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Research Article

PREPARATION, CHARACTERIZATION AND DISSOLUTION ENHANCEMENT OF DIHYDROARTEMISININ MICROPARTICLES

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ABSTRACT

The objective of the present study was to prepare a Dihydroartemisinin microparticles using spray drying method to enhance the solubility and dissolution rate which will help for improvement of oral bioavailability. Dihydroartemisinin is the active metabolite of artemisinin compound and a drug of choice for treatment of malaria. Dihydroartemisinin has poor aqueous solubility, incompletely absorbed after oral intake due to poor dissolution characteristics in the intestinal fluid which limits its application. To address these issues, spray dried microparticles of Dihydroartemisinin were prepared using Poloxamer 188, non-ionic surfactant with different ratios of drug and carrier. Based on results of solubility study, spray dried microparticles formulation with highest aqueous solubility was analyzed for Fourier transform infrared spectroscopy, X-ray powder diffraction and Differential scanning calorimetry study. Spray dried microparticles evaluated for determination of percent yield, solubility, drug content, encapsulation efficiency, micromeritic properties and *in vitro* dissolution parameters. Surface morphology study by Scanning electron microscopy revealed spherical shape of microparticles. Prepared microparticles showed good flow property, improved aqueous solubility and faster *in vitro* dissolution rate compared with pure drug. The spray dried microparticles of Dihydroartemisinin with Poloxamer 188 in a ratio of 1:4 w/w showed 2.5 times enhancement of aqueous solubility and > 95 % drug release in 120 min when compared with pure drug alone. Thus from the result it can be concluded that spray dried microparticles of Dihydroartemisinin using Poloxamer 188 is useful technique to enhance the solubility and dissolution rate that will help to improve oral bioavailability.

Keywords: Dihydroartemisinin, Spray drying, Poloxamer 188, Solubility, *In vitro* dissolution

INTRODUCTION

Malaria is the prime reason for morbidity and mortality worldwide[1]. Effective treatment of malaria needs use of efficacious anti malarial agent in optimized regimen[2]. Malaria is a parasitic infection caused by protozoan parasites from plasmodium genus and transmitted through female mosquitoes *Aonopheles* species[3]. Artemisinin derivatives are the widely used drugs for the treatment of malaria[4]. Dihydroartemisinin (DHA) is a Artemisinin's reduction product, major constituents of *Artemisia annua* which is having activity against malaria. Amongst Artemisinin derivatives, DHA showed improved *in vitro* and *in vivo* potency for malaria treatment. The major hurdle for the DHA is low aqueous solubility. DHA is practically insoluble in water because of glucopyranose rings in its chemical structure[5-7]. Oral DHA has bioavailability of 45 %[8]. Low aqueous solubility with poor bioavailability is the major reason for failure of 40 % new chemical entity[9]. Therefore, there is need to increase the solubility of DHA for better bioavailability. Also, long term use of drug with low solubility and poor bioavailability is reason for malaria drug resistance. Use of drug with high solubility and bioavailability will be of great advantage to reduce the incidence of malaria drug resistance[10].

Various methods were reported in literature to enhance the solubility of poorly soluble drug DHA like micronization with supercritical solution[11], solid dispersion[12], cyclodextrin complexation[13-14]. Preparation of microparticulate drug delivery system using spray drying is one of the methods to enhance the solubility[15]. Spray drying is a process in which solution of drug and carrier evaporated by spraying the solution in fine droplets into chamber under controlled condition of air flow, humidity and heat. Hot air is the source of drying and product separated after drying[16].

Poloxamers are nonionic surfactant, polyoxyethylene-polypropylene block copolymer consists of hydrophilic core (ethylene oxide) and hydrophobic core (polypropylene oxide) blocks arranged in a triblock structure resulting in an amphiphilic copolymer[17]. Poloxamers are hydrophilic non-ionic surfactant used mainly as solubilizing agents, wetting agents and used for enhancing the solubility and bioavailability of poorly soluble drugs[18-19].

