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Der Pharmacia Sinica, 2015, 6(6):27-40

Der Pharmacia Sinica
ISSN: 0976-8688
CODEN (USA): PSHIBD

Solubility enhancement technique for an anti-malarial drug using amino acid

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ABSTRACT

Atovaquone is an Anti-malarial agent and is used in the treatment of malarial complications as chemoprophylaxis. The present research work is focused with an aim to increase solubility and hence dissolution rate of Atovaquone by using the various techniques of preparation of solid dispersion. The polymers like Kollidon VA-64 were used for solid dispersion using amino acids like Arginine was used. For preparation of solid dispersions, various solid dispersion methods (Solvent evaporation, Spray drying) were used. The effect of several variables to both solid dispersion preparations was investigated. IR and UV spectral analysis, Diffrential Scanning Calorimetry were used to characterize solid dispersions. Solid dispersions prepared by various methods were evaluated by methods like Saturation solubility, percent drug content, and by in -vitro dissolution method for percent cumulative drug release. Optimised solid dispersions were further evaluated by XRD, DSC, and SEM. The release rate for pure Atovaquone was found to be 46.7% in 2 hours. This release rate was increased by using amino acid that is arginine in ratio 1:1:1 to 1:1:4. By keeping Arginine constant and only increasing polymer the dissolution rate was improved from 76.6% to 84.4% when solvent evaporation method was used to prepare solid dispersions. The same compositions on spray drying showed increased dissolution rate from 97.5% to 100% in 100 minutes with Kollidon VA-64.

Keywords: Atovaquone; Solid Dispersion; Solubility; *Invitro* dissolution Study; arginine

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INTRODUCTION

Malaria is a disease caused by a parasite called Plasmodium species which are of four types *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malaria*, which lives part of its life in humans and part in mosquitoes (Annopheles). Atovaquone is an Anti-malarial agent and is used in the treatment of malarial complications as chemoprophylaxis. This drug works by inhibiting the mitochondrial electron transport chain at the bc1 complex. Inhibition of bc1 activity results in a loss of mitochondrial function. During the intra-erythrocyte stage of infection, a key role of the parasite mitochondrion is to provide orotate for pyrimidine biosynthesis through the activity of dihydro orotate dehydrogenase (DHODH). Atovaquone is a unique naphthoquinone with broad-spectrum of antiprotozoal activity. It is effective for the treatment and prevention of malaria. Atovaquone is currently used as a fixed-dose combination with proguanil (Malarone) for treating children and adults with uncomplicated malaria or as chemoprophylaxis for preventing malaria in travelers. [1, 2]

Therapeutic effectiveness of a drug depends upon the bioavailability and in turn upon the solubility. The poor aqueous solubility and dissolution rate of API is one of the biggest challenges in pharmaceutical development and is becoming more common among new drug candidates over the past two decades due to the use of high throughput and combotorial screening tools during the drug discovery and selection phase. Rate of dissolution influences the onset, intensity and duration of response of drugs. The rate of dissolution gains more importance as it is rate limiting step in the absorption process. It hence controls the overall bioavailability of the drug from the dosage form. Since

the aqueous solubility of drug influences its dissolution rate it is one of the key determinants of bioavailability of drug. Therefore, one of the major challenges of the pharmaceutical industry is to apply strategies that improve the dissolution and apparent solubility of poorly soluble drugs to develop such problematic compounds into orally bioavailable and therapeutic effective drugs.

Physical modifications often aim to increase the surface area, solubility and/or wettability of the powder particles and are therefore focused on particle size reduction or generation of amorphous states. Several methods have been employed to improve the solubility of poorly water soluble drugs. A solid dispersion technique has been used by various researchers who have reported encouraging results with different drugs. The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole. [3, 4]

Concept of solid dispersion: [5, 6]
The concept of solid dispersions was originally proposed by Sekiguchi and Obi, who investigated the generation and dissolution performance of eutectic melts of a sulphonamide drug and a water-soluble carrier in the early 1960s. Solid dispersions represent a useful pharmaceutical technique for increasing the dissolution, absorption and therapeutic efficacy of drugs in dosage forms. 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.

Definition:
Solid dispersion as defined by Chiou and Riegelman refers to "the dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by melting (fusion), solvent or melting-solvent method." However the dispersion of a drug or drugs in a solid carrier or carriers by traditional mechanical mixing is not considered a solid dispersion.

Factors responsible for observing faster dissolution of drug in solid dispersion:
❖Extremely small particle size of the solid, dispersed molecularly.
❖Solubilization effect of carrier, which acts in the diffusion layer surrounding the particles.
❖Absence of aggregation and agglomeration of particle.
❖Improved wettability of drug due to carrier.
❖Stabilization of metastable forms of drug.

Advantages of solid dispersion:
1. Enhancement of the rate and extend of absorption leading to reduction in dose.
2. Enhancement of dissolution and associated rapid absorption leading to reduction in proportion of presystemic drug metabolism.
3. Potential for acting as sustained release dosage form.

Disadvantages of solid dispersion:
1. Susceptibility of amorphous or molecularly dispersed drug to changes in their physical form during storage.
2. Crystallization of drugs in solid dispersions, reducing the dissolution rate.
3. Decomposition of drug and development of tackiness during the preparation of solid dispersions.

MATERIALS AND METHODS

Table No. 1: List of chemicals/Materials

Sr. No.	Name of Chemical/Material	Manufacturer/Supplier
1.	Atovaquone	Glenmark Industries, Mumbai
2.	Kollidon VA-64	BASF India Pvt. Ltd., Mumbai
3.	L-Arginine	Research Lab. Mumbai
4.	Dichloromethane	Research Lab. Mumbai
5.	Iso-propyl alcohol	Loba Chemie, Mumbai
6.	Methanol	Research Lab. Mumbai
7.	Acetone	Loba Chemie, Mumbai

Characterization of Atovaquone and Excipients: [7-11]
Preparation of calibration curve of Atovaquone:
i) In methanol
10 mg of Atovaquone was accurately weighed and transferred to 100 ml volumetric flask. It was dissolved in methanol and sonicate for 10 min and volume was adjusted with methanol to get stock solution (100 µg/ml). This was further diluted with methanol to give concentrations 5, 10, 15, 20, 25 µg/ml. Absorbance was measured at 276.5 nm and calibration curve was plotted.

ii) In PBS

10 mg of Atovaquone was accurately weighed and transferred to 100 ml volumetric flask. It was dissolved in little quantity of methanol and Phosphate buffer pH 7.4 + 30% Iso propyl alcohol combined solvent system and sonicate for 10 min. then volume was adjusted with Phosphate buffer pH 7.4 + Iso propyl alcohol to get stock solution (100 µg/ml). This was further diluted with Phosphate buffer pH 7.4 + 30% Iso propyl alcohol to give concentrations 5, 10, 15, 20, 25 µg/ml. Absorbance was measured at 277.5 nm and calibration curve was plotted.

iii) In distilled water

10 mg of Atovaquone was accurately weighed and transferred to 100 ml volumetric flask. It was dissolved in little quantity of methanol + distilled water + 30%Iso propyl alcohol combined solvent system and sonicate for 10 min then volume was adjusted with distilled water + Iso propyl alcohol. This was diluted with distilled water + 30% Iso propyl alcohol to give concentrations 5, 10, 15, 20, 25 µg/ml. Absorbance was measured at 277.5 nm and calibration curve was plotted.

