Application of hot melt extrusion for improving bioavailability of artemisinin a thermolabile drug

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Abstract

Abstract: Hot melt extrusion has been used to produce a solid dispersion of the thermolabile drug artemisinin. Formulation and process conditions were optimised prior to evaluation of dissolution and biopharmaceutical performance. Soluplus®, a low Tg amphiphilic polymer especially designed for solid dispersions enabled melt extrusion at 110ºC although some drug-polymer incompatibility was observed. Addition of 5% citric acid as a pH modifier was found to suppress the degradation. The area under plasma concentration time curve (AUC_{0-24hr}) and peak plasma concentration (C_{max}) were four times higher for the modified solid dispersion compared to that of pure artemisinin.

Key words: Extrusion, thermolabile drug, artemisinin, Soluplus®, compatibility, bioavailability.

1. Introduction

Hot melt extrusion (HME) has been widely used in the pharmaceutical industry to prepare solid dispersions to improve bioavailability of poorly water soluble drugs[1,2]. During processing of solid dispersions by HME, the hydrophobic drug is processed with a thermoplastic polymer in the molten state to obtain a stabilised amorphous form. In HME the selection of a suitable polymer plays a vital role in successful formulation, in addition to the choice of suitable extrusion conditions. Typically the extrusion process should be carried out at least 20-40° C above the glass transition temperature (Tg) of the polymer. The suitability of a polymer for HME can be determined by its thermal and rheological properties[3].

Exposure of material to high temperature is one of the major concerns during HME, as this may adversely affect stability of the drug[4] or polymer[5]. There are also increased

chances of interaction between drug and polymer at high temperature and shear during HME. This degradation or interaction may result in generation of impurities[5,6], unexpected change in rheology of the melt[7] or discolouration of the product[5]. Processing at high temperature is not suitable for some Active Pharmaceutical Ingredients (APIs) due to thermal decomposition which may be followed by loss of pharmacological activity[8] and therefore prevention of degradation is a major challenge during extrusion processing. These issues have restricted pharmaceutical applications of HME, yet to date relatively few reports are available on these degradation issues. In such cases, the addition of plasticizer is one of the approaches used to lower the Tg and melt viscosity, allowing extrusion to be performed at lower temperatures[9,10]. Lowering the processing temperature can reduce degradation of the drug and facilitate drug stability in pharmaceutical formulations[11] however, the added plasticiser contributes significantly to the bulk of the formulation and can adversely affect the mechanical properties, drug release rate and stability of the final product[12]. Therefore, alternative approaches are required to facilitate the processing of thermally sensitive drugs. The objective of this work is to investigate and address challenges in the application of HME for processing solid dispersions containing the thermolabile drug, artemisinin using a recently introduced low Tg polymer.

Artemisinin, a keystone of malaria treatment, is effective against *Plasmodium falciparum* infection and cerebral malaria[13]. Artemisinin has low bioavailability and poor water solubility; its molecular structure is displayed in Fig. 1. Due to its thermolabile nature, artemisinin poses significant processing challenges to forming solid dispersions[14]. Several studies have described attempts to improve the solubility of artemisinin, such as micronisation using supercritical fluid technology, solid dispersions prepared using a solvent evaporation method[15] and complexation[16,17]. However, these

methods are complex, difficult to scale-up and yielded relatively poor improvements in drug release properties. Here, an amphiphilic graft copolymer, Soluplus® (polyvinyl caprolactum polyvinyl acetate polyethylene glycol) was used to form solid dispersions with artemisinin using HME, as it has the ability to enhance the solubility of poorly water soluble drugs and is suitable for melt extrusion below 120°C, without the need for incorporation of additional plasticiser[18,19].

During preformulation the polymeric matrix is selected on the basis of drug-polymer miscibility, glass transition temperature and rheology of the mixture in the molten state. Screening at the preformulation level generally involves thermal analysis, rheological testing, miscibility predictions using the Florey–Huggins equation and hot stage microscopy[20,21]. Oscillatory rheometry can also be used to study flow behaviour and stability of the drug polymer mixture under oscillatory shear. This enables the structural dynamics of complex fluids to be investigated at precisely controlled temperature and deformation. Here, oscillatory rheometry has been used as a screening tool to optimise processing temperatures and drug loading and to study the effect of additives under shear. Particular challenges included processing, stability and biopharmaceutical performance, all of which are described in detail.

2. Materials and methods

Artemisinin was supplied from Cipla Pharmaceuticals Ltd (ART25062007). Soluplus® was kindly provided by BASF Chemicals. All other chemicals and solvents used were of analytical grade.

2.1. Thermal analysis

The onset of thermal degradation of artemisinin and Soluplus® was analysed using a Q5000 Thermo Gravimetric Analyser (TGA) (TA Instruments, UK) equipped with a RSC90 cooling unit. Each aluminium pan was calibrated for mass before loading.

Approximately 5 mg of sample was loaded into each aluminium pan and heated at a rate of 10°C/min over the temperature range 25 to 200°C. An inert atmosphere was maintained by purging with nitrogen gas at a flow rate of 30 ml/min. Differential Scanning Calorimetry (DSC) studies were carried out using a Q2000 DSC (TA Instruments, UK) equipped with an RSC90 cooling unit. Indium standards were used to calibrate the DSC temperature and enthalpy scales. For each test approximately 4 mg of sample was hermetically sealed in an aluminium pan and a similar empty pan used as a reference. The pans were heated at a constant rate of 10°C/min over a temperature range of 25 to 170°C for artemisinin and from 25 to 200°C for Soluplus®. An inert atmosphere was maintained by purging nitrogen at a flow rate of 50 ml/min.

