Enhancement of solubility and dissolution profile of artesunate by employing solid dispersion approach: An *in-vitro* evaluation

Muhammad Asad Saeed*, Muhammad Tayyab Ansari and Bashir Ahmad Ch
Faculty of Pharmacy, Bahauddin Zakariya University, Multan, Pakistan

Abstract: Current study was designed with an aim to improve the solubility and dissolution profile of artesunate by preparing solid dispersions through solvent evaporation and freeze-drying techniques using polyethylene glycol 4000 (PEG4000) as solubility enhancer. Developed formulations were characterized for FTIR, XRD, TGA and SEM. Maximum increase in solubility was attained by freeze-dried solid dispersions (FD F444) i.e. 2.99 folds and 2.66 folds by solvent evaporation solid dispersion (SE F44) as compare to pure drug. Amorphous nature of artesunate in solid dispersions was confirmed from XRD diffractographs. Surface morphology indicated the existence of rough surface in freeze- dried solid dispersions (FDDs) and smooth surface in solvent evaporation solid dispersions (SEDs). Rapid dissolution rates were exhibited by fast dissolving tablets of optimized formulations. Moreover, the release of the drug was dominated by the first order kinetics ($R^2 = 0.9932$) with the Fickian type of diffusion mechanism ($n<0.450$).

Keywords: Artesunate, freeze-dried, PEG4000, solid dispersions, solvent evaporation.

INTRODUCTION

More than 40% of the drugs available in the market, and 60 to 70 % new drug candidates exhibit solubility related issues and fall in biopharmaceutical classification system class- II (compounds with low aqueous solubility and high permeability) (Fong *et al*., 2015). Oral rout for the delivery of these drugs, which offer poor aqueous solubility results in low bioavailability, high inter and intra subject variability and lack of dose proportionality**.** These drugs must dissolve to pass through the gastrointestinal wall and get access to the general circulation. Bioavailability of such drugs is solubility dependent (Frank *et al*., 2014). To overcome such problems, high doses of drugs are required to achieve the therapeutic effects. In pharmaceutical industry new approaches are developed and adopted to improve the solubility of active pharmaceutical entities (Vasconcelos *et al*., 2016). Several techniques have been employed to enhance the solubility of drugs and one of them is solid dispersion method. It involves the fine or molecular dispersion of lipophilic drugs in hydrophilic carrier substances, which will result in the enhanced solubility of the drugs due to solubilization, particle size reduction or conversion into amorphous nature (Jackson *et al*., 2015). Moreover, it improves the drug's physical stability by decreasing the mobility of molecules (He and Ho, 2015). Amorphous state of drug exhibits messy structure and possesses higher free energy as compared to its crystalline state. Though, later is advantageous in terms of purity and physico-chemical stability. To solubilize the drug in its crystalline state, the lattice energy should be overcome to get it dissolved. Amorphous state with higher free energy exhibits increased solubility and improved dissolution rate (Teja *et al*., 2016). Amorphous solid dispersions are generally prepared using methods based on solvent evaporation (SE), fusion method, hot melt extrusion, supercritical fluids, spray drying (He and Ho, 2015).

Enhancement in solubility, by applying solid dispersion techniques of various hydrophobic drugs like acetaminophen, indomethacin, piroxicam, itraconazole and nifedipine by using different polymeric materials and formulation methods have been previously reported extensively (Baghel *et al*., 2016). Polyethylene glycol (PEG) is widely used as a polymeric carrier in the formulation of solid dispersions (SDs), both in pharmaceutical industries as well as by formulation scientists. It is due to its effectiveness as solubilizing agent, precipitation inhibitors and wettability enhancer (Momoh *et al*., 2015). PEGs are hydrophilic synthetic polymers having linear molecule, made by joining units of ethylene glycol through an ether linkage. PEGs have the general formula of $H(OCH_2CH_2)_nOH$, where n represents the number of individual ethylene oxide units (Fordtran and Hofmann, 2017).

Artesunate (INN) belongs to the Artemisinin group of drugs that are used for the treatment of malaria. It is a semisynthetic derivative of Artemisinin obtained from *Artemisia annua* belonging to sesquiterpene lactone family having endoperoxide bridge. Mechanisms by which artemisinin and its derivatives acts, may be due to reactive oxygen species (ROS) generated by an endoperoxide moiety, cell cycle arrest, induction of apoptosis, and inhibition of tumor angiogenesis (Zhang *et al*., 2018). It is white crystalline powder that is slightly soluble in water (Chinaeke *et al*., 2014). Artesunate is poorly soluble in acidic and neutral conditions. It has relatively low oral bioavailability of approximately 40%

**Corresponding author:* e-mail: findasadsaeed@gmail.com

(Masiiwa and Gadaga, 2018). It is freely soluble in acetone and ethanol and very soluble in dichloromethane.

Therefore, in view of above-mentioned facts, study was designed to enhance the solubility of very slightly water-soluble drug, artesunate by solid dispersion technique using PEG4000 as solubility enhancer. Furthermore, the optimized formulations were compressed into fast dissolving tablet for immediate oral delivery of the drug. Fast dissolving tablets (FDTs) have advantage of improved compliance, better taste, no need of water and improved stability (Rahane and Rachh, 2018). These tablets were evaluated by applying different kinetic models to investigate the dissolution behavior and possible mechanism of drug release.

MATERIALS AND METHODS

Materials

Artesunate was generously gifted by Genix Pharma Pvt. Ltd. Pakistan. Polyethylene glycol 4000 (PEG4000), NaOH and Ethanol were purchased from Sigma Aldrich Germany. All the chemicals used were of analytical grade.