Preparation and Evaluation of solid dispersion of Atovaquone with Kollidon VA- 64 + Arginine by solvent evaporation method:

Required quantities of Atovaquone, Kollidon VA-64+Arginine, + Arginine (as carrier) in ratio given in **Table No. 7.1** were accurately weighed and added in glass beaker containing Dichloromethane, Iso propyl alcohol and distilled water solvent system. The final solution was stirred until a clear solution was obtained and poured in the Petri dish. The solvent was then removed at 60^0C until dry solid mass was obtained. The product was then pulverized and sieved through 60 meshes. The sieved product was collected and stored in tightly closed containers and used for further study.

Table No. 2: Composition of solid dispersion prepared using Kollidon VA- 64 + Arginine by solvent evaporation method

Carrier used	Solid dispersion system	Method	Drug : Carrier Ratio
Kollidon VA-64 +Arginine	ASD 1	SE	1:1:1
	ASD 2	SE	1:1:2
	ASD 3	SE	1:1:3
	ASD 4	SE	1:1:4
	ASD 5	SE	1:2:1
	ASD 6	SE	1:3:1
	ASD 7	SE	1:4:1

SE – Solvent Evaporation method

Preparation of solid dispersions of Atovaquone with Arginine using Kollidon VA-64 by spray drying method:

Required quantities of Atovaquone, Arginine and Kollidon VA-64 (the carrier) in ratio 1:1:3 and 1:1:4 (Atovaquone: Arginine: Polymer) were accurately weighed and added in glass beaker containing Dichloromethane , Iso propyl alcohol and distilled water solvent system. This solution was stirred until clear solution was obtained. The clear solution was spray dried to obtain a free flowing powder and stored in tightly closed containers until further used.

Table No. 3: Composition of solid dispersion of Atovaquone with Arginine using Kollidon VA-64 prepared by spray drying method

Carrier used	Solid Dispersion system	Method	Atovaquone: Carrier Ratio (Drug: Arginine: Polymer)
Kollidon VA-64 +Arginine	SASD 1	SD	1:1:3
	SASD 2	SD	1:1:4

SD – Spray drying method

Table No. 4: Parameters used for preparation of Solid dispersions of Atovaquone by spray drying method

Parameters	Conditions
Inlet temperature	60^0C
Outlet temperature	50^0C
Inlet high	70^0C
Outlet high	60^0C
Cool temperature	25^0C
Feed pump flow rate	45 nm/m^3
Aspiration flow rate	1 ml/min

Evaluation of solid dispersion of Atovaquone [12, 13]

The prepared solid dispersions were evaluated for

i. Saturation solubility:

To each of the glass vials containing 3 ml of distilled water, excess quantities of Atovaquone and each of the solid dispersions were added separately. These vials were shaken on orbital shaker for 48 hours. The resulting solutions were filtered through membrane filter 0.45µ; appropriate dilutions were made and the absorbance was recorded at

277.5 nm.

ii. Spectral characteristics:

a. UV –visible spectra:

Atovaquone powder and its solid dispersion with different carriers were dissolved in dichloromethane and phosphate buffer containing iso propyl alcohol solvent system and further diluted with PBS 7.4 pH containing 30% iso propyl alcohol. UV spectra of these solutions were recorded and λ max values were compared.

b. IR spectra:

The IR spectra of Atovaquone, individual carriers alone and solid dispersions of Atovaquone with each of carrier were recorded by FTIR-8000 by ATR technique. The presence or absence of major functional groups was noticed in the spectra.

iii. Drug content:

The percentage of Atovaquone content in each of the solid dispersions was estimated by dissolving quantity of solid dispersion equivalent to 10 mg of Atovaquone in 10 ml solvent system containing dichloromethane and iso propyl alcohol. The solutions were further diluted with methanol and the UV absorbances were recorded at 276.5 nm. The contents were estimated using previously prepared calibration curve of Atovaquone in methanol.

iv. In vitro drug release study:

Quantities of each type of solid dispersions equivalent to 20 mg of Atovaquone were subjected to dissolution test using USP XXII (Type- II) tablet dissolution test apparatus. Accurately weighed 20 mg Atovaquone was also subjected to similar test.

Parameters used for dissolution test of Atovaquone and its solid dispersions:

- Apparatus type : USP XXII(Type- II)
- Dissolution medium : 500ml of PBS of pH7.4 +30% IPA
- Speed of paddle : 100 rpm
- Temperature of dissolution medium : $37^0C \pm 0.5^0C$
- Aliquots of sample withdrawn : 1 ml
- Dilution of aliquots : Up to 5 ml
- Frequency of sampling : Every 20 min up to 2 hours

Procedure:

Atovaquone or its solid dispersion powders were filled in empty capsule and placed in dissolution medium and apparatus was run. Aliquots (1 ml) were withdrawn at previously decided frequency. Same volume of fresh dissolution medium which was maintained at same temperature was added after each withdrawal. The samples were filtered through Whattman filter paper (No 41) and further diluted up to 5 ml with dissolution media and then the absorbance were measured at 277.5 nm for PBS of pH 7.4 +30 % Isopropyl alcohol. Cumulative drug release (%) was found out at each time point.

v. X-Ray diffraction study:

X-ray diffraction pattern of the selected complexes were compared with that of plain Atovaquone. The powder X-ray diffraction pattern of drug was carried out using Brukuer AXS D-8 Advance Diffractometer (Germany) with Cu line as a source of radiation. This was done by measuring the 2θ in the range of $3\text{-}50^0$ with reproducibility of ±0.001 on a diffractometer.

\vi. Differential Scanning Calorimetric analysis:

DSC analysis was carried out using Mettler instrument. Solid dispersion was placed in platinum crucible and the DSC thermogram was recorded at a heating rate of 10^0 C/min in the range 40^0C to 300^0C. Nitrogen gas was purged at the rate of 30 ml/min to maintain inert atmosphere.

vii. Scanning Electron Microscopy:

The external morphology of solid dispersion was studied by Scanning Electron Microscopy (SEM). The sample for SEM was prepared by lightly sprinkling powder on a double adhesive tape stuck to an aluminium stub. Afterwards, the stubs containing the coated samples were placed in the Scanning Electron Microscope (JEOL JSM-6360, Japan) chamber. The sample was then randomly scanned and photomicrographs were taken at the acceleration voltage of 10 kV and the results of SEM were reported.