2.2. Oscillatory Rheometry

The rheological behaviour of artemisinin, Soluplus® and physical mixtures in different ratios was studied using an MCR 501 rotational rheometer (Anton Paar, Austria), equipped with a temperature controlled chamber. Physical mixtures of artemisinin and Soluplus® were prepared in 1:1, 1:3 and 1:5 ratios (w/w) (50, 25 and 16.7% (w/w) respectively) by blending in a Turbula mixer for 10 minutes. Parallel plates of diameter 25 mm were used for rheological characterisation with the distance between the plates set to 1 mm. The polymer or physical mixture was added to the bottom plate and preheated to the set temperature for 5 minutes. The separation distance between the plates was then reduced to 1 mm. Time-dependent stability of melts was measured by maintaining a constant oscillation frequency and strain over a fixed period of time. This test was performed at temperatures of 100, 110 and 130°C, at a strain of 1% and a frequency of 10 Hz for 30 minutes, whilst complex viscosity was measured every 5 seconds.

2.3. Extrusion of artemisinin and Soluplus®

Extrusion was carried out using a co-rotating twin screw extruder (Pharmalab, Thermo Scientific, UK) with a screw root diameter of 16 mm and a maximum screw length to diameter ratio of 40:1. Two extruder temperature profiles were applied (T110A and T110B as detailed in Table 1) at a constant screw rotation speed of 50 rpm. Residence time (i.e. the amount of time the extruded material spends at temperature inside the process) has a significant impact on the quality of the extruded material. Here two different screw lengths were employed to study the effect of residence time; the longer extruder screws corresponding to higher residence time. Half and full screw lengths were employed, as described in Table 2. Powdered blends of artemisinin and polymer were fed into the extruder at a rate of 120 g/h using a gravimetric twin screw feeder (Brabender, Germany). Each batch was of 50g. Extruded formulations were labelled ArtSD1, ArtSD2 and ArtSD3 (detailed formulation codes with processing parameters are provided in Table 3). Following extrusion, the extruded strand was air cooled and pelletized. The pellets were of 2mm diameter and 1mm thickness. Extrudates were subsequently milled and analysed through powder X-ray diffraction (PXRD), DSC, *in-vitro* dissolution and pharmacokinetic studies.

2.4. Powder X-ray diffraction

PXRD patterns were recorded using an X-ray Bruker D8 powder diffractometer with an X-ray wavelength of 0.154 nm, Cu source, 40 keV voltage and a filament emission of 40 mA. Samples were scanned from 2 to 30° (2θ) using a 0.01° step width and a 1 second time count. The scatter slit was set at 0.2° and the receiving slit at 1°.

2.5. Assay

Solid dispersions equivalent to 20 mg of artemisinin were weighed accurately and dissolved in a suitable quantity of medium containing 10% (v/v) ethanolic water and 0.1% (w/v) sodium lauryl sulphate. An appropriate quantity was alkali treated using

0.2% NaOH. Drug content was measured at 290 nm using a UV spectrophotometer. Analysis of data was performed using PCP-Disso software (Poona College of Pharmacy, V3, Pune, India).

2.6. *In-vitro* Dissolution

In-vitro dissolution studies were performed using a USP-XXVI type 2 paddle test apparatus (Copley Scientific, UK). Pellet samples equivalent to 20 mg of artemisinin were placed in dissolution vessels containing 600 ml of dissolution medium maintained at $37^{\circ}C \pm 0.1^{\circ}C$ and stirred at 100 rpm. The dissolution medium consisted of ethanol 10% ethanolic water and sodium lauryl sulphate (0.1% w/v). Samples were collected periodically and replaced with fresh dissolution medium. The collected sample was filtered using a 0.45μm cellulose acetate filter and treated with alkali. The concentration of artemisinin was determined spectrophotometrically at 290 nm. Data was analysed by PCP Disso software V3 (Poona College of Pharmacy, Pune, India).

2.7. Pharmacokinetic study

Study protocol

A study was performed with prior approval from the Institutional Animal Ethical Committee (IAEC) of C U Shah College of Pharmacy, Mumbai, India whose guidelines were followed throughout the studies. 36 healthy albino wistar rats with a weight 180-200 gm were divided into three groups; control, pure drug and ArtSD3. A sparse technique was used to collect blood samples (n = 6). The animals were housed in standard metabolism cages and fasted for 12 hours before dosing but allowed free movement and access to water throughout the experiment. 100 mg of artemisinin was dispersed in 0.5% aqueous carboxymethyl cellulose (CMC) solution and the oral dose (equivalent to 100 mg of artemisinin) was administered using an oral syringe. At

predetermined time intervals, blood samples were obtained by the retro orbital technique and collected in ethylene diamine tetra acetic acid (EDTA) tubes.

Sample analysis

Plasma was obtained by centrifugation of the blood sample at 3500 rpm for 15 minutes. A volume of 200 µl plasma was pipetted into Eppendorf tubes and 100 µl of internal standard (artemether solution 1000 µl/ml) and 700 µl methanol were added. The solution was vortexed for 2 minutes and the organic phase separated by centrifugation. The collected sample was then subjected to analysis by HPLC (Agilent Technologies, 1200 series, Wokingham, UK). The plasma level of artemisinin was analysed by HPLC using 65% acetonitrile and 35% water as the mobile phase. The HPLC system utilised a UV detector set at 210 nm and a C18 column (250 x 4.6 mm). Artemisinin exhibits a maximum UV absorption at 210 nm. The limits of detection and quantification were 1.01 and 3.06 µg/ml, respectively. The concentration against peak area graph plot was found to be linear ($r^2 = 0.998$).