Methods

Solid dispersion formulations were prepared by varying ratios of drug to polymer as shown in Table 1. Physical Mixture (PM) and solid dispersions (SDs) were prepared by solvent evaporation (SE) and freeze-drying (FD) method.

Preparation of physical mixture

Artesunate and PEG4000 were weighed precisely and mixed thoroughly in mortar and pestle for 5 minutes, sifted through sieve No. 80 and stored in a tightly closed amber colored glass bottles till further use.

Preparation of solid dispersions by solvent evaporation method

Solid dispersions by solvent evaporation method were prepared as described by Soni *et al* with mild modifications. Accurately weighed quantities of PEG4000 were taken and get dissolved by transferring it into glass flasks containing ethanol followed by addition of precisely weighed amount of artesunate. Mixtures were subjected to continuous stirring using magnetic stirrer, till the uniform mixture formed. Then solvent was removed by using rotary evaporator (IKA RV 10 digital V) and mass obtained was dried in oven at 37^{o}C for the complete removal of solvent (Soni *et al*., 2017). Obtained mass of solid dispersions was scraped, crushed, pulverized and sifted through sieve No. 80. These solid dispersions were packed in dried amber colored glass bottles and stored in desiccator till further use.

Preparation of solid dispersions by freeze-drying method

In the method of freeze drying, precisely weighed amounts of artesunate & PEG4000 were mixed to prepare the soluble mixture. These solutions were placed in the round bottom flasks and shaken on orbital shaker for proper mixing. Solvent was evaporated by using rotary evaporator (IKA RV 10 digital V). A small amount of deionize water was added, shaken and frozen at temperature of −80°C in refrigerator (Arctiko G214 with controller). Frozen forms were lyophilized using VaCO2 lyophilizer (Zirbus, technologies) at 0.100 mBar vacuum for the complete removal of water. After drying, the freeze-dried mixtures were softly grinded in the pestle and mortar, and passed through sieve No. 80 (Ansari *et al*., 2015). These prepared formulations were then kept in dried, amber colored glass bottles and placed in desiccator till further use.

Preparation of fast dissolving tablets

Formulations showing comparatively better outcomes of solubility studies were selected for evaluation and compressed into fast dissolving tablets by direct compression method.

Tablets containing equivalent to10 mg of Artesunate were prepared following the composition tabulated in Table 2
Micromeritics and physical characterization like hardness, disintegration time, friability and weight variations of the all the tablets were performed.

In-vitro evaluation and characterization

Solubility Studies

For solubility studies, concentration was determined by alkali derivatization of artesunate, as described by USP and E. E. Chinaeke *et al* (Chinaeke *et al*., 2015). An excess quantity of the prepared formulations was added to glass vials containing 10 ml of deionized water. These vials were placed in a thermostatically controlled shaker (Bench top shaking incubator S1990R) at 37°C and operated at 150 rpm. After 30 minutes, these samples were removed and filtered through 0.22 µm Millipore filter (Acrodisc GF syringe filter, Pall Life Sciences, USA) and each solution was diluted with deionized water. Diluted samples were treated with 1 N NaOH followed by heating at 50 °C for 45 minutes, cooled immediately to room temperature and analyzed spectrophotometrically at 289 nm using a Shimadzu 1800 UV-Visible spectrophotometer. Concentrations were calculated from the standard curve prepared from alkali derivatized method of artesunate as described above.

Attenuated total reflection fourier transform infrared spectroscopy (ATR-FTIR)

Spectroscopic imaging by FTIR provides comprehensive information regarding chemical composition due to inherent ability of vibrational spectra to provide specific information of molecular structure of material. Fourier transform infrared spectral measurements were performed at room temperature using ATR-FTIR 7600 spectrometer (Lambda). FTIR spectra of the drug, polymer and solid dispersions was obtained in the range 500- 4000cm^{-1}.

X-ray diffractometry (XRD)

X-Ray diffractometric (XRD) patterns of artesunate, polymer, physical mixture and various solid dispersions were done by using X-Rays Diffractometer (JDX-3532 JEOL Japan) to find out the nature of solid dispersions. Scanning range was kept 5^{o}-50^{o} at the scanning rate of 1^{o}/min.

Thermogravimetric analysis (TGA)

Study of the thermograms obtained enables us the quantitative detection of all processes in which energy is required or produced. Thermogravimetric analysis (TGA) can be used to evaluate the thermal stability. TGA of pure artesunate, physical, solvent evaporation and freeze-dried mixtures was performed by heating at a rate of 10°C/min from room temperature to 500°C under a dry nitrogen gas with the flow rate of 30ml/min by using Thermal analyzer, Shimadzu Japan.

Scanning electron microscopy (SEM)

For the identification and confirmation of the nature as well as surface topography of pure drug and formulated samples of artesunate prepared by different techniques, scanning electron microscopy (SEM, Perkin Elmer, USA) was done.

In-vitro dissolution studies

Dissolution study was carried out by using USP dissolution apparatus II. The stirring rate was 100rpm. Distilled water (900 ml) was used as dissolution medium maintained at 37±1°C. On specific time intervals such as 5,10, 15, 20, 25, 30, 45 & 60 min, 5 ml of aliquots were taken out which were immediately replaced by the addition of 5 ml of fresh medium. These obtained samples were then filtered through 0.22µm Millipore filter and analyzed using U.V spectrophotometer at 289 nm using alkali derivatized method as explained earlier.

Kinetic modelling

Pattern of drug release was observed by applying following equations for various kinetic models including, zero order model, first order model, Higuchi model, Hixson Crowell model and korsemeyer-peppas model using DD solver add in MS Excel (Farooq *et al*., 2018).