RESULTS AND DISCUSSION

Spectral analysis:

a. Spectral analysis of Atovaquone in methanol

The UV spectrum of Atovaquone in methanol indicated λ max at wavelength 276.5 nm.

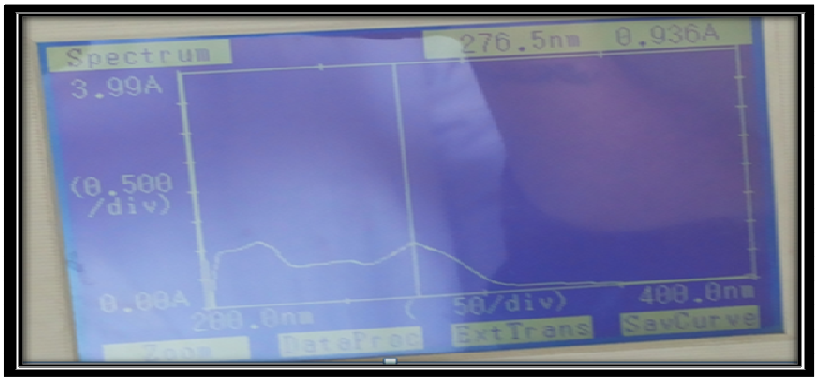


Fig No. 1: λ max of Atovaquone in methanol

Standard Calibration curve of Atovaquone in Methanol, pH 7.4 phosphate buffer and distilled water:

Table No. 5: Standard Calibration curve of Atovaquone in Methanol, pH 7.4 phosphate buffer and distilled water

Concentration (mcg/ml)	Abs in Methanol + 30% IPA	Abs pH 7.4 phosphate buffer + 30% IPA	Abs in distilled water + 30% IPA
0	0	0	0
5	0.375	0.300	0.266
10	0.668	0.562	0.512
15	0.936	0.820	0.768
20	1.180	1.116	0.998
25	1.607	1.448	1.226

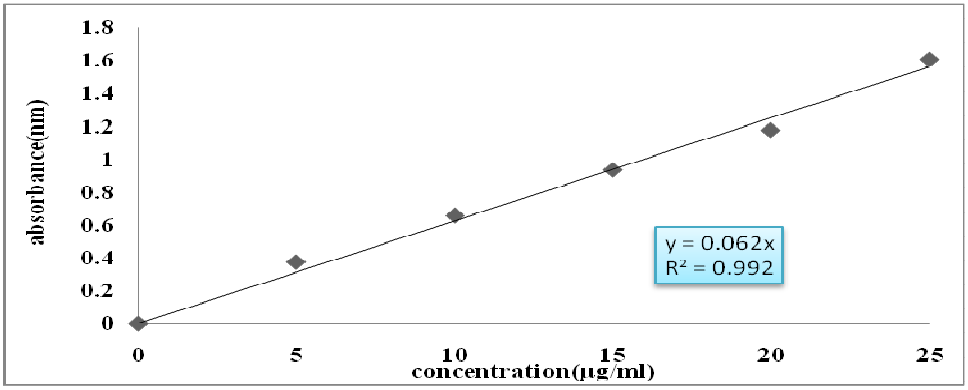


Fig No. 2: Standard curve of Atovaquone in methanol

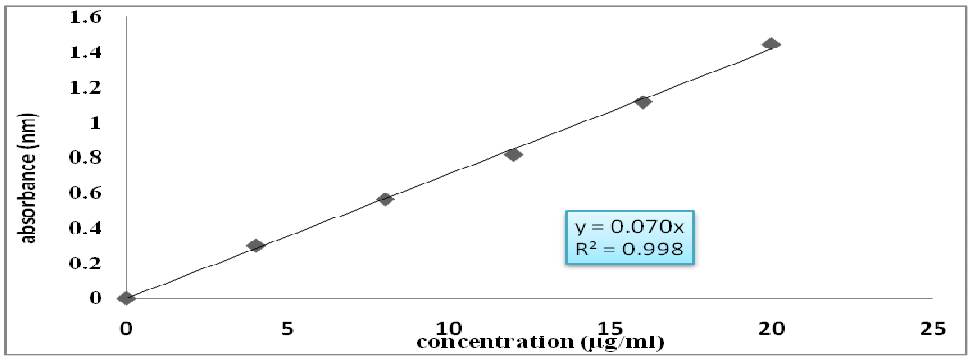


Fig No. 3: Standard curve of Atovaquone in phosphate buffer pH 7.4 + 30% Iso propyl alcohol

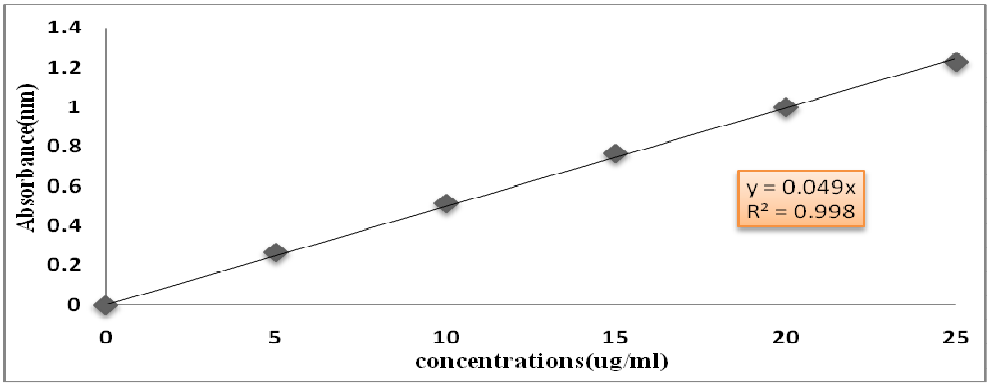


Fig. No. 4: Standard curve of Atovaquone in distilled water + 30% isopropyl alcohol

b. Infrared spectrum of Atovaquone:

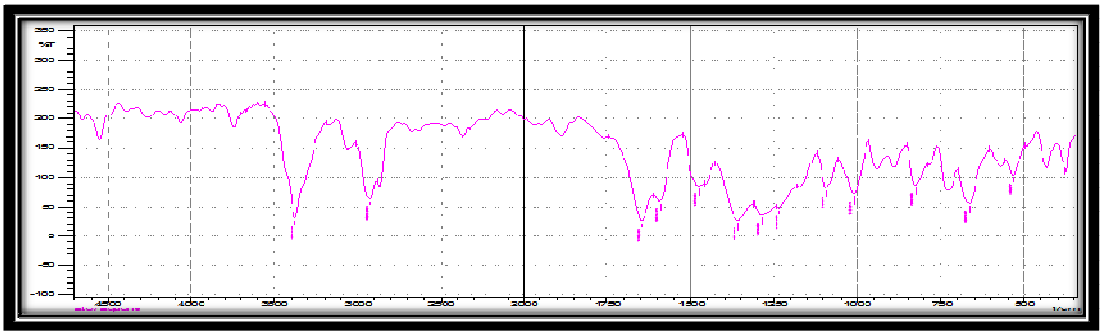


Fig. No. 5: Infrared spectrum of sample of Atovaquone

Interpretation of infrared spectrum of sample of Atovaquone:

