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SOLUBILITY ENHANCEMENT OF ATORVAQUONE USING SOLID DISPERSION TECHNIQUE

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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 , Gelucire 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.

Keywords: *Anti malarial, Solid Dispersions, Atorvoquone, Kollidon, Gelucire.*

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INTRODUCTION:

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion. From a patient's perspective, swallowing a dosage form is a comfortable and a familiar means of taking medication. As a result, patient compliance and hence drug treatment is typically more effective with orally administered medications as compared with other routes of administration, for example: parenteral.

MATERIALS AND METHODS:

Atavoquone was gifted by VerGo Pharma Research Pvt. Ltd.Mumbai, India, Kollidon, Gelucire were purchased from sigma Aldrich.

Phase Solubility Studies

Phase solubility studies were done by taking different concentrations of Kollidon VA 64, gelucire 44/14& 50/13 (2%,4%,6%,8% and 10%), in distilled water [1-4]. To each of these concentrations excess amount of drug was added. Then these solutions were kept for shaking on shaker for 48 h. After 48 h samples were filtered through the whatman filter paper then the solution diluted and estimated for drug dissoved. Three determinations were carried out for each sample to calculate the solubility of each drug.

Formulation Of Solid Dispersions

Preparation 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 600C 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.

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.

Preparation of calibration curve of Atovaquone: In methanol

Calibration curve of Atovaquone was plotted by using UV visible spectroscopic method at 276.6 nm. Linearity was observed between 5-25 µg/mL. Absorbance values obtained are given in table 1 and calibration curve plotted is shown in figure1. Regression equation obtained was used to estimate the Atovaquone from in vitro samples.

Table 1: Absorbance values obtained for Atovaquone

Concentration (µg/mL)	Absorbance (at 276.5 nm)
0	0
5	0.366
10	0.656
15	0.933
20	1.25
25	1.53

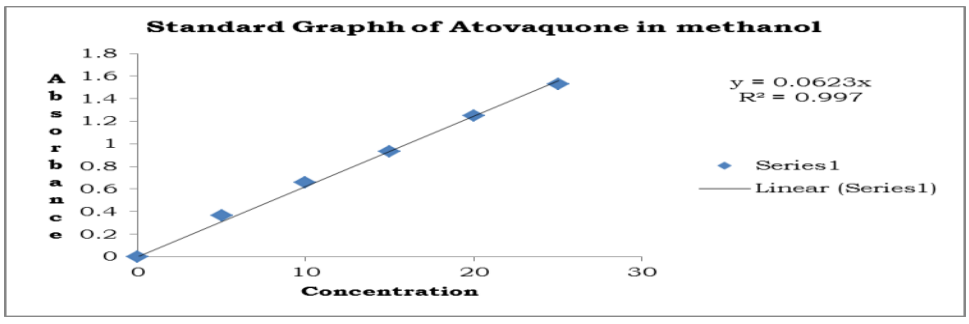

Fig 1: Standard Graph of Atovaquone

Table 2: Micromeritic properties of Atovaquone (n=3)

BULK DENSITY (g/cm^3) (Mean ± SD)	TAPPED DENSITY (g/cm^3) (Mean ± SD)	ANGLE OF REPOSE (Mean ± SD)	CONSOLIDATION INDEX (Mean ± SD)	HAUSNER'S RATIO (Mean ± SD)
0.69 ± 0.05	0.94 ± 0.02	$31^0 22'' \pm 10''$	11-15± 0.11	1.12-1.18±0.03

Preformulation Studies of Pure Drug

Micromeritic properties of Atovaquone obtained are given in table 2. It was observed from the results that the drug is having poor flow characteristics. The angle of repose value was found to be $31^0 22'' \pm 10''$ indicates good flow of powder.

Determination of saturation Solubility: Saturation solubility of Atovaquone was found to be as given in Table No 3.

Table3: Saturation solubility studies of Atovaquone

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

Selection of Hydrophilic/Lipid Based Carriers: Different hydrophilic and lipophilic carriers selected to prepare solid dispersions are given in table 4.