Zero order kinetic model

$$K_{\circ} = \frac{A}{T}$$

First order model

$$K_1 = \frac{2.3 \log(\frac{A_{\circ}}{A})}{t}$$

Higuchi Model

$$K_H = \frac{Q}{\sqrt{t}}$$

Hixson-Crowell cubic root model

$$Kt = \sqrt[3]{M_{\circ}} - \sqrt[3]{M}$$

Korsemeyer-Peppas model

$$K_k = \frac{D_t/D_a}{t^n}$$

Where k_o is zero order rate constant, t is the time, A is the amount of drug release in time t, A_o is the initial concentration of drug and k_1 is the first order constant. k_H is Higuchi dissolution constant. K is cube root dissolution rate constant. D_t/D_a is fraction of drug release at time t.

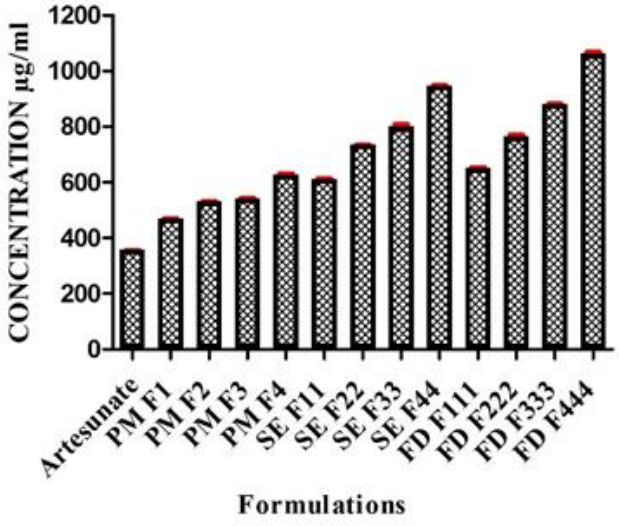

Fig. 1: Solubility of artesunate and different formulations

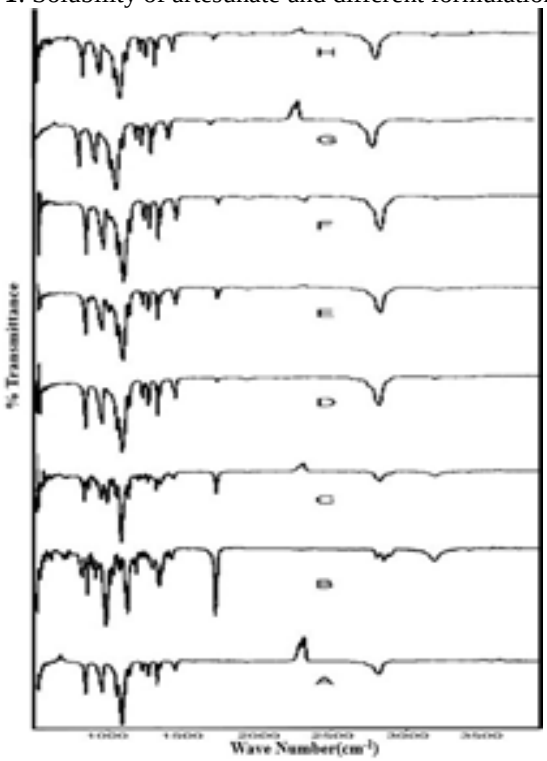

Fig. 2: Comparative FTIR Spectra of Pure Artesunate, PEG4000 & Solid Dispersions A: PEG4000, B: Artesunate, C: PM F3, D: PM F4, E: SE F33 F: SE F44 G: FD F333 H: FD F444.

RESULTS

Solubility studies

Formulation (FD F444) prepared by maximum concentration of the PEG 4000 have shown highest increase in solubility of the artesunate (2.99 folds).