2.8. Stability

All extrudates were stored at room temperature in a desiccator at 33% RH and their stability was studied at 1 month, 3 months, 6 months, 9 months and 12 months by PXRD and dissolution using the above method. The PXRD patterns of ArtSD3 at 1 month, 3 months, 6 months, 9 months, 12 months and 24 months are shown in figure 10. There was no variation in the result due to time, which proves that the stability of the HME prepared artemisinin: Soluplus® solid dispersions.

3. Results and Discussion

Prior to extrusion, all API-polymer mixtures were studied using thermal and rheological analysis. These results are described initially, prior to extrusion results and characterisation of the extruded formulations being presented.

Thermal analysis

HME is performed at an elevated temperature and therefore it is necessary to determine the onset of degradation of the API and polymer. Thermo-gravimetric analysis (TGA) was carried out to determine the onset of degradation of pure artemisinin and Soluplus® (Fig. 2). Results showed the onset of degradation of pure artemisinin at 160°C and rapid weight loss from 170°C. This degradation was found to result in a mass loss of 15.73% between 170°C and 200°C whereas Soluplus® demonstrated good thermal stability up to 200°C. Soluplus® showed the presence of moisture at a level of 2-5% (w/w), evidenced by a mass loss up to a temperature of 100°C.

Rheological Characterisation

API and polymer interaction was evaluated using oscillatory rheometry. Samples may undergo structural changes such as plasticisation, cross linking and change in scissor or degradation when subjected to high temperature and shear for extended periods of time; time dependent data obtained by oscillatory rheometry can be similar to typical HME residence times. Ideally, the viscosity of the polymer should remain constant at a given temperature; changes in viscosity may indicate structural changes in the material. From the TGA results discussed above, temperatures of 110 and 130°C were selected for rheological characterisation. The complex viscosities of the polymer with different drug loadings subjected to constant oscillatory shear at 110°C and 130°C are shown in Fig.3. For pure Soluplus®, the viscosity remained stable for 20 minutes at 110°C and 130°C. The plasticising effect of artemisinin can be clearly observed as a reduction in complex viscosity with increasing drug loading; a colour change of the material from white to brown was also observed, suggesting that degradation had occurred during the test. No discolouration was observed when Soluplus® and artemisinin were separately subjected to oscillatory rheometry at the highest set temperature of 130°C, indicating an

interaction between the two materials lead to the observed degradation. Colour changes in samples tested at 110°C were less intense than samples processed at 130°C and the level of applied shear did not significantly affect the colour or colour intensity of the samples. The colour change was found to occur after approximately 10 minutes of shear application, indicating a time and temperature dependent interaction.

It is reported that although artemisinin itself is acidic in nature, it contains a sesquiterpene lactone ring with an unusual peroxide bridge[22]. This lactone ring undergoes electrochemical reduction at a basic pH. To determine whether the moisture present in the polymer produced a basic pH microenvironment which influenced degradation, pH of the pure Soluplus® slurry was measured and found to be 7.5. Soluplus® contains 2-5% (w/w) moisture which was suspected to cause the alkaline microenvironment which promoted artemisinin degradation. In an attempt to counteract this degradation, small amounts of citric acid were added to the drug and polymer mixture to reduce the pH and the number of heavy metal ions potentially responsible for the discolouration. In addition to prevention of degradation, pH modifier can increase the dissolution profile, reduce the crystallinity of API and inhibit the recrystallization of a solid dispersion system[23]. Yang *et al* reported that the selection of the acid was important for controling the pH of a system and the interactions in the final solid dispersion[24]. Rheological characterisations were carried out with the addition of 2 and 5% (w/w) citric acid to the 50% artemisinin physical mixture. No discolouration of the samples containing 5% citric acid was observed but some discolouration was present with 2% (w/w) citric acid. This indicates that citric acid suppressed degradation by avoiding the exposure of artemisinin to an alkaline microenvironment. When the physical mixture (1:1), containing 5% citric acid, was processed at 110°C, there was a slight decrease in the complex viscosity for the initial 3 minutes, followed by the

viscosity remaining relatively constant (as shown in Fig.2). It was therefore decided to investigate formulations with and without addition of citric acid in HME.

Extrusion

From the results of thermal and rheological characterisations, formulations were processed using HME at a set temperature of 110°C with a 50% artemisinin loading. Artemisinin and polymer were extruded, together with a separate batch containing 50% drug, 45% polymer and 5% citric acid. An extruder temperature profile of 110°C was used, being found to generate moderate levels of torque on the extruder screws and to provide a suitable extrudate consistency. Due to the thermally sensitive nature of the material, full and half-length screws were used to vary the residence time of the material at temperature. Three formulations were extruded for further analysis: ArtSD1, ArtSD2 and ArtSD3. ArtSD1 was produced using the half length extruder screw configuration whereas ArtSD2 (without citric acid) and ArtSD3 (with citric acid) were produced using a full length extruder screw configurations. Full details of temperature profiles, screw configurations and formulations are summarised in Tables 1, 2 and 3 respectively.

Assay

Artemisinin does not contain a chromophore and hence it was difficult to find a sensitive and appropriate analytical method. A UV method was selected which involved post derivatisation. This was based on the formation of an alkali salt of artemisinin (Q292) formed by treatment with 0.2% NaOH at 40°C, however the product was not coloured[25]. From visual observation of the extrudates, ArtSD2 was darker in colour compared to ArtSD1. This degradation was mirrored in the assays; 83.30% and 78.65% for ArtSD1 and ArtSD2 respectively. However, the modified formulation ArtSD3 (containing citric acid) was found to be 99.76%. As ArtSD3 yielded the highest drug

content, this formulation was used for further characterisation. All assay results are presented in Table 4.