Table 4: List of Carriers (Hydrophilic/Lipid Based) used to prepare solid dispersions

S. No	Name of the hydrophilic carrier
1	Kollidon VA 64
2	Gelucire 44/14
3	Gelucire 50/13

Phase Solubility Studies

Phase solubility studies were done by taking different concentrations of Kollidon VA 64, Arginine, gelucire 44/14& 50/13 (2%,4%,6%,8% and 10%) in distilled water. Results obtained are given in table 5 and pictorially represented in figure 2. It was observed from the results that as the concentration of carrier is increased from 2% to 10%, the solubility was increased linearly (A_L type curve was followed).

Table 5: Phase solubility studies of Atovaquone with Kollidon VA 64

S. No.	Solvent	Solubility (mg/mL) (mean ± SD) (n=3)
1	Double Distilled Water	4.145±0.132
2	2 % Kollidon VA 64 in Water	8.46 ±0.63
3	4 % Kollidon VA 64 in Water	13.45 ±0.81
4	6 % Kollidon VA 64 in Water	20.32 ±1.3
5	8 % Kollidon VA 64 in Water	28.30 ±2.31
6	10 % Kollidon VA 64 in Water	35.14 ±2.24

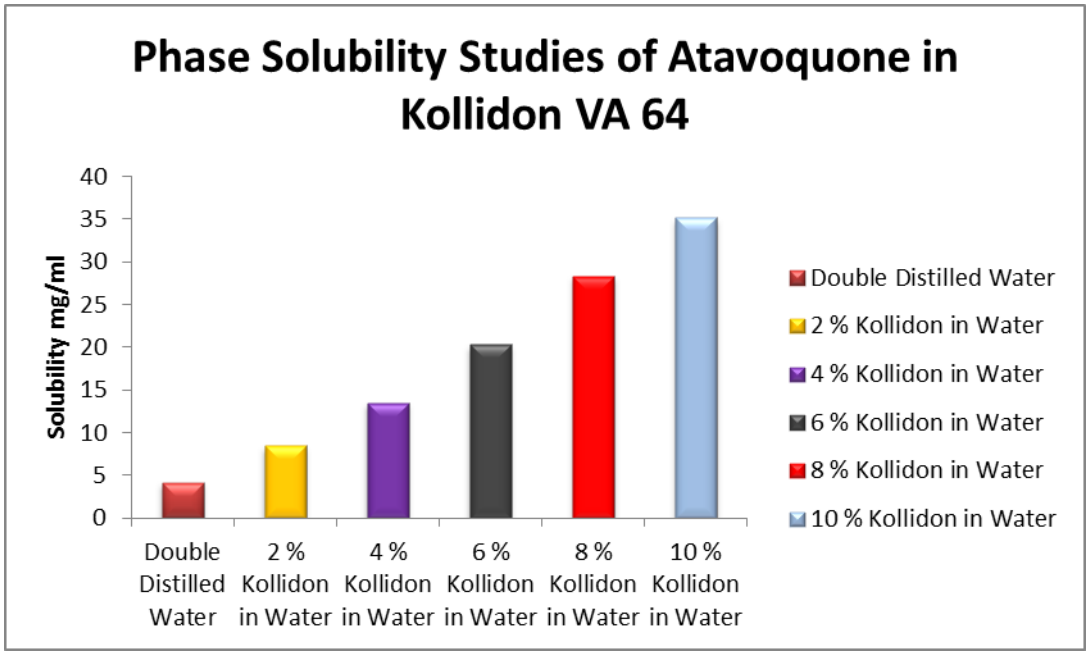

Fig 2: Phase solubility profile of Atovaquone with Kollidon VA 64

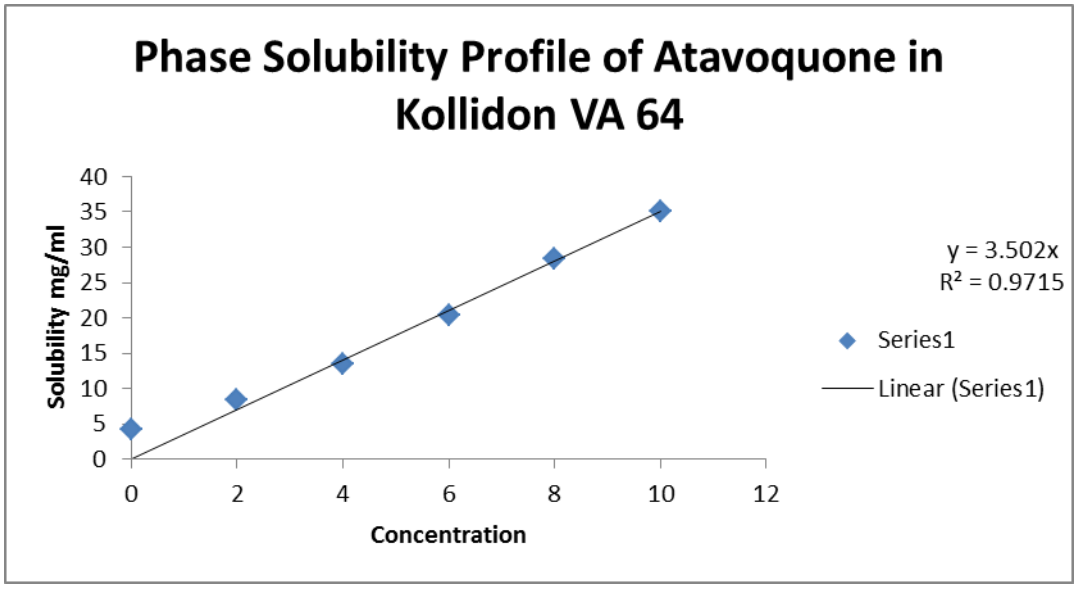

Fig 3: A_L type curve of Atovaquone with Kollidon VA 64

Table 6: Phase solubility studies of Atovaquone with Gelucire 44/14

S. No.	Solvent	Solubility (mg/mL) (mean ± SD) (n=3)
1	Double Distilled Water	4.145±0.132
2	2 % Gelucire in Water	45.16 ±1.07
3	4 % Gelucire in Water	89.31 ±2.27
4	6 % Gelucire in Water	119.23 ±2.42
5	8 % Gelucire in Water	156.23 ±3.17
6	10 % Gelucire in Water	197.34 ±4.27