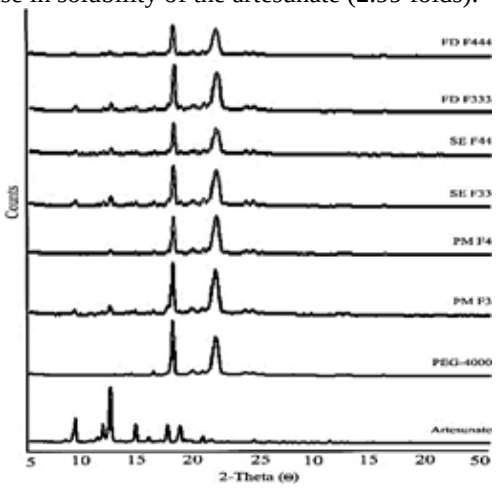

Fig. 3: XRD pattern of pure artesunate, Polymer PEG4000 and Solid Dispersions

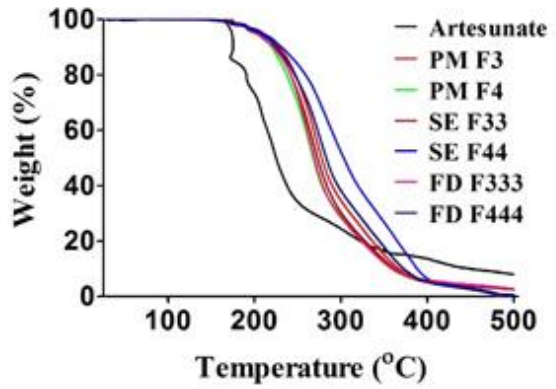

Fig. 4: Thermogravimetric Analysis of artesunate and solid dispersions

Solubility of pure artesunate was found to be 354.58 µg/ml, when the studies were conducted in deionized water. Increase in the solubility in terms of folds for PM F1, SE F11 and FD F111 was 1.32, 1.72 and 1.83 respectively, while for formulations PM F2, SE F22 and FD F222, it was 1.49, 2.06 and 2.15 folds respectively as compare to the pure artesunate as shown in fig. 1. Increase was 1.52, 2.25 and 2.48 folds for PM F3, SE F33 and FD F333 respectively. Maximum increased solubility for PM, SEDs and FDDs (ratio 1:10) was 1.76, 2.66 and 2.99 folds respectively. Order of increase in solubility in all ratios of artesunate to PEG4000 was FD > SE > PM. When solubility was compared among the SEDs and FDDs and ratios 1:1, 1:4, 1:7 and 1:10 simultaneously, it was noted that highest difference between FD F333 and SE F33 was 0.23 folds as compared to 0.11 folds (1:1), 0.09 (1:4) and 0.33 folds (1:10). This represents that if we enhance the polymer content by 3 degrees, FD F333 produced unexpected rise in solubility, different nature of crystalline status and bonding interactions (shown in results of FTIR and XRD). These results of solubility were in accordance to previously reported studies (Shamsuddin *et al*., 2016).

Attenuated Total Reflection Fourier Transform Infrared Spectroscopy (ATR-FTIR)

The comparative FTIR spectra of pure artesunate, PEG4000, Physical mixture and SDs has been shown in fig. 2. FTIR spectrum of pure artesunate showed the characteristic bands at 3276.5 cm^{-1} (O-H stretching), 2886.9 cm^{-1} (C-H stretching), 1756.83 cm^{-1} (C=O stretching), 1467.56 cm^{-1}& 1456 cm^{-1} (CH_2 Scissoring vibration), 1326 cm^{-1}(O-H bending), 1348 cm^{-1}(C-H bending), 1147 cm^{-1}(C-O-C asymmetric saturation) and C-O stretching at 1253cm^{-1} and 1031cm^{-1}. Functional groups, including the endoperoxide function (O-O-C) and the carboxylic groups (-COOH) were reflected in the bands at 873.6 cm^{-1} and 1756.83 cm^{-1}, respectively as reported earlier (Ansari *et al*., 2010a). Though the band at 1756.83 cm^{-1} (C=O stretching) was weak in some formulations, however it is a unique marker of semisynthetic artemisinin derivative artesunate having an epidioxide function. FTIR spectrum of PEG4000 showed characteristic bands at 2886.9 cm^{-1} (C-H stretching), 1467.56cm^{-1} (CH_2 scissoring), 1361.49cm^{-1} (C-H bending), 1342.21 cm^{-1} (O-H bending), and C-O stretching vibrations at 1241.9cm^{-1} and 1062.6cm^{-1}.

X-ray diffractometry (XRD)

XRD pattern of artesunate, PEG4000 and formulations are given in fig. 3 for comparison. Diffraction peaks of artesunate revealed high crystalline nature which was indicated by distinct & high peak counts at diffraction angle 2θ degree of 9.52° (3147), 12.2° (2436), 12.92° (6927), 12.96° (6566), 15.48° (1853), 18.52° (2308), and 19.76° (2161). The PEG4000 exhibited only two sharp and intense peaks at 19.05° (7377) and 23.2° (5277).

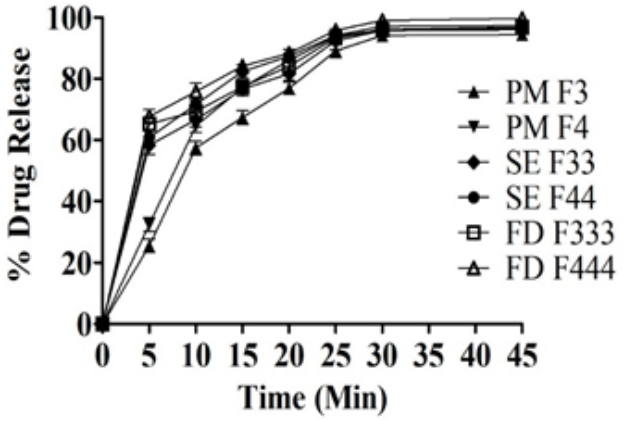

Fig. 6: Dissolution profile of FDTs of solid dispersions in distilled water.

Table 1: Composition of different formulations

Method	Formulation Code	Artesunate: PEG 4000
Physical Mixture	PM F1	1:1
	PM F2	1:4
	PM F3	1:7
	PM F4	1:10
Solvent Evaporation	SE F11	1:1
	SE F22	1:4
	SE F33	1:7
	SE F44	1:10
Freeze-Drying	FD F111	1:1
	FD F222	1:4
	FD F333	1:7
	FD F444	1:10

Table 2: Composition of fast dissolving tablets

Formulation code	PEG4000 (mg)	Lactose (mg)
PM F3	70	187
PM F4	100	157
SE F33	70	187
SE F44	100	157
FD F333	70	187
FD F444	100	157

Constant quantities of Drug (10mg), Glidant (3mg) and Superdisintegrant (30mg) were used in all the formulations

Table 3: Micromeritics results of physical mixture and solid dispersions

Formulations	Angle of Repose (θ)	Bulk density g/cm^3	Tapped Density g/cm^3	Carr's Index (%)	Hausner Ratio
PM F3	33.16± 1.02	0.53±0.04	0.57±0.01	14.07±1.61	1.16± 0.05
PM F4	34.46± 0.72	0.51±0.03	0.58±0.02	13.107±1.31	1.17± 0.03
SE F33	30.84± 1.01	0.49±0.02	0.56±0.04	10.62±2.01	1.13±0.01
SE F44	32.83± 0.87	0.53±0.03	0.59±0.01	12.61±1.07	1.12±0.01
FD F333	31.88± 1.01	0.51±0.01	0.57±0.03	13.21±1.04	1.14±0.03
FD F444	31.13± 1.31	0.53±0.01	0.59±0.03	13.107±1.2	1.15±0.01