Table No. 6 : Peaks observed in infrared spectrum of Atovaquone

IR Frequency (cm^{-1})	Assignments of bands
3366.67	O –H stretch (phenolic group)
2922.25	CH_2-, CH_3 alkanes
1647.26	C-C diketone group
1591.33	C= O stretch (primary amide)
663.53	C – Cl bending vibration

The IR spectrum of Atovaquone reveals the presence of major functional group in the structure of Atovaquone supporting its identity **(Table No. 8.5 and Fig. No. 8.4)**

Determination of saturation Solubility:
Saturation solubility of Atovaquone was found to be as given in **Table No. 8.6**

Table No.7: Saturation solubility of Atovaquone

Solvent	Saturation solubility (µg/ml)
Distilled water	3.98
Phosphate buffer pH 7.4	4.12

Thermal behavior – Differential Scanning Calorimetry (DSC):

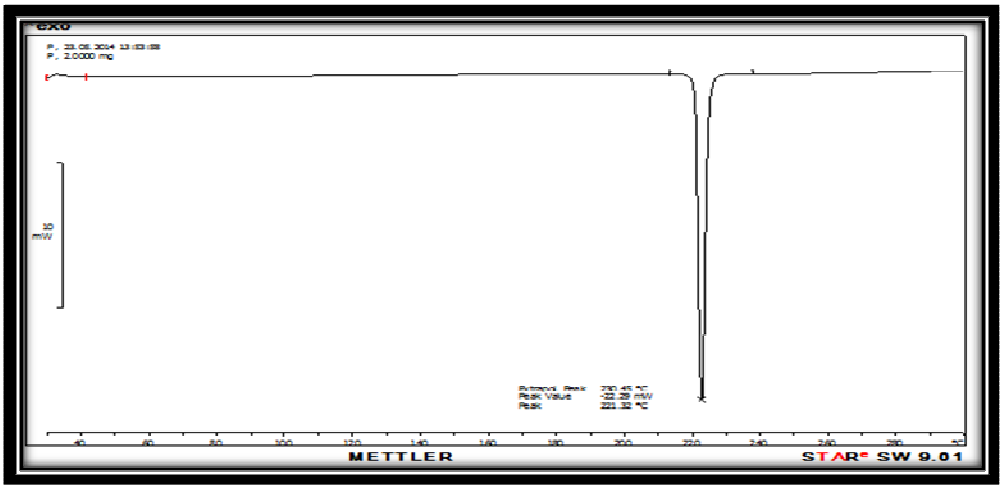


Fig. No. 6: DSC pattern for Atovaquone (pure)

Powder X-ray diffraction pattern:

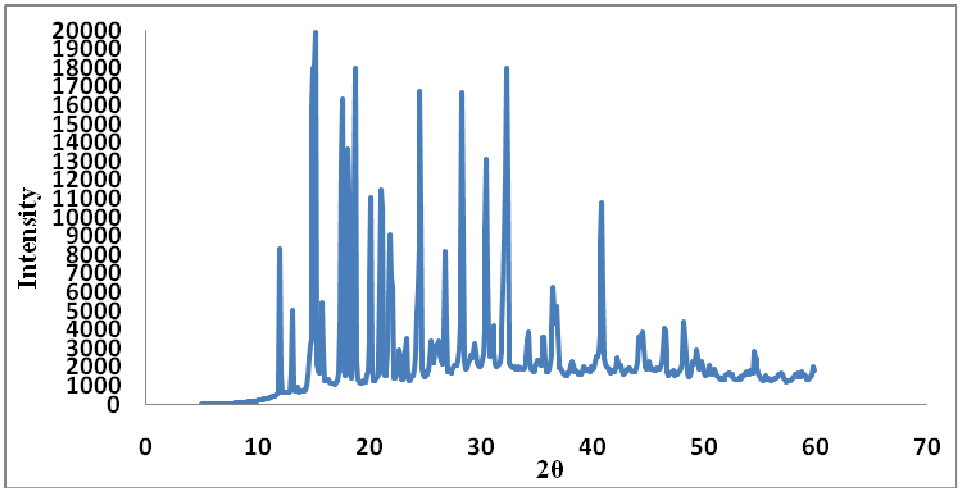
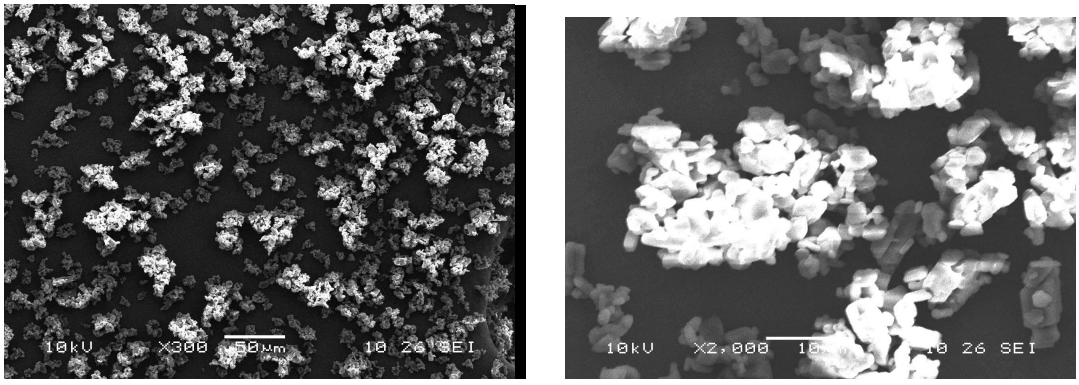


Fig. No. 7: XRPD pattern for Atovaquone (pure)

Scanning Electron Microscopy of Atovaquone (SEM):



[A] **[B]**

Fig. No. 8: Scanning Electron microphotograph of Atovaquone (pure)

Evaluation of Atovaquone Solid dispersions

Saturation solubility of solid dispersion of Atovaquone prepared with Kollidon VA 64 + Arginine in distilled water

Table No. 8: Saturation solubility of solid dispersion of Atovaquone prepared with Kollidon VA 64 + Arginine in distilled water

Carrier used	Solid Dispersion system	Method	Drug: carrier& Drug::amino acids: Polymer	Saturation solubility µg/ml ± S.D.
----	Pure drug	--	--	3.98 ± 0.26
Kollidon VA-64 +Arginine	ASD1	SE	1:1:1	44.12 ± 0.45
	ASD2	SE	1:1:2	47.41 ± 0.26
	ASD3	SE	1:1:3	52.41 ± 0.35
	ASD4	SE	1:1:4	54.11 ± 0.48
	ASD5	SE	1:2:1	25.29 ± 0.40
	ASD6	SE	1:3:1	22.71 ± 0.30
	ASD7	SE	1:4:1	20.88 ± 0.21