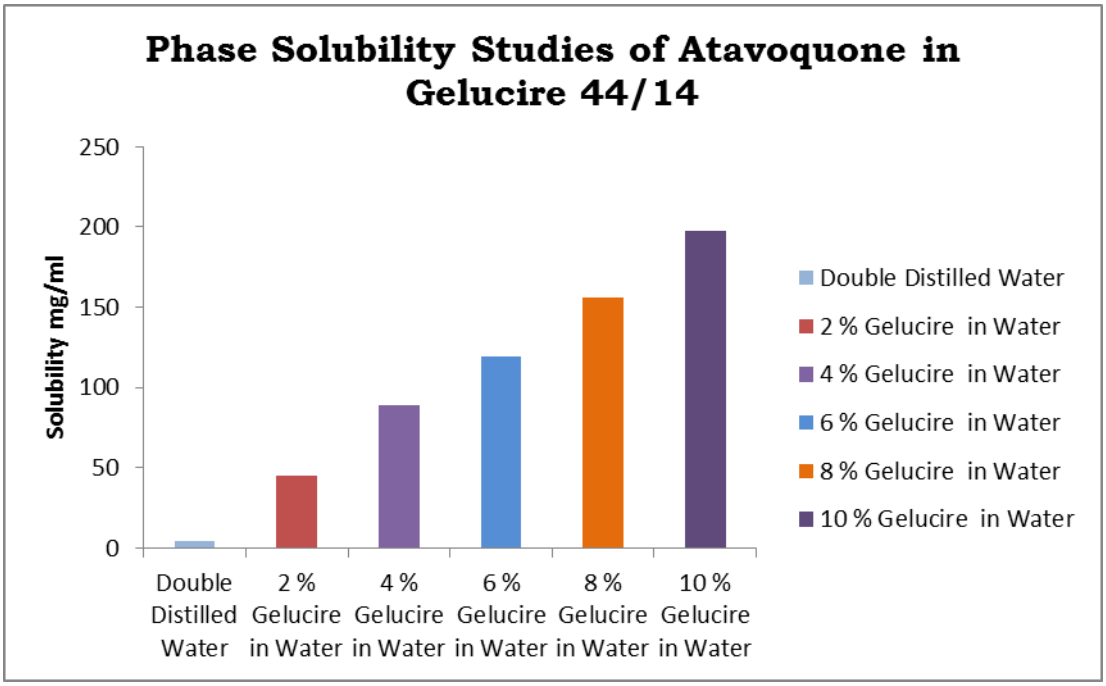

Fig 4: Phase solubility profile of Atovaquone with Gelucire 44/14

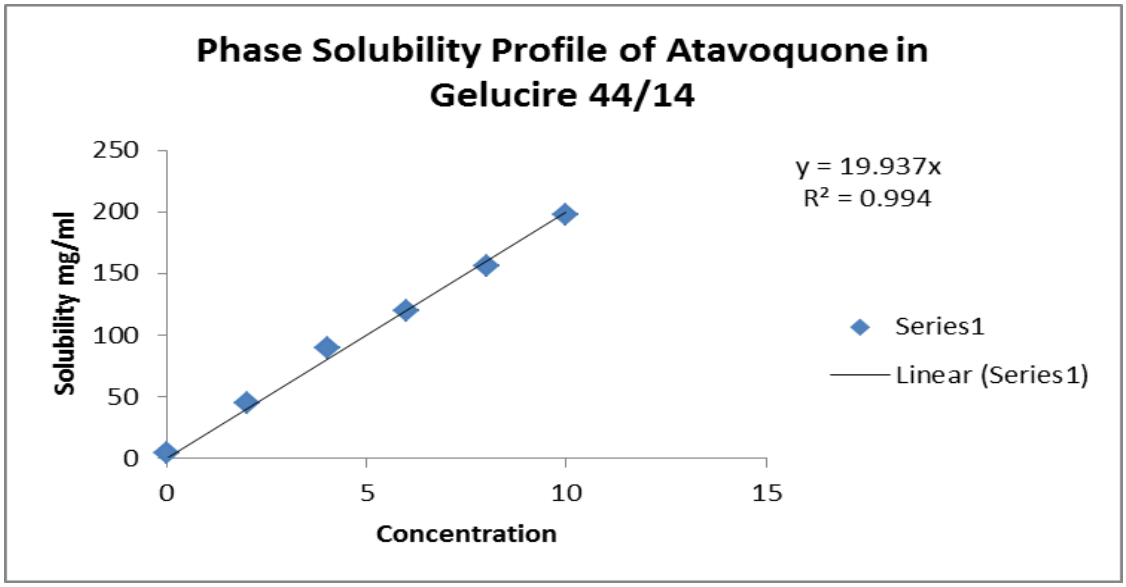

Fig 5: A_L type curve of Atovaquone with Gelucire 44/14

Table 7: Phase solubility studies of Atovaquone with Gelucire 50/13

S. No.	Solvent	Solubility (mg/mL) (mean ± SD) (n=3)
1	Double Distilled Water	4.145±0.132
2	2 % Gelucire in Water	35.18 ±1.21
3	4 % Gelucire in Water	68.31 ±1.95
4	6 % Gelucire in Water	96.32 ±0.18
5	8 % Gelucire in Water	125.26 ±0.32
6	10 % Gelucire in Water	155.34 ±1.89

