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PEG Loaded Solid Dispersion: Solubillity Enhancement of Artesunate

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Abstract

The aim of the present study is to formulate *SOLID DISPERSION* containing Artesunate in different drug to polymer ratio by Solvent Evaporation Method to improve solubility and dissolution rate of poorly water soluble Artesunate by complexation with PEG 6000. The drug carrier interactions in the solid state were investigated using saturated solubility studies, FTIR spectroscopy, X-ray diffraction and differential scanning calorimeter. The developed formulation overcome and alleviates the drawbacks and limitations of Artesunate sustained release formulations and could possibility be advantageous in terms of increased bioavailability of Artesunate. The drug carrier interactions in the solid state were investigated using saturated solubility studies, FTIR spectroscopy, X-ray diffraction and differential scanning calorimeter. The developed formulation overcome and alleviates the drawbacks and limitations of Artesunate sustained release formulations and could possibility be advantageous in terms of increased bioavailability of Artesunate. The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs. The ability to deliver poorly soluble drugs will grow in significance in the coming years as NCEs are relied upon for a larger share of the revenue within the pharmaceutical market by innovator companies. Similarly, generic drug manufacturers will need to employ economically efficient methods of delivery as more low solubility drugs go off patent, in order to maintain a competitive edge and sufficiently compete as profit margins shrink in this price-sensitive industry. Relative to highly soluble compounds, low drug solubility often manifests itself in a host of *in vivo* consequences, including decreased bioavailability, increased chance of food effect, more frequent incomplete release from the dosage form and higher inter patient variability.

Keywords: Artesunate, Solid dispersion. Solubility enhancement, PEG 6000

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1. Introduction

The development of solid dispersions is an appropriate means to overcome insufficient solubility problems in bioavailability, and to guarantee a reasonable bioavailability. Several methods exist to prepare solid dispersions, the melting method being the most convenient. [1] The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles Therefore, based on their molecular arrangement, six different types of solid dispersions can be distinguished. They are described in Moreover, certain combinations can be encountered, i.e. in the same sample; some molecules are present in clusters while some are molecularly dispersed. [6-8]

The effect of the particle size of the drug on their dissolution rates and biological availability was reviewed comprehensively by Fincher. For drugs whose GI absorption is rate limited by dissolution reduction of the particle size generally increases the rate of absorption and or total bioavailability. Oral bioavailability of drugs depends on its solubility and/or dissolution rate, therefore major problems associated with these drugs was its very low solubility in biological fluids, which results into poor bioavailability after oral administration. A drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption.[22]

Therefore, pharmaceutical researchers' focuses on two areas for improving the oral bioavailability of drugs include, Enhancing solubility and dissolution rate of poorly water-soluble drugs.Enhancing permeability of poorly permeable drugs. It has been estimated that 40% of new chemical entities currently being discovered are poorly water soluble. Unfortunately, many of these potential drugs are abandoned in the early stages of development due to the solubility problems. It is therefore important to realize the solubility problems of these drugs and methods for overcoming the solubility limitations are identified and applied commercially so that potential therapeutic benefits of these active molecules can be realized. Therefore lots of efforts have been made to increase dissolution of drug.[24] Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SD) is one of such methods and involves a dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method.The formulation of drugs having low aqueous solubility using solid dispersion technology has been an active area of research since 1960. [35]

Solubility

The term 'Solubility' is defined as maximum amount of solute that can be dissolved in a given amount of solvent to form a homogenous system at specified temperature. The solubility of a drug is represented through various concentration expressions such as parts, percentage, molarity, molality, volume fraction, mole fraction. The pharmacopoeia lists solubility in terms of number of milliliters of solvent required to dissolve 1g of solute. [28]
The Indian pharmacopoeia provides general terms to describe a given range. These descriptive terms are given as:
Table-1 pharmacopoeial Solubility range[29]

Definition	**Parts of solvent required for one part of solute**
Very soluble	< 1
Freely soluble	1 - 10
Soluble	10 - 30
Sparingly soluble	30 - 100
Slightly soluble	100 - 1000
Very slightly soluble	1000 - 10,000
Insoluble	> 10,000

Importance of Solubility

- Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules.
- Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown.
- Currently only 8% of new drug candidates have both high solubility and permeability. [30]

Methods employed to improve Solubility of drugs

Preparation of solid dispersion

Sekiguchi et al., (1961) reported the formulation of eutectic mixture that leads to enhancement of solubility of water soluble drugs .