The objective of the present investigation was to increase the solubility and dissolution rate of DHA using spray drying technique.

MATERIALS AND METHODS

DHA was supplied as a gift sample by Athena Drug Delivery Solutions Pvt. Ltd, India. Poloxamer 188 was supplied as a gift sample by Signet Chemical Corporation, Mumbai, India. All other chemicals used were of analytical grade.

Preparation of DHA Microparticles

Spray drying technique was used to prepare DHA microparticles. The composition of DHA and Poloxamer 188 in different ratios (1:1 w/w to 1:6 w/w, Batch code D1 to D6) are depicted in Table 1. Pure drug and Poloxamer 188 was dissolved in acetone as a solvent to obtain clear solution of 5 % w/v as a feed solution. This feed solution was further spray dried with spray dryer (Mini spray drier B-290-(JISL) at optimized parameters like feed rate (3 ml/min), aspiration (60 %), inlet temperature (58^0C), outlet temperature (25^0C) and atomization air pressure (10 kPa) using a standard 0.7 mm nozzle to obtain spray dried DHA microparticles. Spray dried DHA microparticles were then sealed hermetically and kept in a desiccator for further characterization study.[20-21]

Saturation Solubility Study

Saturation solubility study of pure DHA and microparticles of optimized formulation were carried out in deionized water by shake flask method[22]. An excess quantity of the drug and Spray dried microparticles were added in separate glass stoppered flask containing deionized water and allowed to mixed using orbital shaker (Remi Laboratory instruments, Mumbai, India) at 150 rpm, 37°C for 24 h. After 24 h, solution was centrifuged at 15000 rpm for 10 min and supernatant was collected and filtered through Whatman filter paper No. 41 and analyzed spectrophotometrically (Shimadzu UV 1700, Japan).

Percent (%) Yield

The percent yield of microparticles were calculated according to following formula

$$\% \text{ yield} = \left\{\frac{\text{mass of microparticles}}{\text{mass of drug} + \text{mass of polymer}}\right\} \times 100$$

Drug Content

An accurately weighed 100 mg of microparticles was completely dissolved in phosphate buffer pH 6.8. After suitable dilutions, the drug content of microparticle was determined using UV spectrophotometer (Shimadzu UV 1700, Japan) at 248 nm.

Encapsulation Efficiency

Accurately weighed amount of DHA microparticles equivalent to 40 mg DHA were transferred to 100 ml volumetric flask containing phosphate buffer pH 6.8 and volume was made using phosphate buffer pH 6.8. The solution was filtered and absorbance was measured by UV spectrophotometer (Shimadzu UV 1700) at 248 nm. Entrapment efficiency was estimated using following formula:

$$\% \text{ Entrapment efficiency} = \left\{\frac{\text{Amount of drug actually present}}{\text{Theoretical drug content}}\right\} \times 100$$

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra of pure DHA and spray dried formulation D4 (1:4 w/w) were recorded by FTIR spectrometer (Agilent technologies Cary 630) to evaluate drug-polymer interactions. The sample was analyzed in the region of 400-4000 cm^{-1}.

Differential Scanning Calorimetry (DSC)

DSC thermograms of pure drug and spray dried formulation D4 (1:4 w/w) were analyzed by DSC (SDT Q600 V20.9 Build 20) calibrated with indium and zinc. Sample quantity was placed in aluminum pan and nitrogen was used as atmosphere with flow rate 10 ml/min and scanning rate at 10^0C/min for the range of 0-300^0C

X-ray Powder Diffraction (XRPD)

XRPD patterns of pure drug and spray dried formulation D4 (1:4 w/w) were recorded using Philips Analytical X-RD (PW 1729, Philips, Netherland) with copper target. The measurements were performed at 40 kV voltage, 30 mA current. The scanning angle ranged from 5 to 60^0 of 2θ, steps were 0.02^0 and counting rate was 0.4 s/step.