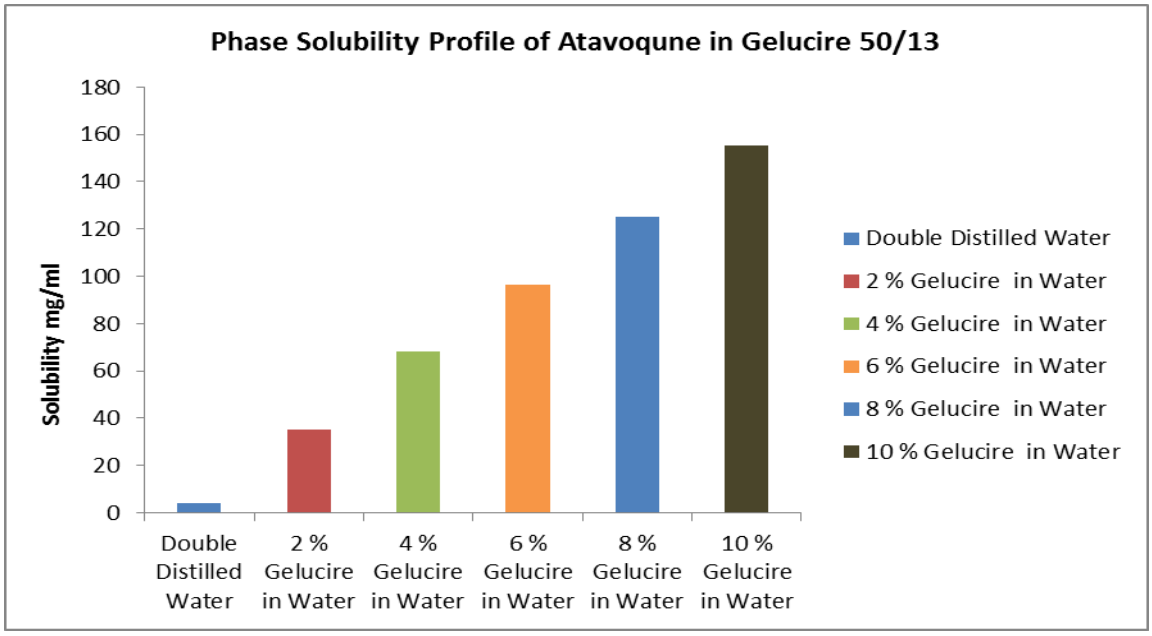

Fig 6: Phase solubility profile of Atovaquone with Gelucire 50/13

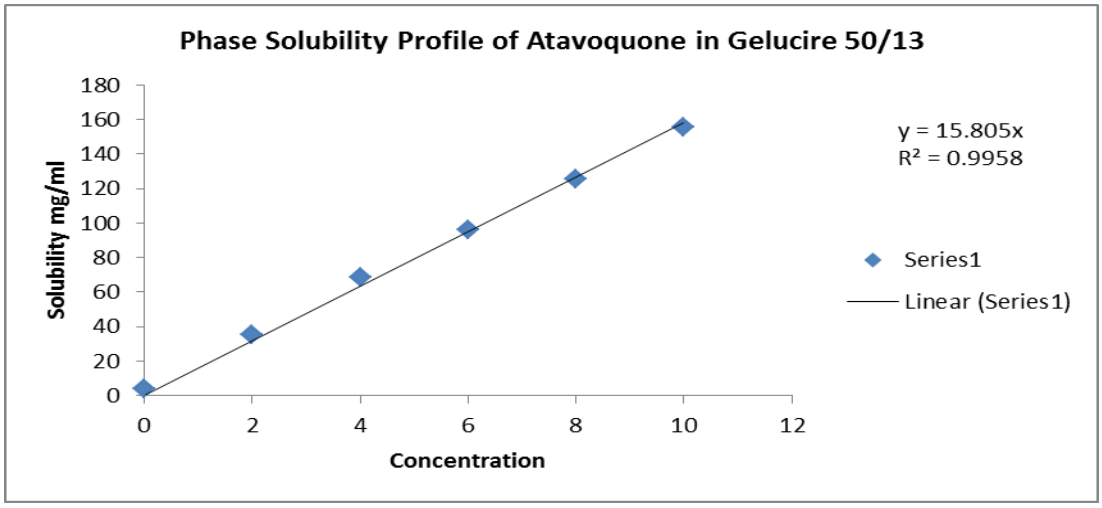

Fig 7: A_L type curve of Atovaquone with Gelucire 50/13

Formulation Development of Solid Dispersions of Atovaquone

Solid dispersions of Atovaquone were prepared by using different hydrophilic/lipid based carriers such as Kollidon VA 64, gelucire 44/14 and gelucire 50/13 in different ratios such as 1:1,1:2 &1:3. These ratios were decided based on the results obtained in phase solubility studies. Composition of prepared solid dispersions are given in table 8.

Table 8: Solid dispersions of Atovaquone prepared with PVP

Formulation Code	Drug (mg)	Carrier (Kollidon VA 64) (mg)	Ratio	Method
ASD1	250	250	1:1	Solvent Evaporation
ASD 2	250	500	1:2	Solvent Evaporation
ASD 3	250	750	1:3	Solvent Evaporation
ASD 4	250	250	1:1	Spray Drying
ASD 5	250	500	1:2	Spray Drying
ASD 6	250	750	1:3	Spray Drying

Table 9: Solid dispersions of Atovaquone prepared with Gelucire 44/14

Formulation Code	Drug (mg)	Carrier (Gelucire) (mg)	Inert Carrier (Aerosil 380) (mg)	Ratio	Method
ASD 7	250	125	125	1:1	Melting
ASD 8	250	250	250	1:2	Melting
ASD 9	250	375	375	1:3	Melting
ASD 10	250	250	125	1:1	Solvent Evaporation
ASD 11	250	500	250	1:2	Solvent Evaporation
ASD 12	250	750	375	1:3	Solvent Evaporation

Table 10: Solid dispersions of Atovaquone prepared with Gelucire 50/13

Frmulation Code	Drug (mg)	Carrier (Gelucire) (mg)	Inert Carrier (Aerosil 380) (mg)	Ratio	Method
ASD13	250	125	125	1:1	Melting
ASD 14	250	250	250	1:2	Melting
ASD 15	250	375	375	1:3	Melting
ASD 16	250	250	125	1:1	Solvent Evaporation
ASD 17	250	500	250	1:2	Solvent Evaporation
ASD 18	250	750	375	1:3	Solvent Evaporation