Thermal analysis

DSC thermograms of artemisinin, Soluplus® and their physical mixture are shown in Fig. 4. Artemisinin exhibited two melting endotherms a major endotherm at 154.81°C and an exotherm at 180°C, representing the liberation of formic acid, the same exotherm was also observed in the physical mixture but commenced at a lower temperature. Soluplus® exhibited a Tg at 70°C whereas the physical mixture exhibited Tg at 80°C and a sharp endotherm at 154.75°C.

The DSC thermograms of citric acid, the physical mixture containing 5% citric acid and ArtSD3 are shown in Fig. 5. Citric acid exhibited a melting endotherm at 156°C followed by thermal degradation. The physical mixture containing citric acid exhibited a glass transition temperature at 90°C. ArtSD3 showed an exotherm at 180°C, representing the liberation of formic acid; however the material did not exhibit a melting endotherm corresponding to that of artemisinin, indicating that an amorphous state of the solid dispersion had been achieved.

Powder X-ray Diffractometry

The effect of processing parameters on physical properties was examined by comparing X-ray diffraction patterns of ArtSD3 with artemisinin, Soluplus® and physical mixtures as shown in Fig. 6. Artemisinin exhibited characteristic peaks at 2θ of 7.5, 12, 14.5, 20.2 and 21.9 degrees, while Soluplus®, being amorphous in nature, did not show any crystalline peaks. For the physical mixture, crystalline peaks of artemisinin were clearly observed. The complete disappearance of crystalline peaks in ArtSD3 illustrated that the prepared solid dispersion using Soluplus® was transformed into an amorphous state. The intensity of the crystalline peaks was low for the physical mixture when compared

to those for pure artemisinin. This signifies that the presence of Soluplus® had no influence on the physical state of artemisinin.

In-vitro dissolution study

The pharmaceutical performance of the extrudates was investigated by *in-vitro* dissolution and compared with the pure drug and physical mixture, as shown in Fig. 7. The dissolution profile of ArtSD3 was significantly higher compared to that of the pure drug. The dissolution rate of the physical mixture was greater than that of pure artemisinin, although not considerably. In the first 45 minutes, 92% of the drug was released from ArtSD3 which is presumably due to transferring the crystalline state to the amorphous state resulting in a higher dissolution rate. This compared to release of only 12% in the same time for pure Artemisinin. In a previous study, 75% of drug release was achieved in 60 minutes from solid dispersions of artemisinin with PVP (1:5 ratio) prepared by supercritical fluid technology[16]. Therefore, Soluplus® was found to be more effective in improving the dissolution rate of artemisinin. Soluplus® has the ability to solubilise the hydrophobic drug due to its amphiphilic nature through micelle formation[26]. In addition, the incorporation of pH modifier may have contributed to dissolution enhancement.

Artemisinin is a Biopharmaceutical Classification System (BCS) class II drug meaning that it has low solubility and high permeability. It has been reported that artemisinin has only 8-10% bioavailability, a short half-life and a high first pass metabolism[27]; these properties contribute to partial parasite removal resulting in artemisinin recrudescences[16]. Jinadasa *et al* observed that the absorption of artemisinin was negligible when it reached the lower gastrointestinal (GI) tract specifically the colon[28]. Thus, enhancing the solubility of artemisinin could ensure better drug dissolution in the upper GI tract, greater bioavailability and in turn lower chances of recrudescence. A

rapid dissolution rate and hence absorption could lead to enzyme saturation during the first pass in the liver, resulting in a higher fraction of unmetabolized drug entering the systemic circulation, compared to a slower rate of drug dissolution.

Pharmacokinetic study

The bioavailability of pure artemisinin and ArtSD3 were studied in albino rats, in order to verify the correlation between *in vivo* data and data obtained by the *in vitro* dissolution method. Twelve rats were used for each formulation and samples were analysed once. A plasma concentration against time curve was obtained after oral administration of formulations. The plasma concentrations for pure artemisinin and ArtSD3 are displayed in Table 5 and 6 respectively. Plasma concentration of ArtSD3 clearly shows the enhanced bioavailability of ArtSD3 compared to the pure drug, as shown in Fig. 8. Maximum artemisinin concentration in plasma was reached by ArtSD3 which is approximately five times greater than the pure drug demonstrating significantly improved release in the amorphous state. A typical chromatogram of a rat plasma sample spiked with 120 µg/ml artemisinin RT 9.96 and internal standard artemether RT 16.68 is shown in Fig. 9. The areas under the curves for both pure artemisinin and ArtSD3 are shown in table 7. ArtSD3 showed a three-fold increase in AUC compared to pure artemisinin. The average C_{max} concentration (maximum plasma concentration) for artemisinin and the ArtSD3 were 16µg/ml and 40µg/ml respectively, whereas T_{max} (time to reach C_{max}) was 4 hours for both.

Stability

Although an interest in solid dispersions is growing rapidly, the commercialisation of solid dispersions in the pharmaceutical industry is limited. The formulation stability is a major issue for solid dispersions owing to phase separation[29]. There are also chances of crystallisation occurring during storage as the drug is molecularly dispersed. The PXRD

pattern, DSC thermograms and dissolution profiles of the solid dispersion (ArtSD3) were analysed after 1, 3, 6, 9 and 12 months. The amorphous solid dispersion was found to be stable for more than a year without evidence of recrystallization. The improved stability of ArtSD3 during storage is attributed to strong intermolecular interaction between the drug and polymer which reduces the chances of molecular mobility and recrystallization.