Scanning Electron Microscopy (SEM)

The morphological study of pure drug and spray dried formulation D4 (1:4 w/w) were carried out by scanning electron microscope (SEM) (JEOL, Tokyo, Japan). The samples were fixed on aluminum stubs with conductive double sided adhesive tape and coated with the gold by sputter coater at 50 mA for 50s (JEC 550 Twin Coater).

Micromeritic Properties

Microparticles were characterized for flow properties using Angle of repose, Carr's Index and Hausner ratio by determination of bulk density and tapped density.

In vitro Dissolution Study

In vitro dissolution of all formulations (equivalent to 40 mg DHA) was performed in triplicate using USP paddle dissolution test apparatus (Lab India 2000, Mumbai, India). The dissolution media used was 1000 ml of phosphate buffer with pH 6.8 maintained at 37^0C at 100 rpm. Aliquots of 5 ml were withdrawn at predetermined time points and the amount withdrawn was immediately replaced with freshly prepared media. The samples collected were filtered at 15, 30, 45, 60, 75,90 and 120 min time interval and filtered through Whatman filter paper No. 41, analyzed spectrophotometrically (Schimadzu UV 1700 Japan) at 248 nm for determination of % release of drug.

RESULTS AND DISCUSSION

DHA has poor aqueous solubility and low oral bioavailability. Attempt made to enhance the solubility and dissolution rate of DHA using Poloxamer 188 with spray drying technique which will help to improve bioavailability. Different formulation batches D1 to D6 were taken with increase in concentration of Poloxamer 188. Further spray dried formulations were studied for solubility, drug content, encapsulation efficiency, micromeritic properties and *in-vitro* dissolution study. Optimized formulation batch was evaluated for physical characterization using DSC, PXRD and FTIR study. Surface morphology study characterized using SEM. All the results depicted as below.

Table 1: Different ratio of DHA and Poloxamer 188

Batch Code	Composition for Binary system	Ratio(w/w)	Batch Size (mg)
D1	DHA: Poloxamer 188	1:1	1000
D2	DHA: Poloxamer 188	1:2	2000
D3	DHA: Poloxamer 188	1:3	3000
D4	DHA: Poloxamer 188	1:4	4000
D5	DHA: Poloxamer 188	1:5	5000
D6	DHA: Poloxamer 188	1:6	6000

Table 2: Aqueous saturation solubility study for DHA and spray dried formulations using Poloxamer 188

Batch Code	Drug: Carrier system	Ratio(w/w)	Solubility in deionized water (µg/ml) at 37^{0}C
D0	DHA	-	132 ± 1.9
D4	DHA: Poloxamer 188	1:4	340 ±2.3

mean ± SD, n = 3

Table 3: Percent (%) Yield, Drug Content and Encapsulation Efficiency of Spray Dried Microparticles

Batch Code	Yield (%)	Drug Content (%)	Encapsulation Efficiency (%)
D1	68.03±3.75	99.11±0.40	73.79± 1.10
D2	72.63±2.34	97.51±1.27	83.26±1.80
D3	77.27±1.89	96.44±1.43	87.07±0.81
D4	79.62±5.15	93.64±1.36	91.69±1.74
D5	74.57±2.57	92.17±1.48	82.60±1.24
D6	71.52±6.01	91.18±0.92	79.69±1.76

mean ± SD, n = 3

Table 4: Micromeritic Properties of Spray Dried Microparticles

Parameter	D1	D2	D3	D4	D5	D6
Carr's Index (%)	11.28±1.112	10.94±1.165	12.38±0.548	10.73±1.249	12.19±1.711	10.51±1.819
Hausner ratio	1.12±0.017	1.12±0.016	1.13±0.014	1.11±0.017	1.13±0.024	1.11±0.020
Angle of repose (^{0})	33.48±0.68	23.34± 1.18	24.44±0.55	20.28±1.43	19.13±1.14	22.19±0.44