Characterization of Atovaquone Solid Dispersions

Micromeritic evaluation: The prepared solid dispersions were characterized for their micromeritic properties. Results are tabulated in table no11. It was observed that flow property was improved with all the formulations compared to pure drug.

Table 11: Micromeritic properties of Atovaquone Solid Dispersions

S.NO.	Angle of Repose (^{0})	Tapped Density (g/cc)	Bulk Density (g/cc)	Consolidation Index (%)	Hausner's Ratio
ASD1	$29^0 15'' \pm 14''$	0.90±0.03	0.77 ± 0.02	14.5± 0.14	1.19± 0.02
ASD2	$29^0 56'' \pm 23''$	0.83±0.01	0.74± 0.06	14.4± 0.30	1.20 ± 0.02
ASD3	$30^0 13'' \pm 24''$	0.9 ± 0.06	0.72± 0.07	12.7± 0.82	1.15± 0.03
ASD4	$30^0 56'' \pm 42''$	0.88±0.05	0.73± 0.08	12.11± 0.34	1.14± 0.05
ASD5	$30^0 16'' \pm 6''$	0.84±0.06	0.74± 0.02	11.98± 0.35	1.14± 0.05
ASD6	$27^0 21'' \pm 4''$	0.79±0.07	0.69± 0.08	12.7± 0.36	1.14 ± 0.07
ASD7	$26^0 15'' \pm 21''$	0.78±0.05	0.67± 0.10	13.09± 0.37	1.16 ± 0.06
ASD8	$29^0 54'' \pm 32''$	0.77±0.06	0.69 ± 0.08	13.5± 0.77	1.17± 0.08
ASD9	$27^0 18' \pm 21''$	0.80±0.08	0.70 ± 0.03	12.8± 0.80	1.15± 0.07
ASD10	$27^0 5'' \pm 7''$	0.75±0.06	0.66 ± 0.05	14.4± 0.79	1.18± 0.01
ASD11	$27^0 6'' \pm 2''$	0.71±0.08	0.60 ± 0.03	14.6± 0.59	1.17± 0.02
ASD12	$30^0 49'' \pm 45''$	0.69±0.05	0.59 ± 0.02	14.8± 0.99	1.18± 0.02
ASD13	$29^0 39'' \pm 72''$	0.68±0.06	0.55± 0.02	15.5± 0.85	1.19± 0.01
ASD14	$28^0 46'' \pm 56''$	0.66±0.07	0.54± 0.03	15.7± 0.79	1.19± 0.01
ASD15	$26^0 29'' \pm 28''$	0.65±0.06	0.53± 0.05	16.3± 0.67	1.19± 0.03
ASD16	$31^0 45'' \pm 50''$	0.69±0.08	0.58± 0.06	14.99± 0.70	1.18± 0.03
ASD17	$28^0 25'' \pm 34''$	0.67±0.05	0.57± 0.09	15.3± 0.97	1.18± 0.04
ASD18	$30^0 24'' \pm 6''$	0.68±0.07	0.57± 0.08	16.2± 0.87	1.20± 0.09