4. Conclusions

A novel melt extruded formulation of the poorly soluble thermolabile drug artemisinin was developed, using the amphiphilic copolymer Soluplus®. The extruded material was completely amorphous in nature and a small amount of citric acid was incorporated to suppress degradation of the drug at extrusion temperatures. Release rates of the drug were significantly improved compared to the pure drug and physical mixture or drug and polymer, in both *in vitro* and *in vivo* studies. The system was shown to be stable up to at least 12 months, highlighting the potential for enhancement in delivery of this important but challenging API.

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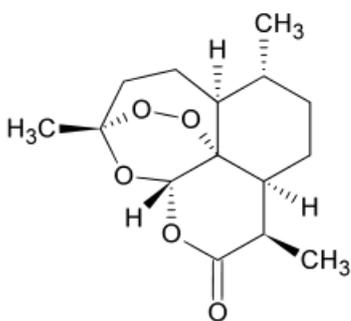
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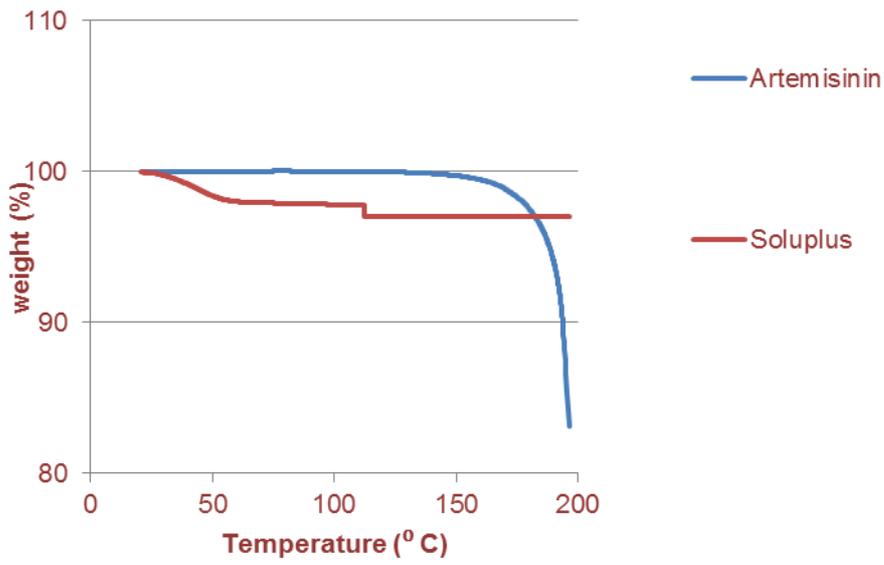**List of figures:**

Fig.1. Molecular structure of artemisinin

Fig.2. Thermo-gravimetric analysis of artemisinin and Soluplus®
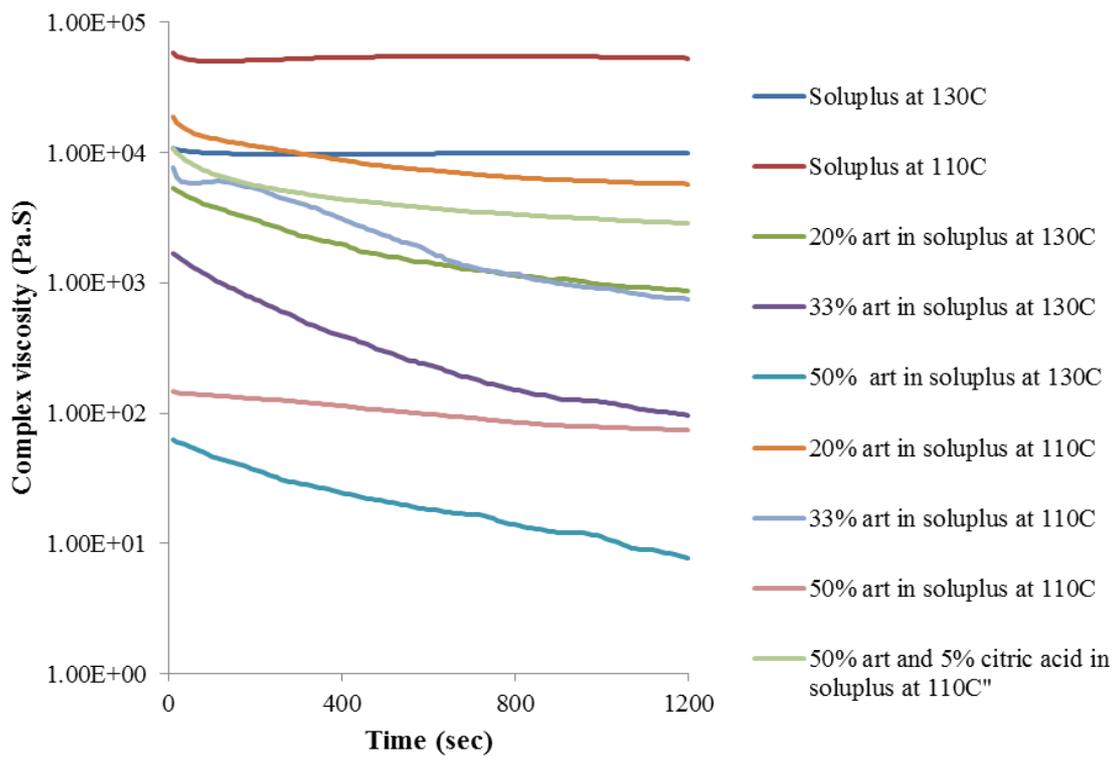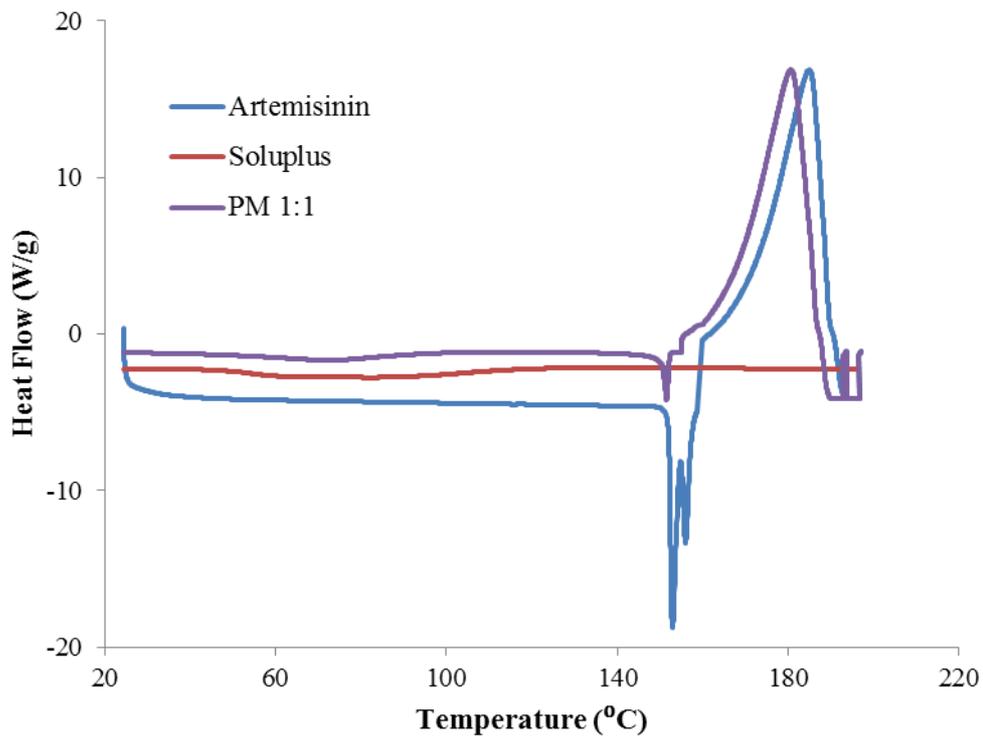