Solvent evaporation method:

A solution of poorly water soluble guest in suitable organic solvent is added to aqueous solution of PEG-600 and agitated at about 40 to 50 0C for 30 min and toward the end of addition turbidity will develop in the mixture, at the end of this period the solution is filtered, and the moist solid is kept in air/oven for removal of last trace of solvent. [19]

2. Materials and Methods

Pure drug Artesunate was obtained from Avyukt pharmaceuticals, Bengaluru as a gift sample. Polyethylene glycol 6000, Methanol,Potassium dihydrogen phosphate,Sodium hydroxide, Tween 80, poloxamer, was supplied by S.D Fine Chemicals, Ltd, Mumbai,India.

Methods for the Preparation of Solid Complexes

Complexes of ART & PEG-6000 were prepared in the molar ratio of 1:1(on the basis of phase solubility study) by Solvent evaporation.

Solvent evaporation Method:

A solution of ART in methanol was gradually added to equi-molar concentration of ART & PEG-6000 in /Methanol water and agitated at 500C for 30 min and toward the end of addition turbidity developed in the mixture. At the end of this period the solution was filtered, and the moist solid was kept in oven 500C for removal of last trace of solvent. The mass was then pulverized and passed through sieve no 100.

Table.2 Composition of solid complexes by using ART & *PEG-6000*

Type of	ART: *PEG-6000*	Solid dispersion	Media
ASE	1:1	Solvent Evaporation	Methanol

Preparation of Tablets

The composition of the tablets is as shown in Table 3.The basic approach used in the development of oral tablets is the use of disintegrants. disintegrant used was crospovidone (CP).

Table. 3 Preparation of Artesunate tablets

Intragranular							**Extragranular**	
Drug (mg)	**Lactose (mg)**	**MCC (mg)**	**Mannitol (mg)**	**Saccharine (mg)**	**CP (mg)**	**Flavour**	**CP**	**Mg stearate**
6.25	82	27	20	2	4	q.s.	6	2

All the excipient and complex were passed through mesh # 60 respectively. Complex, microcrystalline cellulose (MCC), lactose, saccharine sodium, and disintegrant (CP) were mixed well using a glass mortar and pestle for 15 min. Sufficient amount of water was then added to the mixture to bind the mass. The wet mass was passed through a mesh # 36. The granules were dried in an oven at 60C for ½ hour to achieve moisture content of less than 1%. Dry granules were then mixed with extra granular components (disintegrant & 1% Mg stearate as lubricant) in a mixing jar for 20 min. to obtain uniform mixing. The granules so obtained were ready for compression and compressed into tablets using a 11mm flat-faced punch on a rotary tabletting machine (Rimek Tab letting Machine, MINI PRESS-I, B-tooling). The parameters of machine were set as follows to obtain uniform tablet properties. The weight and hardness of tablet was adjusted to 200mg and 4Kp respectively. Tablets were evaluated for hardness, weight, % friability and disintegration time. The results are the mean of 10 tablets for each formulation.

Standard calibration curve for artesunate in phophate buffer:

Preparation of phosphate buffer solution -PH 6.8

13.61 grams of potassium dihydrogen phosphate and 3.128 grams of sodium hydroxide were dissolved in 2 liters of distilled water.

Procedure:

100 mg Artesunate pure drug was taken into a 100ml standard flask and dissolved in distilled water. The volume of stock solution was made up to 100 ml with distilled water. From the above stock solution, 10 ml was transferred into a 100 ml volumetric flask and volume was adjusted to 100 ml that corresponded to 100 µg/ml Artesunate in solution.

From that solution different aliquots of 0.2, 0.4, 0.6, 0.8, and 1.0 ml were transferred to 10ml volumetric flask, volume was adjusted with distilled water, which gave a concentration of 2, 4, 6, 8,10 and 12 µg/ml of final standard solution and absorbance of final standard solution was measured at 251.8 nm.

Saturation Solubility Studies

Saturation solubility of drug was determined by equilibrating excess of drug in different media at ambient temperature for 48 hours as a function of pH. Table 4 depicts the saturation solubility of Artesunate.