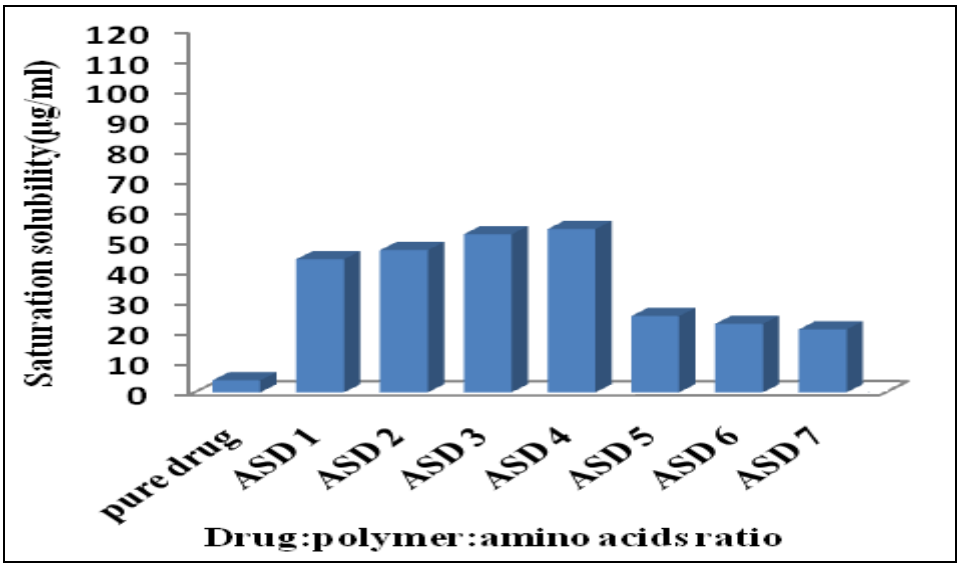


Fig. No. 9: Bar diagram for saturation solubility of solid dispersion of Atovaquone prepared with Kollidon VA-64 + Arginine in distilled water by solvent evaporation method

Saturation solubility of solid dispersions of Atovaquone prepared with Kollidon VA-64 Arginine in distilled water:

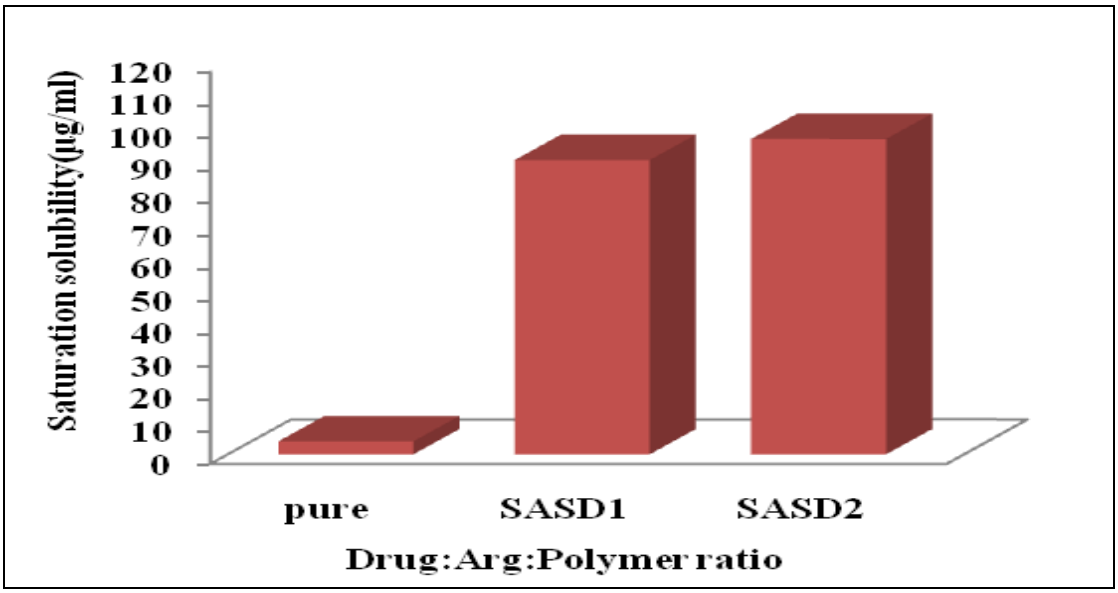


Fig. No.10: Bar diagram for saturation solubility of solid dispersion of Atovaquone prepared with Kollidon VA-64 + Arginine in distilled water by spray drying method

Table No. 9: Saturation solubility of solid dispersions of Atovaquone prepared with Arginine using Kollidon VA-64 in distilled water by spray drying method

Carrier used	Solid Dispersion system	Method	Drug: carrier ratio (Drug: polymer)	Saturation solubility µg/ml ± S.D.
--	Pure drug	--	--	3.98 ± 0.26
Kollidon VA64 +Arginine	SASD 1	SD	1:1:3	91.11 ± 0.47
	SASD 2	SD	1:1:4	95.44 ± 0.51

All values are expressed as mean ±SD, n=3

Spectral analysis:

UV spectral analysis:

The UV spectra indicated λ max at near about 277.5 nm for all solid dispersions. These values are almost identical with that of pure Atovaquone (277.5 nm). Hence it can be concluded that there was no probable interaction between drug and carriers used for the preparation of solid dispersions.

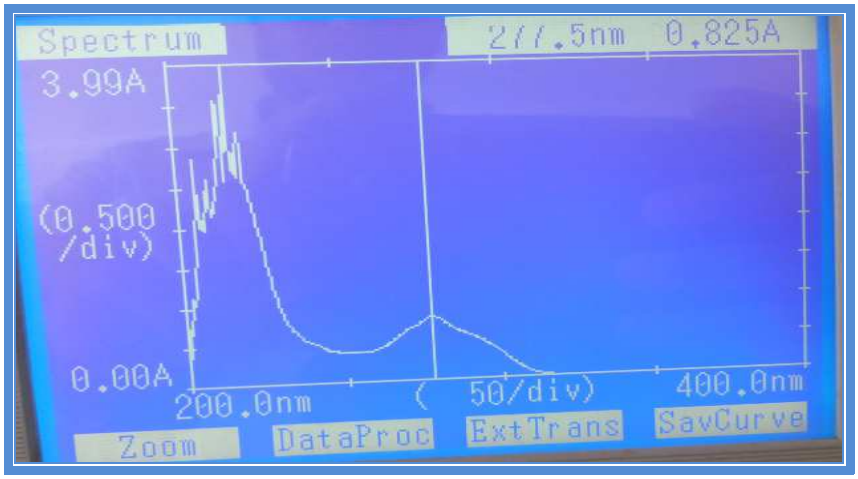


Fig. No. 11: λ max of Atovaquone solid dispersion with Kollidon VA-64 + Arginine

X-Ray powder diffraction studies of solid dispersions:

