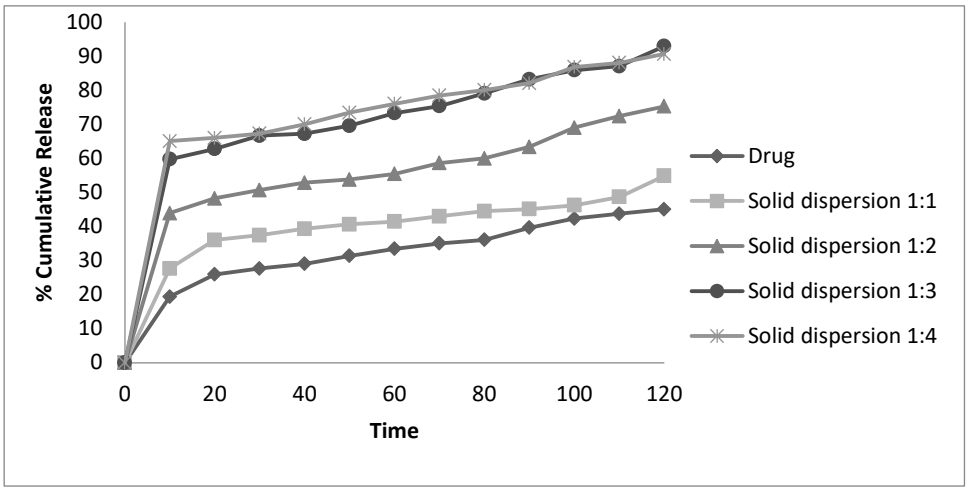

Figure 4: Dissolution profile of pure drug and solid dispersion in 0.1N HCl

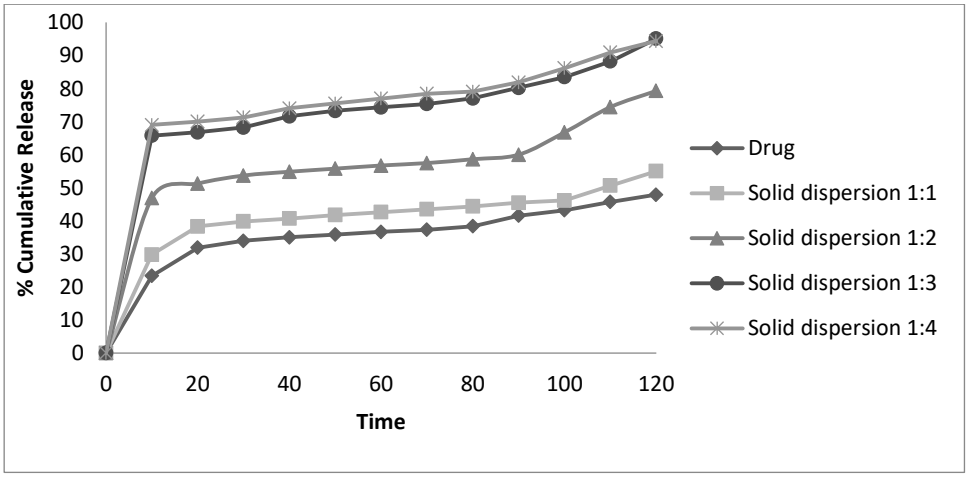

Figure 5: Dissolution profile of pure drug and solid dispersion in phosphate buffer pH 6.8

CONCLUSION:

Solid dispersion in different drug (artemether) and polymer (soluplus) ratios by spray drying was performed. IR and DSC studies revealed that drug and polymer were compatible. In solid dispersion solubility was increased with increased concentration of soluplus. Solid dispersion prepared by using 1:3 drug polymer ratio show significant ($p < 0.001$) increase in solubility than the other drug polymer ratio. Above this ratio, the solubility was not significant. From dissolution study it was found that drug release was increased only up to 1:3 ratios. In case of 1:4 ratios drug release was also increased but it was negligible than 1:3 ratio. In case of 1:3 ratio drug release was found to be 92.95 ± 1.435% at the end of 120 min in 900 ml of pH 6.8 phosphate buffer. So it was concluded that 1:3 ratio considered as optimized ratio for the preparation of solid dispersed and above this ratio drug release was not found to be increased much.

CONFLICT OF INTEREST: None

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