Table.4 Saturation Solubility Studies

Solvents	**Saturation Solubility ±SD(mg/ml)**
pH1.2	0.567±0.028
pH4.5	0.707±0.044
Distilled Water(pH5.5)	0.0085±0.0026
Simulated Saliva(pH6.2)	0.0744±0.0033
pH6.8	0.0131±0.0095
pH7.4	0.0075±0.0014
0.2%SLS	0.405±0.077

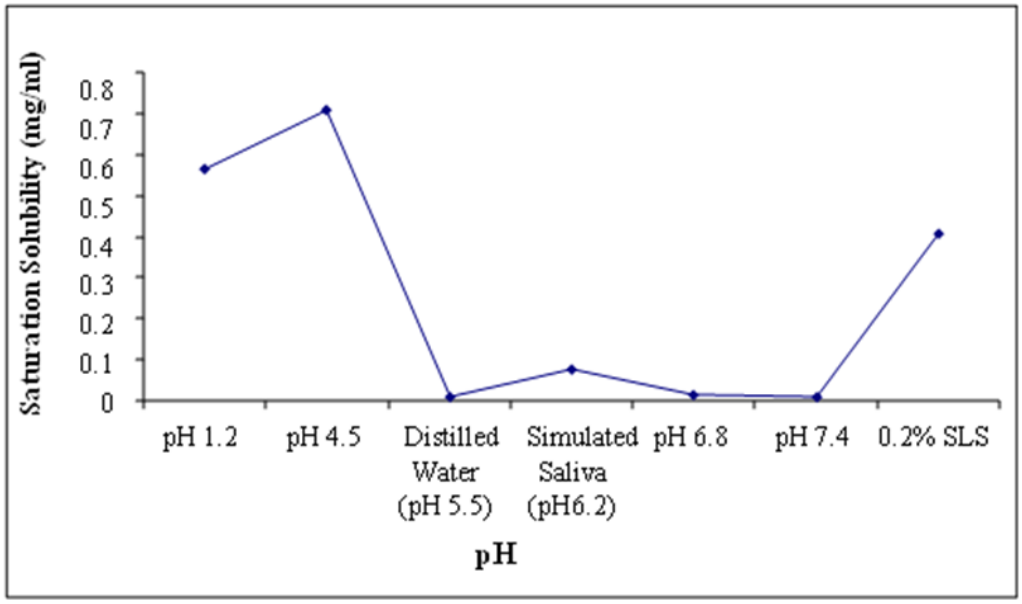

Figure.1 Saturation Solubility in various media.

At acidic pHs of 1 to 4 in buffers, solubility is limited by the solubility of Aretsunate formed in in-situ. The hydrochloride salt generated in-situ in an acidic medium, such as simulated gastric fluid, is less soluble in water Aretsunate itself. It was also observed that solubility increased significantly in 0.2% SLS solution (0.405 ± 0.077) because of reduction in interfacial tension and increased wetting of the drug particles. Increase in solubility (0.0744 ± 0.0033) was also observed in case of simulated saliva due to the presence of Sodium Chloride and Calcium Chloride salts which may contribute to the increased solubility.

3. Results and Discussion

Preparation of Solid Dispersion:

A solution of ART in methanol was gradually added to equi-molar concentration of ART & PEG-6000 in water and agitated at 500C for 30 min and toward the end of addition turbidity developed in the mixture. At the end of this period the solution was filtered, and the moist solid was kept in oven 500C for removal of last trace of solvent. The mass was then pulverized and passed through sieve no 100.

Phase Solubility Studies

The phase solubility diagrams for the complex formation between Artesunate and PEG-6000 is shown in Figure 3. From this curve, it can be seen that the aqueous solubility of Artesunate was increased linearly as a function of the concentration of PEG-6000. Solubility of Artesunate is increased by 7.9 fold at 15 mM concentration of PEG-6000.

The phase-solubility diagram for the complex formation between Artesunate and PEG-6000 was obtained by plotting the changes in guest solubility as a function of PEG-6000 concentration. The diagram obtained was of AN type, according to Higuchi and Connors classification. From the curve it can be seen that the apparent solubility of Artesunate increases due to the formation of a soluble inclusion complex between Artesunate and PEG-6000. It was found that Artesunate forms a stable 1:2 complex with PEG-6000. These results are in support of findings X. Wen, 2003, who reported formation of 1:2 inclusion complex of Artesunate with PEG-6000. The negative deviation from linearity may be associated with PEG induced changes in the dielectric constant of the aqueous complexation media, changes in complex solubility or self-association of PEG molecules. Values of increase in solubility of the drug with PEG-6000 are shown in Table 5.