Fig.3. Time dependent complex viscosity

Fig.4. DSC thermograms of artemisinin, Soluplus and physical mixture
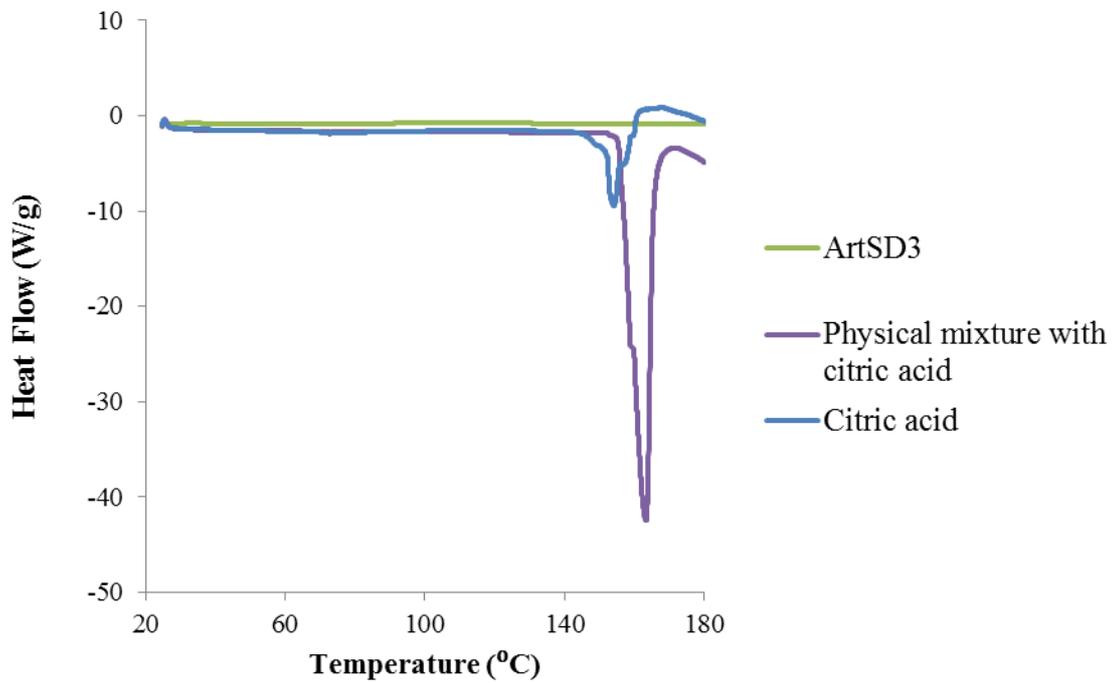