Saturation solubility studies of solid dispersions: All the prepared solid dispersions were evaluated for saturation solubility studies. Results are given in table 12 and pictorially represented in figure 8. It was observed that the solubility was improved with all the solid dispersions as the ratio of carrier is increased. Highest solubility was observed with lipophilic carrier gelucire 44/14 and it was also observed that the solubility was slightly higher with solvent evaporation method than melting method.

Table 12: Saturation solubility studies of solid dispersions prepared with Kollidon VA 64

S. No.	Formulation	Solubility (mg/mL) (mean ± SD) (n=3)
1	Double distilled water	4.145±0.132
2	ASD 1	36.80 ±1.65
3	ASD 2	78.91 ±2.20
4	ASD 3	104.34 ±3.56
5	ASD 4	42.32 ±3.71
6	ASD 5	85.34 ±4.63
7	ASD 6	107.36 ±5.68

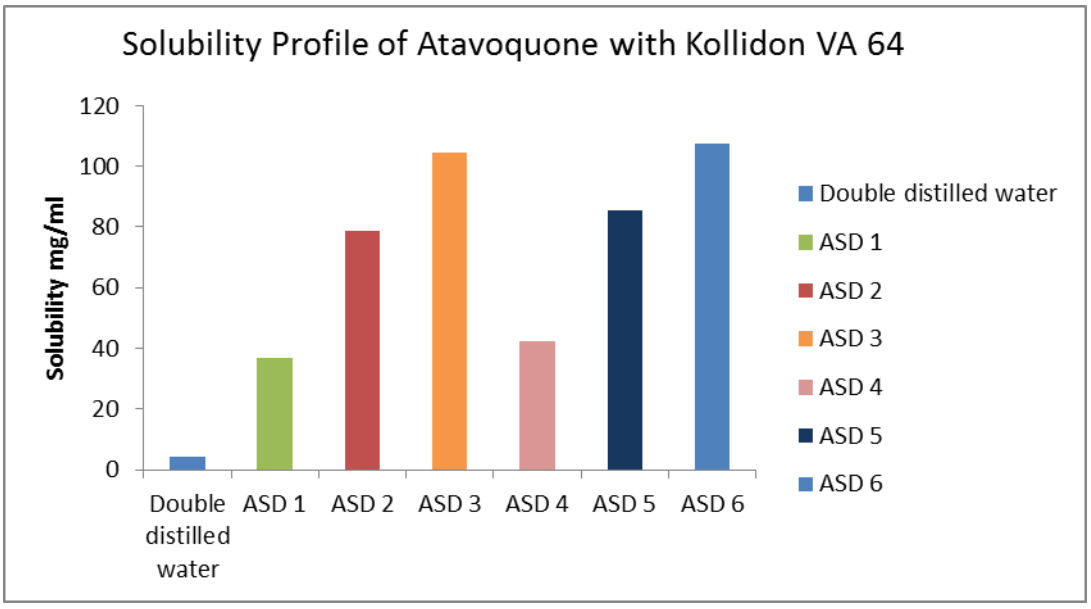

Fig 8: Solubility Profile of Atovaquone Solid Dispersions with Kollidon VA 64

Table 13: Saturation solubility studies of solid dispersions prepared with Gelucire 44/14