Table.5 Phase Solubility Studies with β-CD

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Molar Conc. of -2 β-CD(10M)	**Molar solubility of Drug -5 (10M)±SD**
0	2.474±0.03
1.0	5.003±0.015
2.0	7.786±0.020
3.0	9.732±0.01
4.0	10.979±0.11
5.0	11.62±0.09

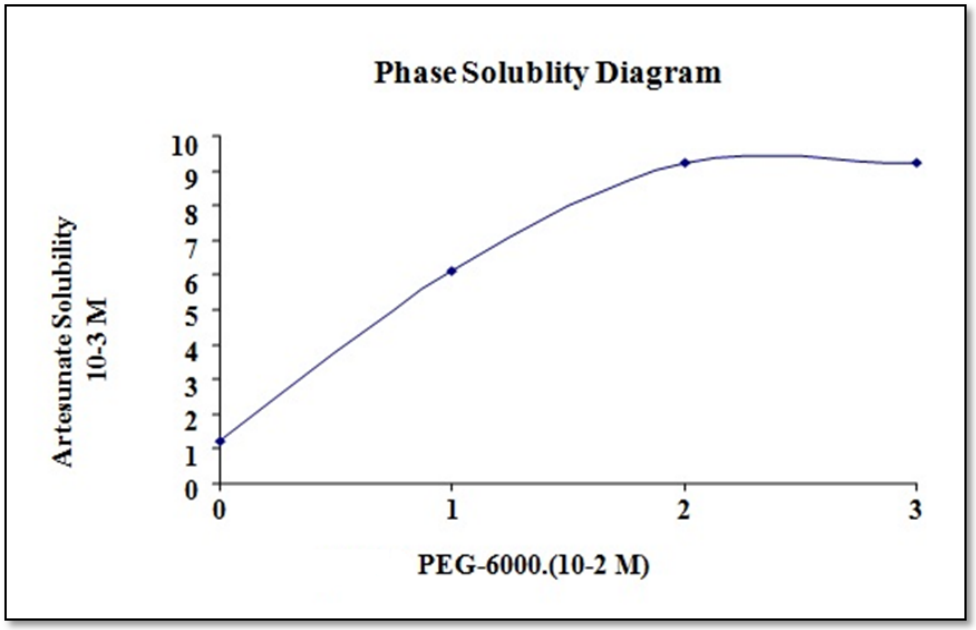

Figure.2 Phase solubility diagram of Artesunate in aqueous solutions of PEG-6000

Fourier-Trans form Infrared Spectroscopy

The FTIR spectra were obtained by using an FTIR spectrometer – 430 (JASCO, Japan).The sample (Artesunate, Phospholipid) were previously ground and mixed thoroughly with potassium bromide in the ratio1:1.5 (Sample: KBr) respectively. The scanning range was 4000 to 400 cm-1. FTIR spectrum of pure drug Artesunate **&** complex shown in fig 4,5.