Mean ± S.D

Thermogravimetric analysis (TGA)

TGA results of pure artesunate and prepared formulations have been described in fig. 4 which was the illustration of thermal stability of pure artesunate and its SDs. Thermogravimetric (TG) curve of pure artesunate showed the loss in weight of about 92.121% in two steps. The peak onset temperature was 166.2^{o}C. The first loss in mass was possibly due to the decomposition product Formic acid and succinic anhydride at the second step (Dong *et al*., 2007). When onset temperatures were compared among SEDs and FDDs as shown in fig. 4, FD F444 had higher onset temperature (243.94^{o}C) than respective SE F44 (242.35^{o}C) while reverse was true in case of FD F333 (231.15^{o}C) and SE F33 (232.42^{o}C) respectively. This indicates different type of packing in FD F333 compared to FD F444.

Scanning electron microscopy (SEM)

SEM images of artesunate, PEG4000 and solid dispersions are shown in fig. 5. Surface morphology micrographs of pure artesunate crystals were in rod shaped or irregular crystals, which is in confirmation with the earlier reports.

Evaluation of prepared tablets

Evaluation of tablets as shown in table 3 and table 4 have proposed the suitable and satisfactory results as there was negligible variations (±2.28 to 3.58 mg) in the weight of the prepared tablets. Similarly, tablets have shown good mechanical strength as the hardness was greater than 3 kg/cm^2, which was found dependent on the polymeric contents. Results tabulated in Table 4 were the evident of this stated trend in the hardness. Friability of the tablets

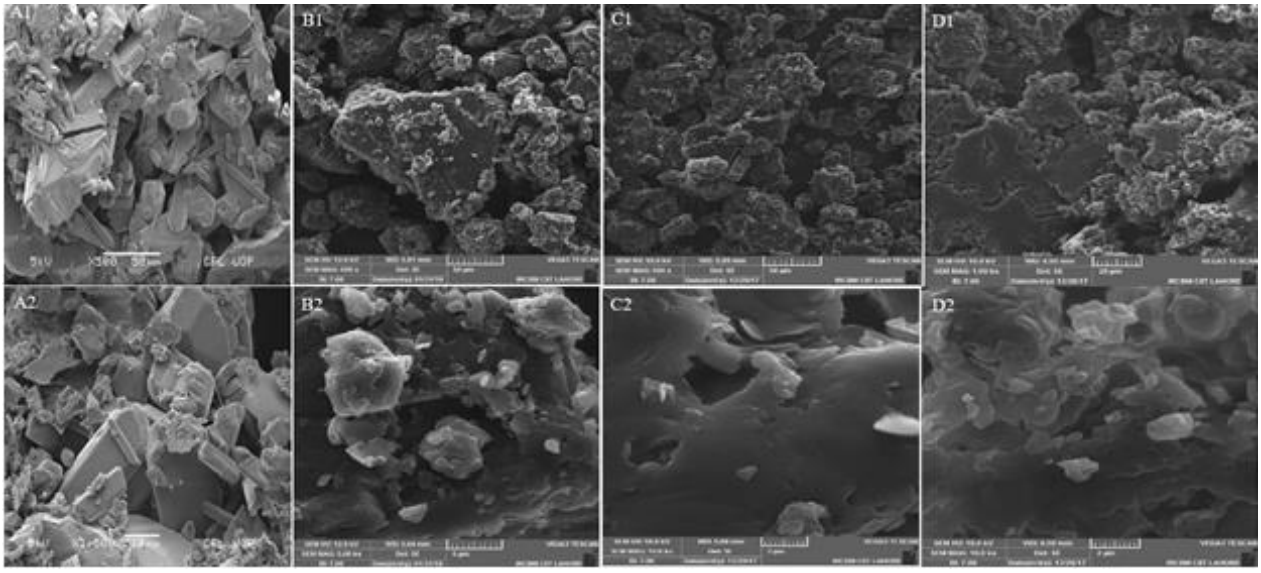

Fig. 5: Scanning Electron Micrographs of pure artesunate and Solid Dispersions A): Artesunate B): PM F4 C): SE F44 D): FD F444

was in the range of 0.42±0.14% to 0.61±0.14%, satisfying the official limits, as according to the pharmacopoeia specification, it should be less than 1%.

In vitro dissolution studies

Dissolution results of fast dissolving tablets prepared from the optimized SDs are shown in fig. 6. Immediate release products having ideal dissolution profile generally show 100% recovery of active pharmaceutical product within 45 to 60 minutes.

Difference in the percentage drug released after 5 minutes (Q_5) was quite prominent i.e. PM F3 and PM F4 showed 25.46% & 32.41% respectively while SE F33 and SE F44 showed 58.25% & 60.75% respectively. FD F333 and FD F444 showed 65.19% & 67.69% drug release respectively. FDDs showed the highest percentage release immediately after the disintegration of tablets possibly due to the rough disordered structure of FDDs as discussed earlier in SEM results. Percentage drug released from the selected PM and SDs after 15 minutes (Q_{15}) was 67.41%, 77.13%, 76.58%, 82.41%, 77.41% and 84.08 for PM F3, PM F4, SE F33, SE F44, FD F333 and FD F444 respectively. However, after 30 minutes almost all the formulations showed more than 90% drug release. Improvement in the dissolution behavior of artesunate was due to the solubilization effect of PEG4000 and conversion of the crystalline artesunate to the less crystalline form which was confirmed by the XRD and SEM graphs.