Fig.5. DSC thermograms of citric acid, physical mixture containing 5% citric acid and ArtSD3
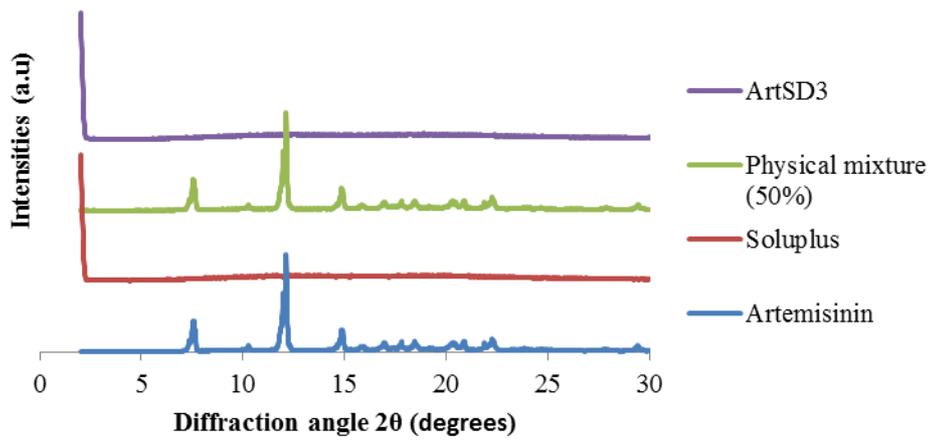
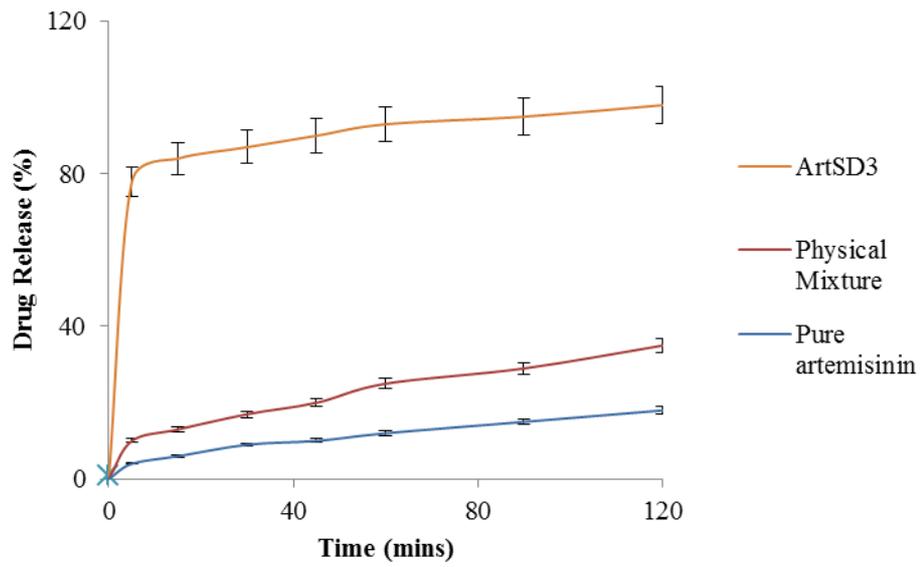Fig.6. PXPD patterns of artemisinin, Soluplus®, physical mixture and ArtSD3

Fig.7. Drug release rates from pure drug, physical mixture of drug and polymer and ArtSD3
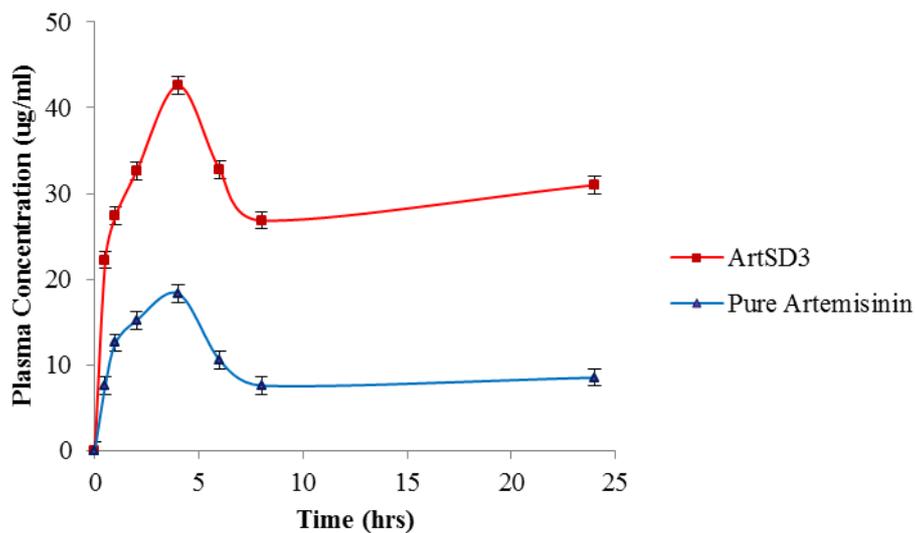
Fig.8. Plasma concentration after oral administrating pure artemisinin and ArtSD3
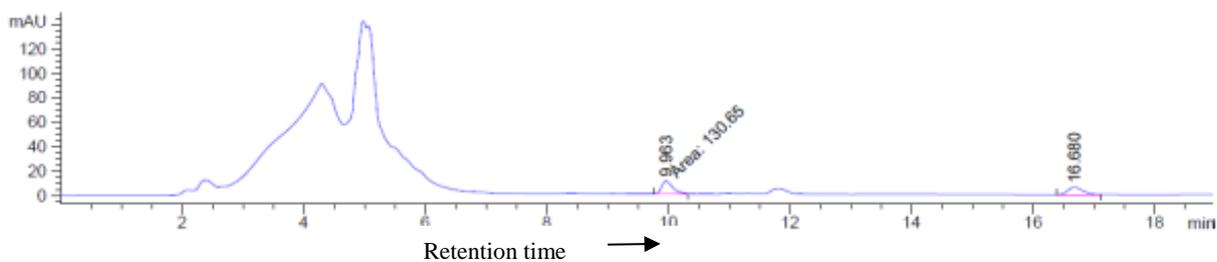