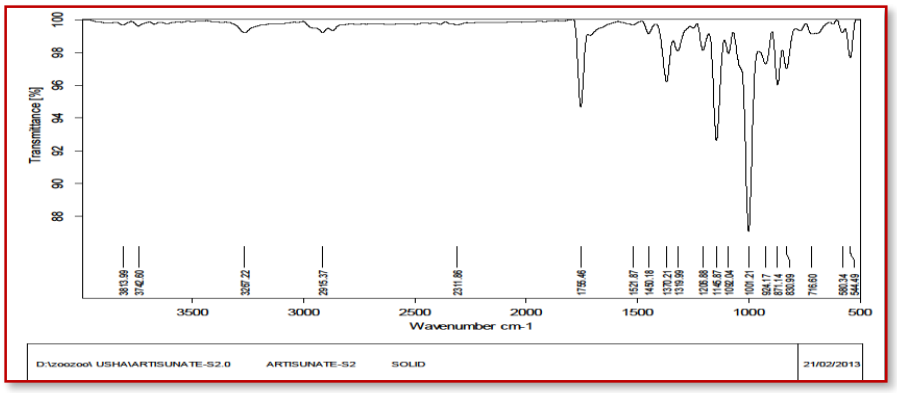

Fig. 3 FTIR spectrum of pure drug Artesunate

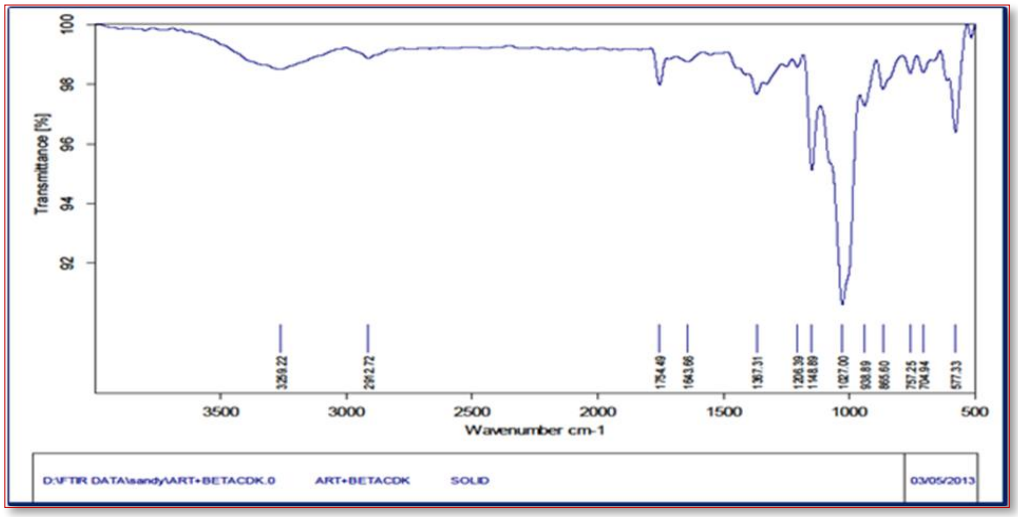

Figure .4 FTIR spectrum of ASE (ART with PEG-600 complex prepare by solvent evaporation Method).

X-Ray Diffractometry

The X-ray diffractometry (XRD) pattern of Artesunate and its complexes with ART & PEG -6000 are shown in fig. 28 (raw data); fig 35-44 (peak search data). The XRD pattern of Artesunate has sharp peak at different angle (2θ) higher intensity 6.72 θ, 14.17θ, 18.97 θ, 22.18 θ, 25.85θ show a tropical crystalline pattern showed diffraction peaks with a higher number of reflections of higher intensity indicating a crystalline structure.