Obtained dissolution data of formulations was analyzed by applying different kinetic models. Main parameter considered for the interpretation of results was coefficient of determination as shown in table 5. Regression coefficient R^2 of dissolution data of artesunate revealed that best fit model for release mechanism was First Order kinetics and it was in accordance with the release mechanism followed by ziprasidone HCl tablets (Shiv *et al*., 2013) and the Clobazam fast dissolving tablets (Bala *et al*., 2013). Mode of drug release from the formulation was assessed by Korsmeyer-Peppas model from release exponent **n** by using first 60% release data which revealed that the formulations PM F3 and PM F4 followed the anomalous release (Non-Fickian diffusion) i.e. 0.592 and 0.495 while rest of all formulations followed the Fickian diffusion (n<0.450)(Shoaib *et al*., 2006).

DISCUSSION

A polymeric concentration dependent augmentation in the solubility was noticed in the current study. Dispersion of the drug in the polymer may lead to particle size reduction and increased surface area. Moreover, no energy will be required to break the crystal lattice which will ultimately increase the wettability and solubility of the drug being surrounded by hydrophilic polymeric material. Drug release also increases from the solid dispersion by increasing the polymeric content. Sadia *et al* has also reported earlier that by increasing the concentration of PEG, the release of drug also increases (Sadia *et al*., 2018).

Basic chemistry of artesunate reveals the presence of C=O, C-O, C-H, CH_2, CH_3, C-O-O, C-O-C, C-O-C=O & CH_2-CH_2 groups. It has already been reported that FTIR spectrum of **δ**-Lactone presents carbonyl mode at 1757cm^{-1} (Wu *et al*., 2018). PM and SEDs showed red shift from 3276.5cm^{-1} (O-H stretching) to 3280.3 cm^{-1} and 3282.25 cm^{-1} respectively. While FD F333 showed

Table 4: Results of weight variation, hardness, friability and disintegration time of FDTs

Formulation	Weight Variation (mg)	Hardness (Kg/cm^2)	Friability (%)	Disintegration time (Sec)
PM F3	300 ± 2.72	3.4 ± 0.2	0.61 ± 0.14	28.17 ± 2.32
PM F4	298.6 ± 3.58	4.3 ± 0.3	0.50 ± 0.18	41.67 ± 2.16
SE F33	299.7 ± 2.28	3.46 ± 0.11	0.65 ± 0.21	28.83 ± 2.31
SE F44	299.1 ± 2.55	4.48 ± 0.40	0.59 ± 0.21	42.17 ± 2.64
FD F333	299.1 ± 3.3	3.42 ± 0.31	0.54 ± 0.18	29.5 ± 2.74
FD F444	300.3 ± 2.45	4.24 ± 0.11	0.42 ± 0.14	43.67 ± 3.56

Mean ± S.D

Table 5: Statistical parameters of formulations fitting drug release profile to various kinetic models

Kinetic Models		Fast Dissolving Tablets containing					
		PM F3	PM F4	SE F33	SE F44	FD F333	FD F444
Zero order	K_O	3.648	3.917	3.921	4.075	3.989	4.171
	R^2	0.8728	0.7795	0.5146	0.4438	0.3986	0.3365
1^{st} order	K_1	0.078	0.097	0.115	0.137	0.131	0.164
	R^2	0.9875	0.9932	0.9494	0.9701	0.9268	0.9586
Higuchi model	K_H	17.182	18.621	18.941	19.760	19.364	20.311
	R^2	0.9736	0.9756	0.9390	0.9204	0.8951	0.8776
Korsmeyer- peppas Model	k_K	13.039	18.897	34.609	39.214	41.535	46.370
	n	0.592	0.495	0.297	0.269	0.242	0.221
	R^2	0.9814	0.9756	0.9962	0.9993	0.9931	0.9987
Hixson- Crowell	Kt	0.021	0.026	0.030	0.036	0.034	0.042
	R^2	0.9906	0.9934	0.9005	0.9306	0.8690	0.9158

unexpectedly greater blue shift to 3272.6 cm^{-1} than FD F444 i.e. 3274.5 cm^{-1} (O-H stretching). Band at 1756.83cm^{-1} (C=O stretching) of pure artesunate also showed red shift to 1758.8 cm^{-1} in SEDs and blue shift to 1754.9cm^{-1} in FD F444. Shifting in the bands indicates the presence of bonding interactions, however the bonding interactions of FDDs were of different nature as compared to PM and SEDs. With the rise of polymer content, the representative peaks of artesunate diminished. The same behavior has already been reported in case of domperidone by Patel and his co-researcher (Patel *et al*., 2011). From the obtained FTIR data, presence of bonding interactions between artesunate and PEG4000 were confirmed.

XRD pattern of solvent evaporation solid dispersions (SEDs) SE F33 produced lowest peak intensity at 12.92^o, 18.52^o and at 23.2^o degree of angle 2θ (representative of PEG4000) as compared to their respective formulations of PM and FDDs. In case of formulation ratio 1:7, Physical mixtures produced highest peak count followed by FDDs and SEDs, respectively. While at 19.76^o, FDDs showed unusual behavior i.e. the decrease in intensity was less than respective PM and SEDs formulations respectively. This unusual behavior of FDDs was also supported by the FTIR results. Comparatively less distinct peaks present in PM, SEDs and FDDs were of PEG4000 i.e. at the degree of 19.05^o and 23.2^o. The intense diffraction peaks of artesunate were almost absent in all the formulations. Decreased intensity of numerous peaks of artesunate in PM, SEDs & FDDs indicated that maximum quantity of drug has been successfully entrapped in solid carrier matrix. This suggested that crystallinity of artesunate in all formulations was greatly reduced and with increased PEG4000 contents, peak intensities decreased. This behavior was in accordance with the results as reported earlier for allopurinol (Changdeo *et al*., 2011) and artemether (Ansari *et al*., 2010b).