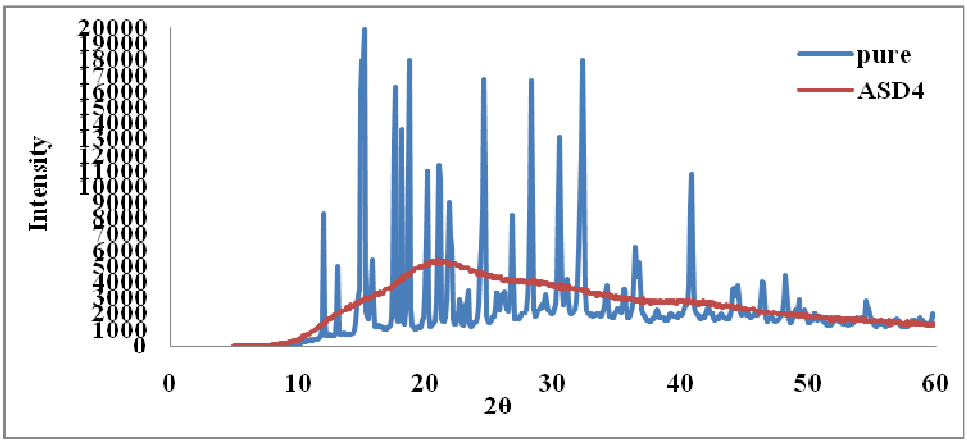


Fig. No. 12: XRD pattern for Atovaquone (pure) and solid dispersion of Atovaquone prepared using Kollidon VA-64 + Arginine (ASD 4) by solvent evaporation method

Differential Scanning Calorimetry:

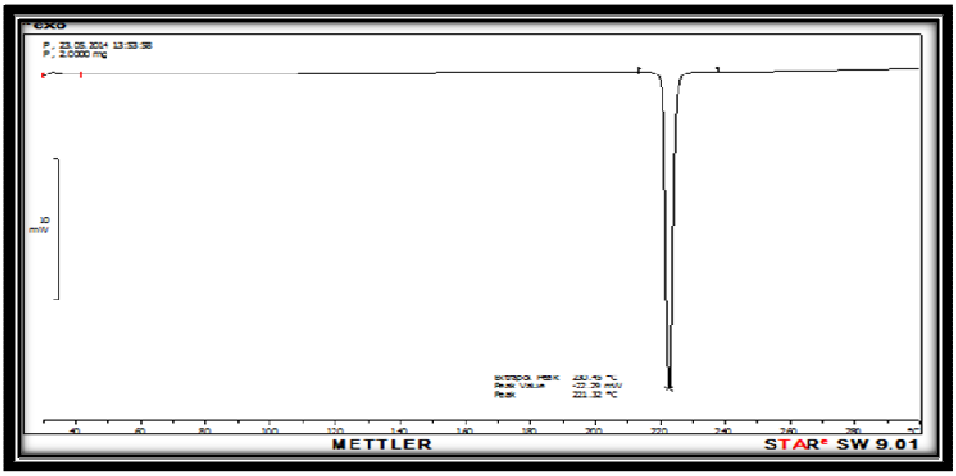
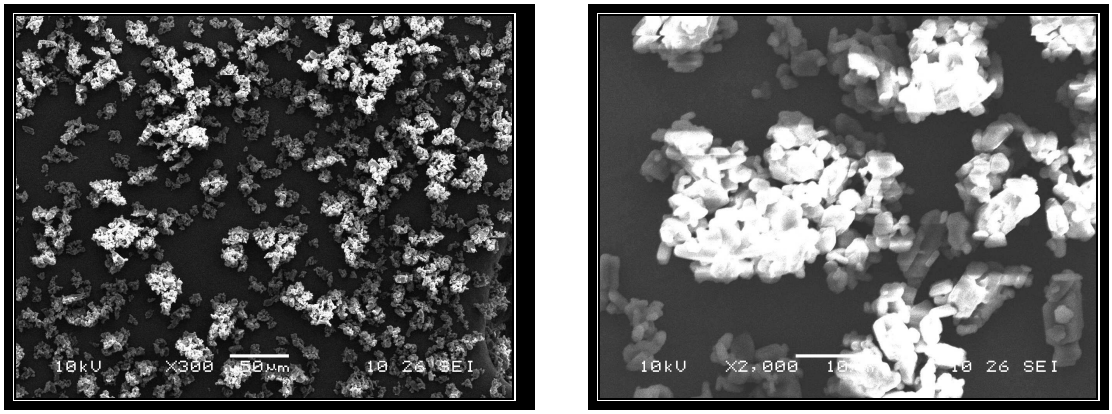


Fig. No. 13: DSC thermogram of Atovaquone (pure)

vii. Scanning Electron Microscopy (SEM):



[A] [B]

Scanning Electron Micrograph of Atovaquone (pure)

b. IR spectral analysis:

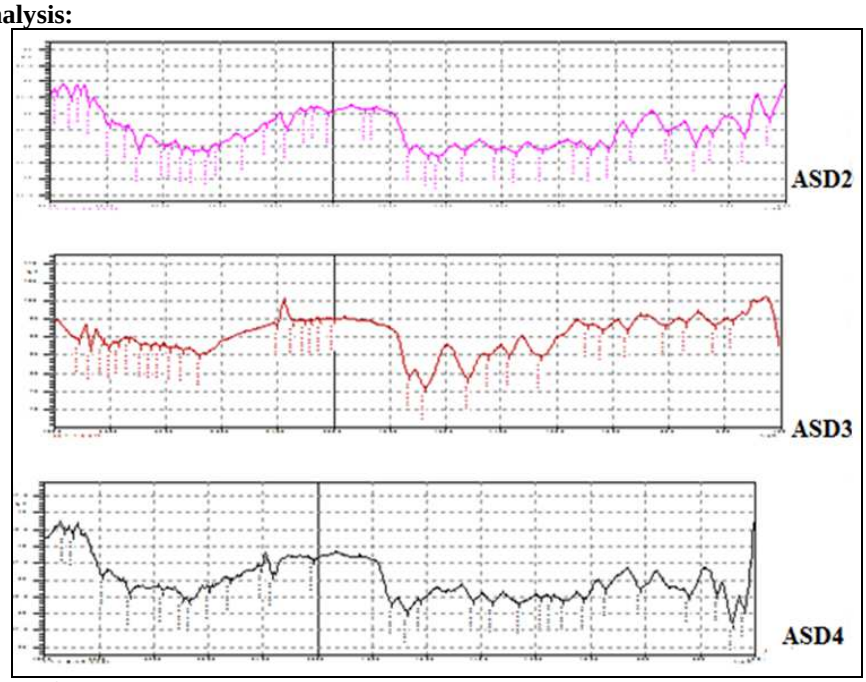


Fig. No. 14: IR spectra of Atovaquone (pure), Kollidon VA-64, Arginine and solid dispersions prepared by solvent evaporation method