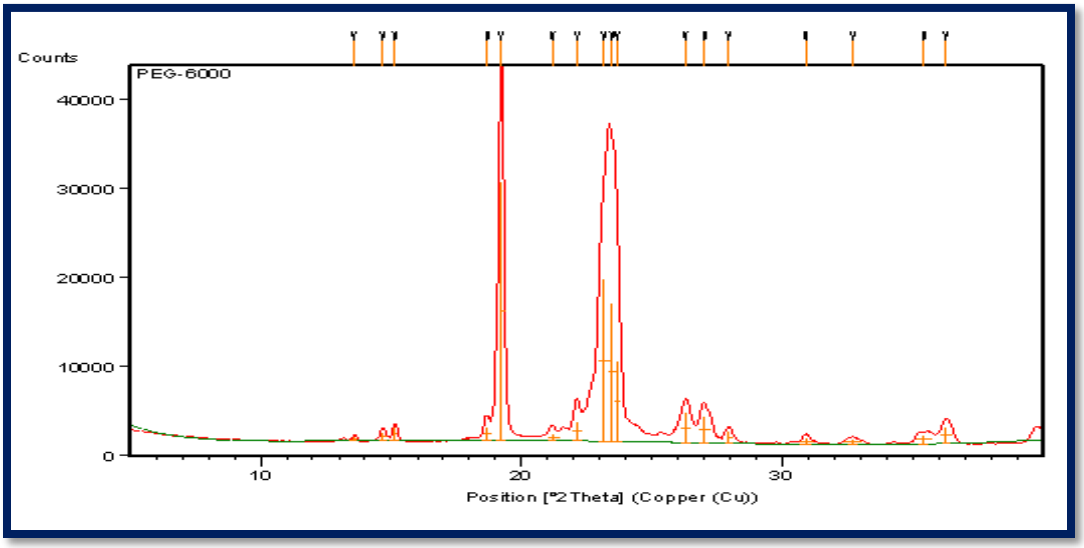

Fig.5 XRD pattern (raw data) of PEG-6000

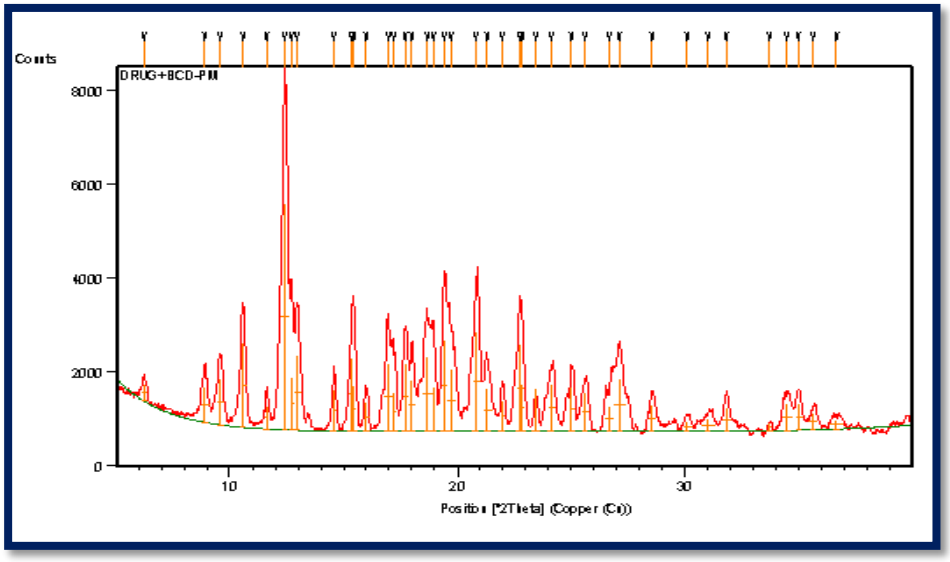

Fig. 6 XRD Pattern of APSE (ART with PEG-6000 complex prepared by solvent evaporation method)

Percent Dissolution Efficiency (%DE)

The dissolution efficiency is a suitable parameter for the evaluation of in-vitro dissolution data. Dissolution efficiency is defined as the area under dissolution curve up to a certain time "t" expressed as percentage of the area of the rectangle described by 100% dissolution in the same time. The obtained % DE of different ART with PEG-6000 complex formulation in phosphate buffer (pH 7.4) at different time interval is presented in table 6.

The % dissolution efficiency of SE formulation - ASEM was found to be sufficiently higher than other formulations. The %DE of ASEM was found to be highest i.e. 61.80, 78.4, and 84.16% at 30, 60 and 90 min interval.

Table.6 % Dissolution efficiency of different ART with PEG-6000Formulations

Formulation	%DE30min	%DE60min	%DE90min
ASE	32.13	48.53	57.18
ASEM	35.13	50.98	59.52

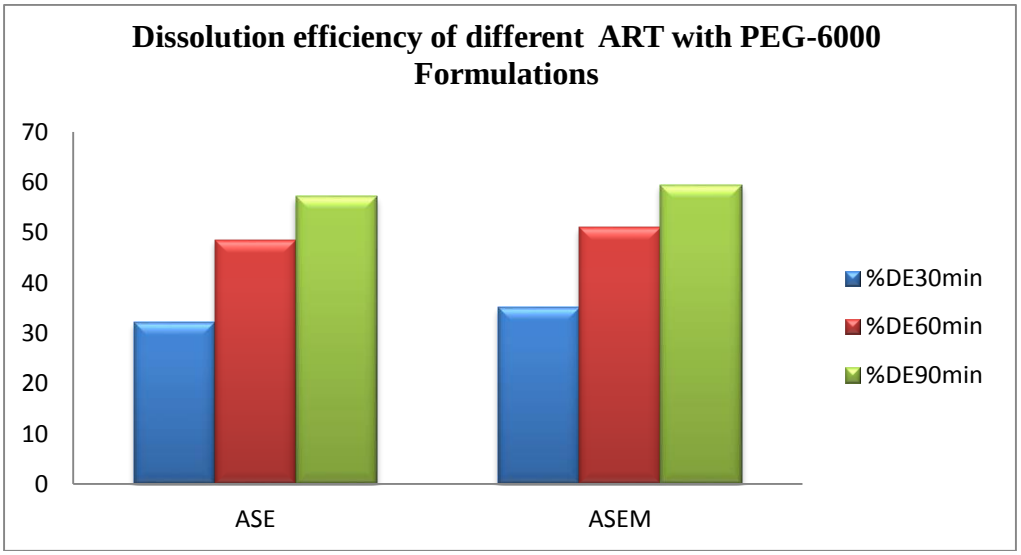

Fig.7 Dissolution efficiency of different ART with PEG-6000 in water & Methanol Formulations

Dissolution Profile of Tablets

Different formulations of ART were compressed into tablets as per the composition given in table 7. the tablet thickness and hardness were in the range of 3.6-3.8 mm and 5-6 Kg/cm2,
respectively.