The results of TG curves of PMs and SDs indicated the substantial increase in onset temperature of artesunate supporting that its thermal stability was increased, and it was completely wrapped by polymer PEG4000.

Surface characteristics of FDDs showed intact and rough disordered structure, which ultimately helps to dissolve the drug when encounters aqueous fluid. Existence of rough surface advocates that the hydrophilic polymer was spread throughout on the surface of drug (Fule and Amin, 2014). It was almost impossible to distinguish crystals of artesunate. Artesunate appears to be uniformly incorporated in the polymer. Apparent change in the particles and shape indicates the presence of new solid phase as reported earlier in case of nimodipine (Gorajana and Rao, 2010). Micrographs of SEDs showed smooth surface as compare to the FDDs. However crystalline rods of artesunate were totally absent proving the dispersion of artesunate in the polymer. These micrographs clearly

showed that in the SDs, the original morphology of artesunate disappeared and it was difficult to distinguish between the active drug and polymer.

Prepared tablets were found to be disintegrating in less than 1 min, satisfying the objective of the study. Outcomes of the studies have proposed strong linkage between the hardness, friability and disintegration time (DT) of the tablets with the polymer concentration. Hardness and DT increased, while friability was found to be decreasing with increase in concentration of the polymers.

Dissolution studies have proposed that, SDs increased the dissolution rate and possible mechanism of this includes crystallite size reduction, absence of aggregation of drug crystallites, dispersibility and wettability improvement by the carrier, dissolution of the drug in carrier and conversion of drug to the amorphous state/less crystalline state. All the SDs and PMs showed the improved dissolution profile. Highest dissolution was with 1:10 drug-polymer ratio. Findings of the current studies have suggested that by increasing the content of PEG 4000, there was an increase in the rate of dissolution (Yang *et al*., 2016). High concentration of polymer provided wetting of the artesunate which ultimately increased the dissolution. Clonazepam was reported to have same dissolution profile with Kollicoat IR (Minhaz *et al*., 2012). Employed kinetic models have revealed that except FD F333, all the SDs have shown suitable R^2 values for Hixson-Crowell cube root ranging from 0.9005 (SE F33) to 0.9934 (PM F4) indicating the uniform exhaustion of dosage form. Uniform exhaustion is desirable because it assists the uniform disintegration as well as dissolution to provide smooth release of the drug from reservoir (Zaman and Hanif, 2018).

CONCLUSIONS

It can be concluded from the current study that preparation of solid dispersions using polymer PEG4000 by freeze-Drying method can be effective for solubility and dissolution improvement of artesunate. The solubility & dissolution enhancement of prepared dispersions were significantly dependent on both drug to polymer ratio and method of preparation. When PEG 4000 ratio was enhanced by 3 degree, as in the case of FD F333 (1:7 ratio), a comparatively greater improvement in the solubility of the drug was noticed. The reason behined this effect, noitced in the study was the different nature of bonding interactions between drug and polymer, as confirmed by the FTIR and XRD analysis. Furthermore, fabricated fast dissolving tablets of optimized fromulation have successfully provided rapid disintegrastion and instant release of the drug satisfying the objective of the studies.

REFERENCES

Ansari MT, Haneef M and Murtaza G (2010a). Solid dispersions of artemisinin in polyvinyl pyrrolidone and polyethylene glycol. *Adv. Clin. Exp. Med,* **19**: 745-754.

Ansari MT, Hussain A, Nadeem S, Majeed H, Saeed-Ul-Hassan S, Tariq I, Mahmood Q, Khan AK and Murtaza G (2015). Preparation and characterization of solid dispersions of artemether by freeze-dried method. *BioMed Res. Int.,* pp.1-11.

Ansari MT, Karim S, Ranjha NM, Shah NH and Muhammad S (2010b). Physicochemical characterization of artemether solid dispersions with hydrophilic carriers by freeze dried and melt methods. *Arch. Pharm. Res.,* **33**: 901-910.

Baghel S, Cathcart H and O'reilly NJ (2016). Polymeric amorphous solid dispersions: A review of amorphization, crystallization, stabilization, solid-state characterization, and aqueous solubilization of biopharmaceutical classification system class II drugs. *J. Pharm. Sci.,* **105**: 2527-2544.

Bala R, Khanna S and Pawar PK (2013). Formulation and optimization of fast dissolving intraoral drug delivery system for clobazam using response surface methodology. *J. Adv. Pharm.Technol. Res.,* **4**: 151.

Changdeo JS, Vinod M, Shankar KB and Rajaram CA (2011). Physicochemical characterization and solubility enhancement studies of allopurinol solid dispersions. *Braz. J. Pharm. Sci.,* **47**: 513-523.

Chinaeke E, Chime S, Onyishi V, Attama A and Okore V (2015). Formulation development and evaluation of the anti-malaria properties of sustained release artesunate-loaded solid lipid microparticles based on phytolipids. *Drug Deliv.,* **22**: 652-665.

Chinaeke EE, Chime SA, Ogbonna JD, Attama AA, Müller-Goymann C and Okore VC (2014). Evaluation of dika wax-soybean oil-based artesunate-loaded lipospheres: *in vitro in vivo* correlation studies. *J. Microencapsul.,* **31**: 796-804.

Dong JX, Qi ZD, Zhang ZH and Liu Y (2007). Standard molar enthalpies of formation and thermal stabilities of artemisinin and its two derivatives: Artemether and artesunate. *J. Chem. Eng. Data,* **52**: 1045-1049.