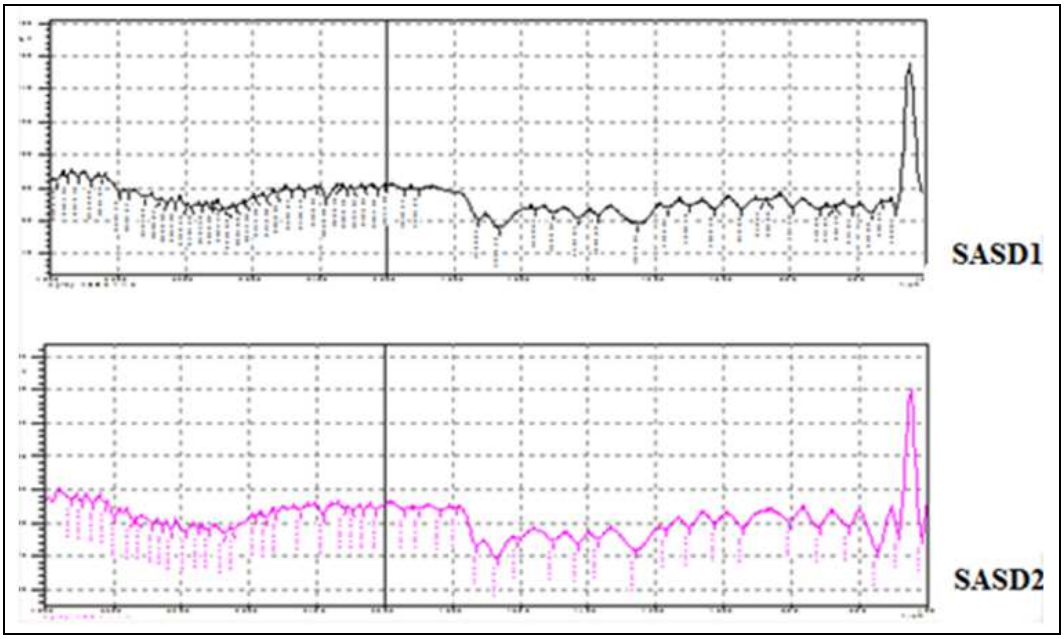


Fig No. 15: IR spectra of Atovaquone (pure), Kollidon VA-64, Arginine and solid dispersions prepared by spray drying method

Atovaquone content estimation:

Table No. 10: Percent Atovaquone content of various solid dispersions systems prepared by solvent evaporation method

Carrier used	Solid dispersion system	Method	Drug: Carrier ratio(Drug: Polymer) & (Drug: Amino A.: Polymer)	% Atovaquone content ± S. D.
KollidonVA64 +Arginine	ASD 1	SE	1:1:1	98.88 ± 0.42
	ASD 2	SE	1:1:2	99.36 ± 0.36
	ASD 3	SE	1:1:3	99.36 ± 0.22
	ASD 4	SE	1:1:4	99.92 ± 0.15
	ASD 5	SE	1:2:1	96.81 ± 0.35
	ASD 6	SE	1:3:1	96.33 ± 0.24
	ASD 7	SE	1:4:1	96.17 ± 0.41

All values expressed as mean ±SD, n=3

Table No. 11: Percent Atovaquone content of various solid dispersions systems prepared by spray drying method

Carrier used	Solid dispersion system	Method	Drug: Carrier ratio(Drug: Polymer) & (Drug: Arginine: Polymer)	% Atovaquone content ± S. D .
KollidonVA64 +Arginine	SASD 1	SD	1:1:3	99.36 ± 0.38
	SASD 2	SD	1:1:4	99.52 ± 0.20

All values expressed as mean ±SD, n=3
SD – Spray drying method

iv. *In-vitro* dissolution study:

Table No. 12: Dissolution data for solid dispersions of Atovaquone prepared with Kollidon VA-64 + Arginine by solvent evaporation method in PBS pH 7.4 + 30% Iso propyl alcohol

Time (min.)	Cumulative Atovaquone release (%)				
	Atovaquone (pure)	ASD 1	ASD 2	ASD 3	ASD 4
20	2.9 ± 0.50	15.1 ± 0.58	19.3 ± 0.22	21.9 ± 0.52	23.3 ± 0.29
40	10.3 ± 0.29	43.8 ± 0.60	46.9 ± 0.66	50.7 ± 0.85	54.4 ± 0.33
60	19.7 ± 0.42	56.8 ± 0.81	59.2 ± 0.33	62.3 ± 0.51	66.1 ± 0.54
80	29.6 ± 0.35	67.2 ± 0.56	73.6 ± 0.22	75.4 ± 0.68	79.3 ± 0.29
100	38.2 ± 0.38	69.6 ± 0.38	76.9 ± 0.54	78.3 ± 0.70	82.4 ± 0.44
120	46.7 ± 0.26	76.6 ± 0.40	79.3 ± 0.69	81.3 ± 0.59	84.4 ± 0.15

All values are expressed as mean ±SD, n=3

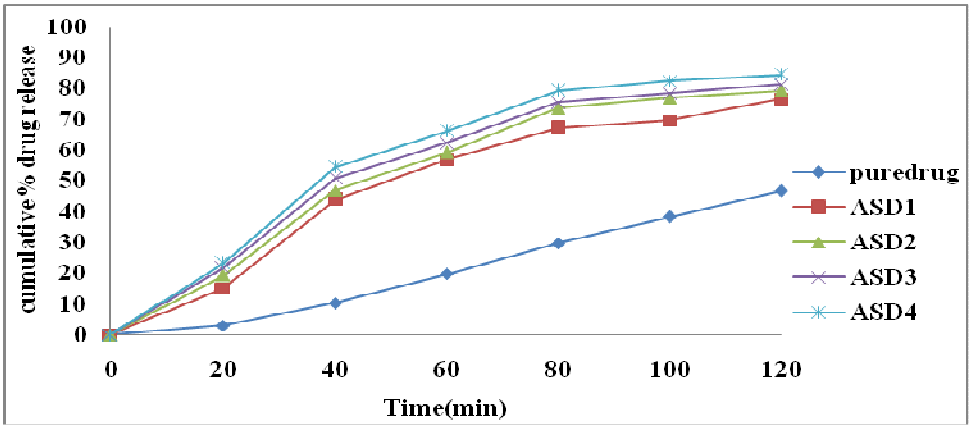


Fig. No. 16: Dissolution data for solid dispersion of Atovaquone in different ratios with Kollidon VA-64 + Arginine prepared by solvent evaporation method

Formulations ASD1-ASD4 was studied for *in vitro* drug release. Results shown that solid dispersions prepared with Kollidon VA64 + Arginine by solvent evaporation method shown the increase in dissolution as compare to plain drug. At 120 min batch ASD1 gave 76.6% & batch ASD4 gave 84.4% drug release. Dissolution of solid dispersion shown that dissolution rate increases with increase in concentration of Kollidon VA-64.