Table.7 Drug content of ART+ β-CD complexes (% Drug content)

Time(min)	% Drug Release from the formulations(mean;n=3)	
	ASEM	ASE
0	0	0
10	40.48	25.2
20	48.18	41.1
30	65.12	55.4
40	74.82	63.1
50	81.13	68.4
60	90.1	70.2
70	93.23	74.1
80	95.25	80.1
90	97.25	82.2
100	98.37	84.2

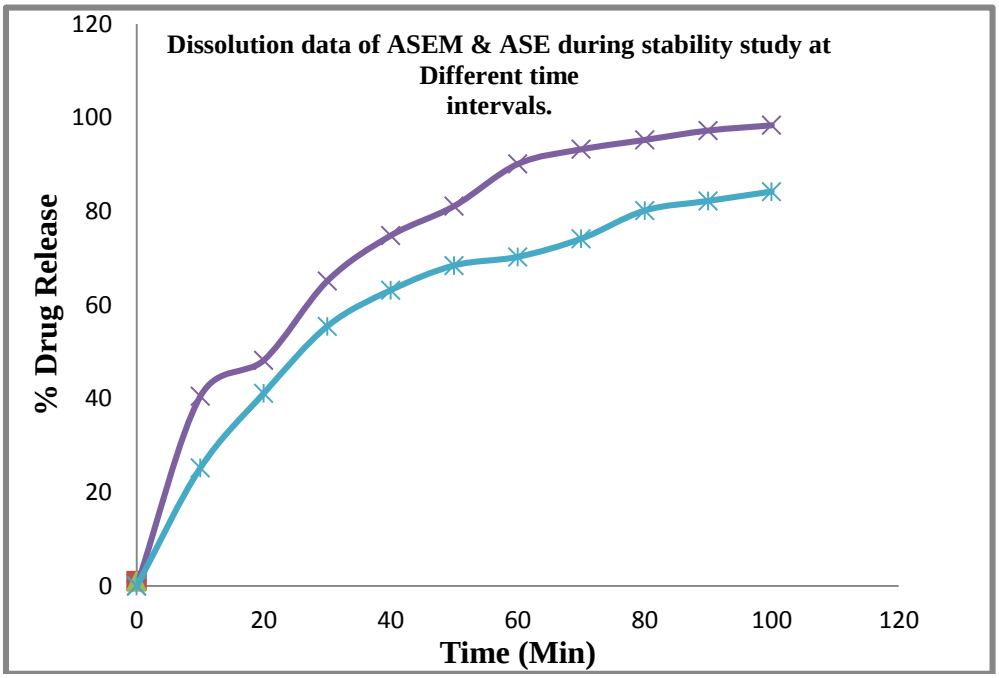

Figure.8 Comparison of % Drug content drug content of different formulation

Saturation Solubility of Different Formulations of Artesunate

The saturation solubility of pure ART and its complexes with β -CD is shown in table 8**.** The saturation solubility of pure ART is 11.9µg/ml while the saturation solubility of all other complex prepared by various methods exhibited dramatic increase in the saturation solubility. APM and PEG-6000 (complex prepared by physical mixing) showed a lower value for saturation solubility than that of other complexes, the low saturation solubility can be attributed to poor complexation efficiency during solvent evaporation.

Table.8 Saturation solubility data of different formulation of Artesunate with PEG-6000

Formulation	**Saturation solubility (µg/ml)**
Pure ART	12.05 ± 0.23
ASE	101.65 ± 2.65
ASEM	109.34 ± 2.24

Mean saturation solubility ± SD (n=3)

Formulation Stability Study

Based on the result of initial characterization the kneaded formulations (AKM, and APKM) were thought to be the superior formulations and hence were subjected to accelerated stability study.