Farooq M, Shoaib MH, Yousuf RI, Qazi F and Hanif M (2018). Development of extended release loxoprofen sodium multiparticulates using different hydrophobic polymers. *Polym. Bull.,* pp.1-22.

Fong SYK, Ibisogly A and Bauer-Brandl A (2015). Solubility enhancement of BCS Class II drug by solid phospholipid dispersions: Spray drying versus freeze-drying. *Int. J. Pharm.,* **496**: 382-391.

Fordtran JS and Hofmann AF (2017). Seventy years of polyethylene glycols in gastroenterology: The journey of PEG 4000 and 3350 from nonabsorbable marker to colonoscopy preparation to osmotic laxative. *Gastroenterology,* **152**: 675-680.

Frank KJ, Westedt U, Rosenblatt KM, Holig P, Rosenberg J, Mägerlein M, Fricker G and Brandl M (2014). What is the mechanism behind increased permeation rate of a poorly soluble drug from aqueous dispersions of an amorphous solid dispersion? *J. Pharm. Sci.,* **103**: 1779-1786.

Fule R and Amin P (2014). Development and evaluation of lafutidine solid dispersion via hot melt extrusion: Investigating drug-polymer miscibility with advanced characterisation. *Asian J. Pharm. Sci.,* **9**: 92-106.

Gorajana A & Rao ARNK (2010). Preperation and in vitro evaluation of solid dispersions of nimodipine using PEG 4000 and PVP K30. *Asian J. Pharm. Res. & Health Care,* **2**: 163-169.

He Y and Ho C (2015). Amorphous solid dispersions: utilization and challenges in drug discovery and development. *J. Pharm. Sci.,* **104**: 3237-3258.

Jackson MJ, Kestur US, Hussain MA & Taylor LS (2015). Dissolution of danazol amorphous solid dispersions: Supersaturation and phase behavior as a function of drug loading and polymer type. *Mol. Pharmaceut.,* **13**: 223-231.

Masiiwa WL and Gadaga LL (2018). Intestinal permeability of artesunate-loaded solid lipid nanoparticles using the everted gut method. *J. Drug Deliv.,* Apr 30; 2018: 3021738.

Minhaz MA, Rahman MM, Ahsan MQ, Khalipha ABR & Chowdhury MR (2012). Dissolution enhancement of poorly soluble drug by solvent evaporation method using hydrophilic polymer: A solid dispersion technique. *Int. J. Pharm. Life Sci.,* **2**(1): 1-18

Momoh MA, Mahmud GS, Adedokun MO, Chukwuemeka MC & Oyi A (2015). Preparation and Characterization of Lumefantrine PEG 4000 solid dispersions. *World J. Pharma. Res.,* **4**: 444-459.

Patel K, Prasad K and Bajpai M (2011). Enhancement of dissolution rate of domperidone using melt granulation technique. *Der. Pharmacia. Lett.,* **3**: 25-33.

Rahane R and Rachh PR 2018. A review on fast dissolving tablet. *J. Drug Del. Therap.,* **8**: 50-55.

Sadia S, Dhanalakshmi M and Rao BN 2018. Solubility Enhancement of Cefixime throughSolid Dispersion Technique. *World J. Pharm. & Pharma. Sci.,* **7**: 1222-1237.

Shamsuddin MF, Ansari SH and Ali J (2016). Atorvastatin solid dispersion for bioavailability enhancement. *J. Adv. Pharm. Technol. Res.,* 7: 22-26.

Shiv G, Ajay P, Prateek P, Sanket T, Deepu P, Pramod S., Sohanlal C and Shubhangi C (2013). Formulation and evaluation of fast dissolving tablet of ziprasidone HCL. *Am. J. Pharm. Res.,* 3.

Shoaib MH, Tazeen J, Merchant HA and Yousuf RI (2006). Evaluation of drug release kinetics from ibuprofen matrix tablets using HPMC. *Pak. J. Pharm. Sci.,* **19**(2): 119-124.

Soni L, Ansari M, Thakre N, Singh A, Bhowmick M and Rathi J (2017). Development and *in-vitro* evaluation of furosemide solid dispersion using different water Soluble Carriers. *Int. J. Res. Dev. Pharm. Life Sci.,* **6**: 2571-2575.

Teja SB, Patil SP, Shete G, Patel S and Bansal AK (2016). Drug-excipient behavior in polymeric amorphous solid dispersions. *J. Excip. Food Chem.,* **4**(3):70-94

Vasconcelos T, Marques S, Das Neves J and Sarmento B (2016). Amorphous solid dispersions: Rational selection of a manufacturing process. *Adv. Drug Del. Rev.,* **100**: 85-101.

Wu G, Li L, Chen B, Chen C, Luo D and He B (2018). Natural meroterpenoids isolated from the plant pathogenic fungus Verticillium albo-atrum with noteworthy modification action against voltage-gated sodium channels of central neurons of Helicoverpa armigera. *Pest. Biochem. Physiol.,* **144**: 91-99.

Yang XD, Li WS, Tian YJ, Liu CG, Gao DH and Ma HL 2016. Dissolution rate enhancement of repaglinide by solid dispersion. *Trop J. Pharm Res.,* **15**: 1123-1128.

Zaman M and Hanif M (2018). *In vitro* and *ex vivo* assessment of hydrophilic polymer and plasticizer based thin buccal films designed by using central composite rotatable design for the delivery of meloxicam. *Adv. Polym. Tech.,* **37**: 1823-1836.

Zhang D, Zhou C, Lv P, Zhao Y, Liang J, Liao X and Yang B (2018). Preparation and characterization of a novel host-guest complex based on folate-modified β-cyclodextrin and artesunate. *Mat. Sci. Eng. C.,* **86**: 48-55.