mean ± SD, n = 3

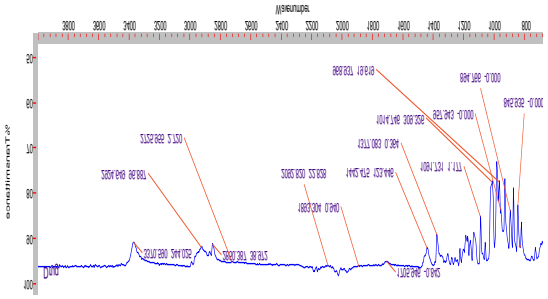

Figure 1: FTIR spectra of DHA

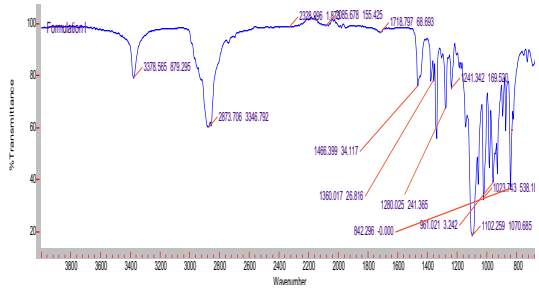

Figure 2: FTIR spectra of Spray dried microparticles D4 (1:4 w/w)

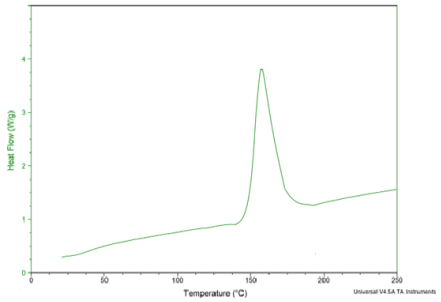

Figure 3: DSC thermograms for DHA

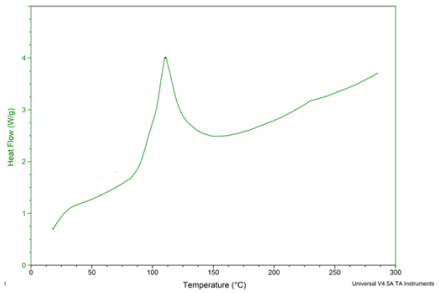

Figure 4: DSC thermogram for spray dried microparticles D4 (1:4 w/w)

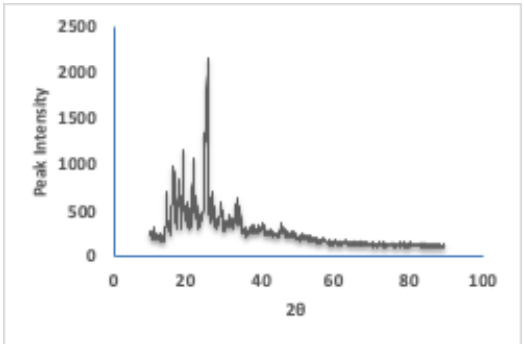

Figure 5: PXRD pattern for DHA

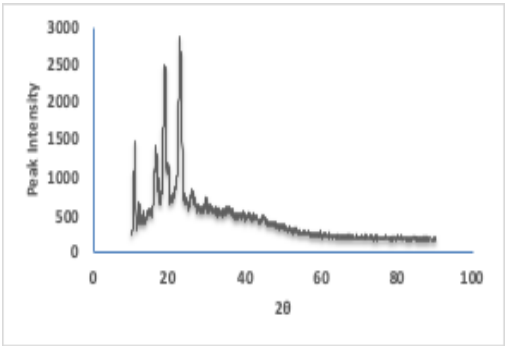

Figure 6: PXRD pattern for spray dried microparticles D4 (1:4w/w)