Table. 9 Dissolution data of AKM & APKM during stability study at Different time intervals

Time(Min.)	%Drug Release from the formulations(mean;n=3)			
	Initial		After3months	
	ASEM	ASE	ASEM	ASE
0	0	0	0	0
10	40.48	25.2	40.32	24.86
20	48.18	41.1	47.98	41.01
30	65.12	55.4	65.12	55.4
40	74.82	63.1	74.82	63.1
50	81.13	68.4	81.13	68.4
60	90.93	70.2	90.71	70.01
70	93.23	74.1	92.63	73.45
80	95.25	80.1	94.55	79.46
90	97.25	82.2	97.21	82.01
100	98.37	84.2	97.21	83.91

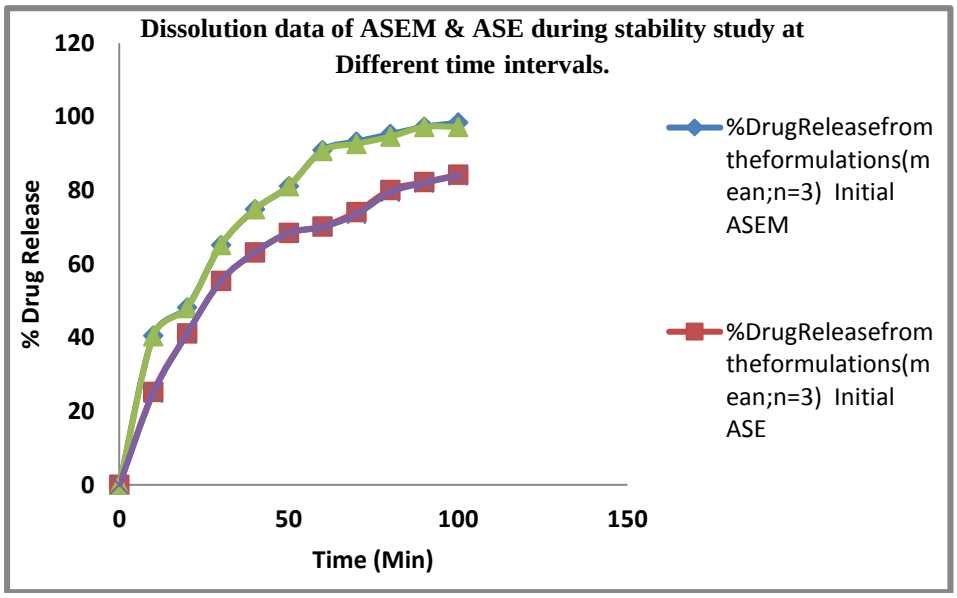

Fig. 11 Dissolution profile of ASEM & ASE during stability study

Discussion

The phase solubility study showed that the solubility of Artesunate increases linearly as a function of PEG-6000 over the entire concentration range and was characteristic of the AL type of curve and it suggests that water-soluble complex was formed in solution. Solubility studies showed a significant, linear increase in the aqueous solubility of the Artesunate with increasing concentration of PEG-6000, maximum concentration of PEG-6000 (12.67mM/L) so improvements in the saturation solubility of Artesunate. The complex of Artesunate with PEG-6000 prepared successfully by the physical mixing, kneading, solvent evaporation and fusion methods in the molar ratio of 1:1. This was confirmed by FTIR and XRD studies. PEG-6000 (PEGs) improve solubility significantly they are still limited in their drug inclusion capacity and retain disadvantageous processing characteristics for oral dosage forms; the volume of (PEGs) complexes is often much greater than the volume of drug alone, which may severely limit the types of delivery technologies that may be employed The saturation solubility of the drug in the freeze-dried complex and spray-dried complex was increased to 29.33±1.08 mg/ml and 28.76±0.56mg/ml respectively.

4. Conclusion

Thus it can be concluded that Artesunate should contain a stabilizing agent to protect its conversion in lactone form. Here, PEG-6000 proved a better stabilizing agent than buffering agent, which not only increased the solubility of the drug but also acts as a stabilizer in drug formulation. Thus the complexation of Artesunate has a dual advantage over the existing formulation.

The results of drug content of the Solvent Evaporation complexation are in good agreement with the theoretical value. The ASEM ternary showed 109.34 ± 2.24 of drug due to lesser drug loss as compared to the spray dried ternary which showed drug content of 101.65 ± 2.65

5. Acknowledgement

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