Fig. 9. Typical chromatogram of a rat plasma sample spiked with 120 μg/ml artemisinin RT 9.96 and internal standard artemether RT 16.68

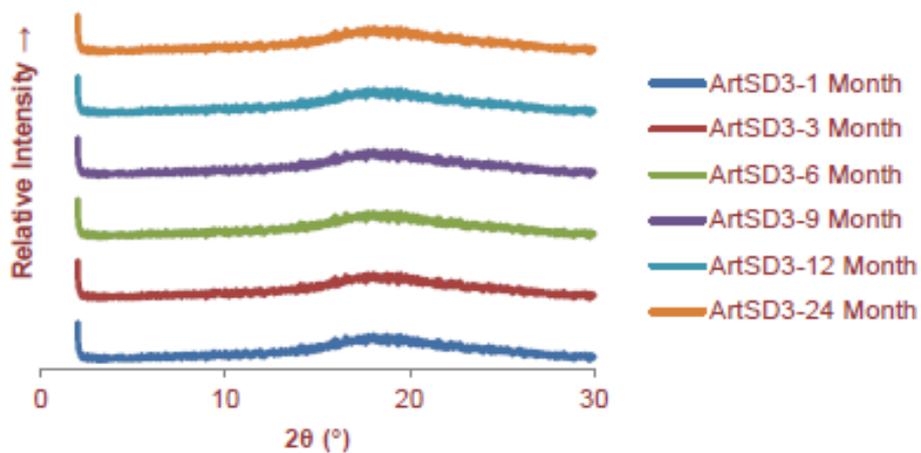Fig. 10. PXRD patterns of ArtSD3 at different time intervals.

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Tables

Table 1. Temperature profiles across the different zones of the extruder barrel

Temperature Profile	Zone 2	3	4	5	6	7	8	9	Die
T110 A	-	-	-	-	25	25	110	110	110
T110 B	20	25	80	90	100	110	110	110	110

Table 2. Screw configurations

(a: in terms of diameter   ID: 16 mm)

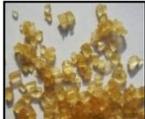| A			B		
Length (D)[a]	Element		Length (D)[a]	Element	
9	Forwarding		28	Forwarding	
2.25	30°		2.25	30°	
1.25	60°		1.25	60°	
1	90°		1	90°	
6	Forwarding		6	Forwarding	
1.5	Discharge		1.5	Discharge	
20	**Total length**		**40**	**Total Length**	
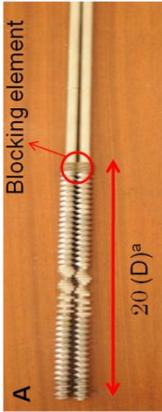
Table 3. Formulations codes with process parameters

Batches	Screw configuration (shown in Table 3.3)	Proportion			Temperature Profiles (shown in Table 3.4)	Visual Observation
		Drug	Polymer	Citric acid		
ArtSD1	A (Half screw length)	1	1	-	T110A	
ArtSD2	B (Full screw length)	1	1	-	T110B	
ArtSD3	B (Full screw length)	1	0.95	0.05	T110	

Table 4. Assay results of extrudates

Formulations	Average Purity (%)	Standard deviation
ArtSD1	83.30	1.85
ArtSD2	78.65	2.79
ArtSD3	99.76	3.54
Extruded artemisinin crystals (neat)	99.33	0.57
Extruded Soluplus® (neat)	-	-

Table 5. Plasma concentration of pure artemisinin

Plasma Concentration of pure artemisinin(µg/ml)							
Time(h)	Rat 1	Rat 2	Rat 3	Rat 4	Rat 5	Rat 6	Mean
0	0	0	0	0	0	0	0
0.5	7.78	6.67	7.78	7.78	8.89	6.67	7.59
1	15.56	8.89	10	11.11	12.22	17.78	12.59
2	31.11	8.89	10	11.11	12.22	17.78	15.18
4	18.89	17.78	20	18.89	17.78	16.67	18.33
6	16.67	12.22	10	8.89	7.78	7.78	10.55
8	10	7.78	7.78	6.67	6.67	6.67	7.59
24	8.89	10	8.89	6.67	7.78	8.89	8.51

Table 6. Plasma concentration of ArtSD3

Plasma Concentration of ArtSD3 (µg/ml)							
Time(h)	Rat 1	Rat 2	Rat 3	Rat 4	Rat 5	Rat 6	Mean
0	0	0	0	0	0	0	0
0.5	22.22	24.44	21.11	22.22	23.33	20.00	22.22
1	27.78	26.67	26.67	26.67	28.89	27.78	27.41
2	33.33	31.11	28.89	34.44	32.22	35.56	32.59
4	43.33	41.11	45.56	41.11	42.22	42.22	42.59
6	26.67	33.33	35.56	32.22	33.33	35.56	32.78
8	20.00	23.33	28.89	27.78	30.00	31.11	26.85
24	13.33	18.89	20.00	18.89	20.00	17.78	18.15

Table 7. Area under curves for pure artemisinin and ArtSD3

Rats	Pure artemisinin (µg.hr/ml)	ArtSD3 (µg.hr/ml)
Rat 1	47.01	127.15
Rat 2	58.33	147.22
Rat 3	37.77	164.03
Rat 4	32.56	157.64
Rat 5	34.65	165.49
Rat 6	55.83	165.49