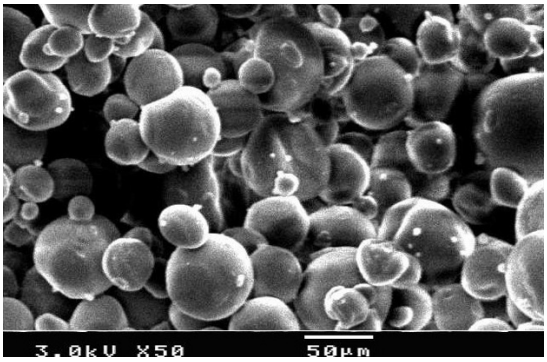

Figure 7: SEM of Spray dried microparticles D4 (1:4w/w)

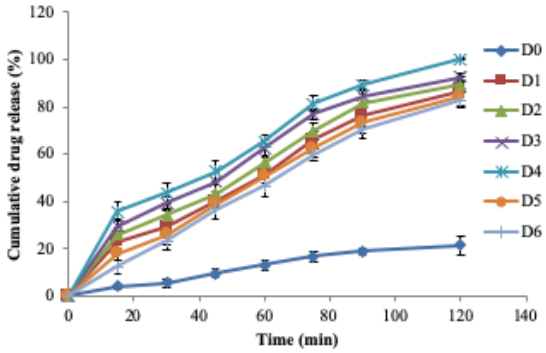

Figure 8: Comparative *In vitro* dissolution study for pure drug DHA and spray dried microparticles

Saturation Solubility Study

The results of Saturation solubility study for pure drug and its spray dried formulations showed in Table 2. Pure drug (D0) showed 132 µg/ml solubility in deionized water at 37^0C. Pure drug DHA showed poor solubility in aqueous media. Optimum formulation batch D4 with 1:4 w/w drug carrier ratio showed enhancement in solubility i.e. 340 µg/ml solubility in water which was 2.5 times greater than pure drug. Possible reason for increase in solubility of spray dried microparticles was due to increased surface area, wettability and solubilizing effect of Poloxamer 188.

Percent Yield, Drug Content and Encapsulation Efficiency

Results of percent yield, drug content and encapsulation efficiency are depicted in Table 3; prepared spray dried micro particle batches showed drug content ranging from 91.18 ± 0.92 % to 99.11 ± 0.40 and encapsulation efficiency from 73.79 ± 1.10 % to 91.69 ± 1.74 %. The percent yield was found from 68.03 ± 3.75 % to 79.62 ± 5.15 %. At optimum polymer concentration, drug entrapment efficiency was increased but it was diminished after further increase in polymer concentration due to gelling of polymer.

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR study of pure drug and spray dried microparticles are presented in Figure 1 and Figure 2 respectively. Pure drug (Figure 1) showed characteristic absorption peak at 3370 cm^{-1}, 2800 cm^{-1}- 3000 cm^{-1} and 800-900 cm^{-1} for stretching vibrations of -OH bond, C-H bond and C-O bond (in seven membered ring) respectively[23-24]. Spray dried microparticles D4 in ratio 1:4 w/w (Figure 2) showed band shifting from 3370 cm^{-1} to 3378 cm^{-1} of -OH groups. The peak of C-H stretching is shifted from 2850 cm^{-1} to 2873cm^{-1}. Compared to Pure drug, changes observed with these characteristic peaks in spray dried microparticles. It showed new solid phase formed in spray dried microparticles.

Differential Scanning Calorimetry (DSC)

DSC study of pure drug and spray dried microparticles showed in Figure 3 and Figure 4 respectively. DSC study of pure drug (Figure 3) showed sharp exothermic peak at 162.17°C corresponding to melting point of drug indicating crystalline nature. As per result stated by author Zahra Shoormeij *et al*[25] in his research work, Poloxamer 188 showed sharp endothermic peak at 60.6°C, indicating its melting. Spray dried microparticles D4 in ratio 1:4 w/w (Figure 4) prepared using Poloxamer 188 does not showed melting peak of Poloxamer 188 suggesting uniform distribution of polymer. Sifting of melting peak of DHA from 162.17^0C to 114.62^0C with reduced peak intensity was observed for spray dried microparticles.