Table No. 13: Dissolution data for solid dispersions of Atovaquone prepared with Kollidon VA-64 + Arginine by solvent evaporation method in PBS pH 7.4 + 30% Iso propyl alcohol

Time (min.)	Cumulative Atovaquone release (%)				
	Atovaquone (pure)	ASD 1	ASD 5	ASD 6	ASD 7
20	2.9 ± 0.55	15.1 ± 0.52	3.1 ± 0.28	6.1 ± 0.58	10.8 ± 0.28
40	10.3 ± 0.24	43.8 ± 0.64	14.4 ± 0.64	20.9 ± 0.88	36.9 ± 0.32
60	19.7 ± 0.42	56.8 ± 0.84	26.7 ± 0.30	31.3 ± 0.54	47.4 ± 0.52
80	29.6 ± 0.38	67.2 ± 0.57	36.5 ± 0.20	44.7 ± 0.64	61.7 ± 0.22
100	38.2 ± 0.32	69.6 ± 0.36	48.8 ± 0.56	53.2 ± 0.72	65.3 ± 0.46
120	46.7 ± 0.22	76.6 ± 0.44	54.2 ± 0.65	65.2 ± 0.54	70.1 ± 0.82

All values are expressed as mean ±SD, n=3

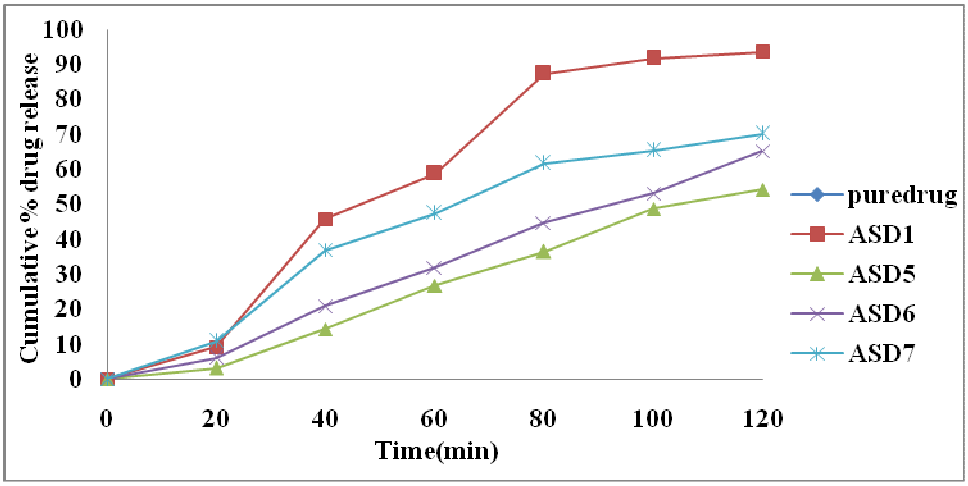


Fig. No. 17: Dissolution data for solid dispersion of Atovaquone in different ratios with Kollidon VA-64 + Arginine prepared by solvent evaporation method

Formulations ASD1, ASD5, ASD6, and ASD7 were studied for *in vitro* drug release. Results shown that solid dispersions prepared with Kollidon VA64 + Arginine by solvent evaporation method shown the increase in dissolution as compare to plain drug. At 120 min batch ASD1 gave 76.6% & batch ASD4 gave 70.1% drug release. Here dissolution decreases because of concentration of Arginine was increased, so it kept constant in further formulations.

Table No. 14: Dissolution data for solid dispersions of Atovaquone prepared with Kollidon VA-64 + Arginine by spray drying method in PBS pH 7.4 + 30% Iso propyl alcohol

Time (min.)	Cumulative Atovaquone release (%)		
	Atovaquone (pure)	SASD 1	SASD 2
20	2.9 ± 0.54	44.6 ± 0.22	49.6 ± 0.20
40	10.3 ± 0.22	89.5 ± 0.26	92.8 ± 0.60
60	19.7 ± 0.44	93.3 ± 0.38	96.7 ± 0.55
80	29.6 ± 0.38	95.4 ± 0.66	98.8 ± 0.28
100	38.2 ± 0.34	97.5 ± 0.78	100.1± 0.48
120	46.7 ± 0.28	99.5 ± 0.70	

All values are expressed as mean ±SD, n=3

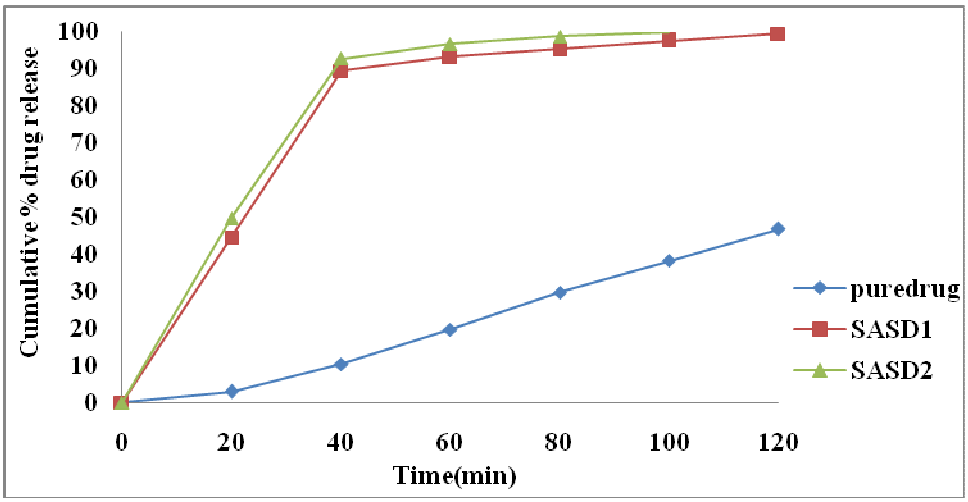


Fig. No. 18: Dissolution data for solid dispersion of Atovaquone in different ratios with Kollidon VA-64 + Arginine prepared by spray drying

Formulations SASD1-SASD2 were studied for *in vitro* drug release. Results shown that solid dispersions prepared with Kollidon VA64 + Arginine by spray drying shown the increase in dissolution as compare to plain drug. At 120 min batch SASD1 gave 99.5% & batch SASD2 gave 100% drug release in 100 min. Dissolution of solid dispersion shown that dissolution rate increases with increase in concentration of Kollidon VA-64.

CONCLUSION

From the findings of various physical and chemical tests, it can be concluded that Solid dispersions method significantly improved the dissolution profile of Atovaquone. IR and UV spectral analysis of solid dispersions indicated that there was no probable interaction between drug and carriers. Dissolution rate of solid dispersions increased with increased concentration of polymer like Kollidon VA-64. Solid dispersions prepared by spray drying method showed more solubility enhancement with enhanced dissolution as compared to solid dispersions prepared by solvent evaporation method. SEM studies showed well separated, dense spherical particles with a smooth surface of Atovaquone.

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