X-ray Powder Diffraction (XRPD)

XRPD study used to evaluate the degree of crystallinity of microsphere formulation compared to degree of crystallinity of pure drug. The XRPD pattern of pure DHA and spray dried microparticle D4 in ratio 1:4 w/w are depicted in Figure 5 and Figure 6 respectively. X-ray diffraction of pure drug DHA (Figure 5) showed sharp peaks with diffraction angles (2θ) at 25.43^0, 25.45^0, 25.47^0 and 25.49^0 with peak intensity of 2138, 2109, 2005 and 1958 respectively signifying substantial crystallinity of drug. Poloxamer 188 showed characteristic peak at 18.83^0 and 22.86^0 with peak intensity 2504 and 2857 indicating crystallinity[25]. Spray dried microparticles (Figure 6) showed peaks at 25.43^0, 25.45^0, 25.47^0 and 25.49^0 with peak intensity of 670, 670, 668 and 646 respectively. Relative decrease in crystallinity (RDC)[26] value was calculated for spray dried microparticles by comparing the representative peak height in diffraction pattern of spray dried microparticles to pure drug. For

RDC calculation, peak height at 25.43^0 was used for calculation and RDC value for spray dried microparticle was found 0.313. PXRD study of spray dried microparticles showed significant reduction in peak intensity compared with PXRD pattern of pure drug. This may be due to crystalline drug was converted to amorphous form and its merger in the carrier structure[27].

Scanning Electron Microscopy (SEM)

SEM study results for spray dried microparticles are depicted in Figure 7. SEM study revealed the microparticles prepared by spray drying technique has a smooth surface and are spherical in shape. Some amorphous aggregates with irregular size particles were also observed.

Micromeritic Properties

Characterization of microparticles for micromeritic properties would assist in understanding its flowability and behavior during processing. Results of micromeritic properties for spray dried microparticles were depicted in Table 4. The results obtained for Carr's Index (10.51 ± 1.819 % to 12.38 ± 0.548 %), Hausner ratio (1.11 ± 0.017 to 1.13 ± 0.024) and angle of repose (19.13 ± 1.14^0 to 33.48 ± 0.68^0) were observed within prescribed limits which is indicative of good flowability of prepared microparticles. This may be due to the uniform diameter and spherical shape of the particles.

***In vitro* Dissolution Study**

In vitro dissolution study results of pure drug and spray dried microparticles showed in Figure 8. Compared with dissolution profile of pure drug (D0), spray dried formulation dissolution profile showed great improvement in cumulative drug release study. Pure drug showed only 21 % drug release at 120 min time interval while the spray dried microparticles D4 in ratio of 1:4 w/w showed complete drug release in 120 min. Improvement in drug dissolution rate was attributed to reduction in drug crystallinity as confirmed by DSC and PXRD study and better wettability by Poloxamer 188. It was observed that Poloxamer 188 in higher ratios (1:5 w/w and 1:6 w/w) showed retardation in release of drug from corresponding binary systems. This might be due to gelling property of Poloxamer at higher concentration which retards release[28-29]. It can be concluded that 1:4 w/w drug carrier ratio was found superior compared with other drug carrier ratios and could be considered as proper choice of carrier for dissolution enhancement of DHA.

CONCLUSION

Based on data, formulation batch D4 showed optimum results with entrapment efficiency 91.69 ± 1.74 %, saturation solubility 340 ± 2.3 µg/ml and complete drug release. Compared to other formulation batches, batch D4 showed optimum entrapment efficiency and drug release in desired manner. DHA microparticles were successfully prepared using hydrophilic non-ionic surfactant with spray drying technique which will help to improve bioavailability. Prepared DHA microparticles are spherical in shape and showed good flow property. PXRD and DSC study revealed the amorphous state of the DHA. Concentration of Poloxamer 188 carrier play important role in enhancement of drug dissolution.

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