S. No.	Formulation	Solubility (mg/mL) (mean ± SD) (n=3)
1	Double distilled water	4.145±0.132
2	ASD 7	81.30 ± 2.41
3	ASD 8	170.60 ± 2.44
4	ASD9	238.60 ± 3.58
5	ASD10	87.56 ± 4.60
6	ASD 11	175.28± 5.72
7	ASD 12	235.61 ± 3.59

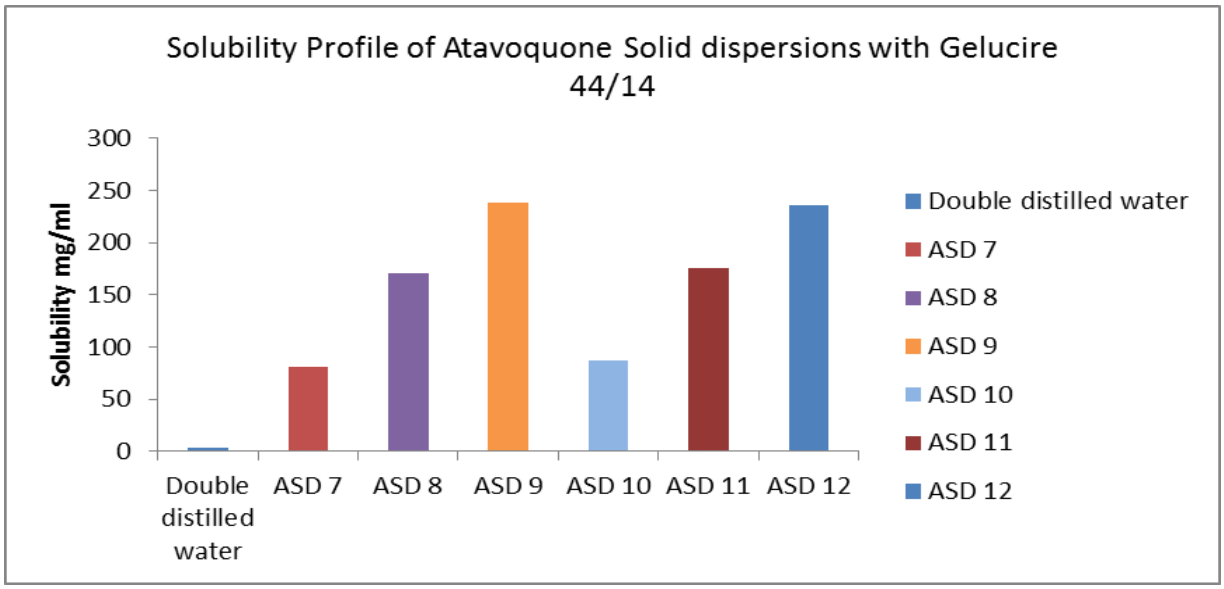

Fig 9: Solubility Profile of Atovaquone Solid Dispersions prepared with Gelucire 44/14

Table 14: Saturation solubility studies of solid dispersions prepared with Gelucire 50/13

S. No.	Formulation	Solubility (mg/mL) (mean ± SD) (n=3)
1	Double distilled water	4.145±0.132
2	ASD 13	63.30 ± 3.50
3	ASD 14	126.61 ± 4.66
4	ASD 15	194.58 ± 5.51
5	ASD 16	64.29 ± 2.39
6	ASD 17	128.70 ± 6.67
7	ASD 18	200.87 ± 8.72

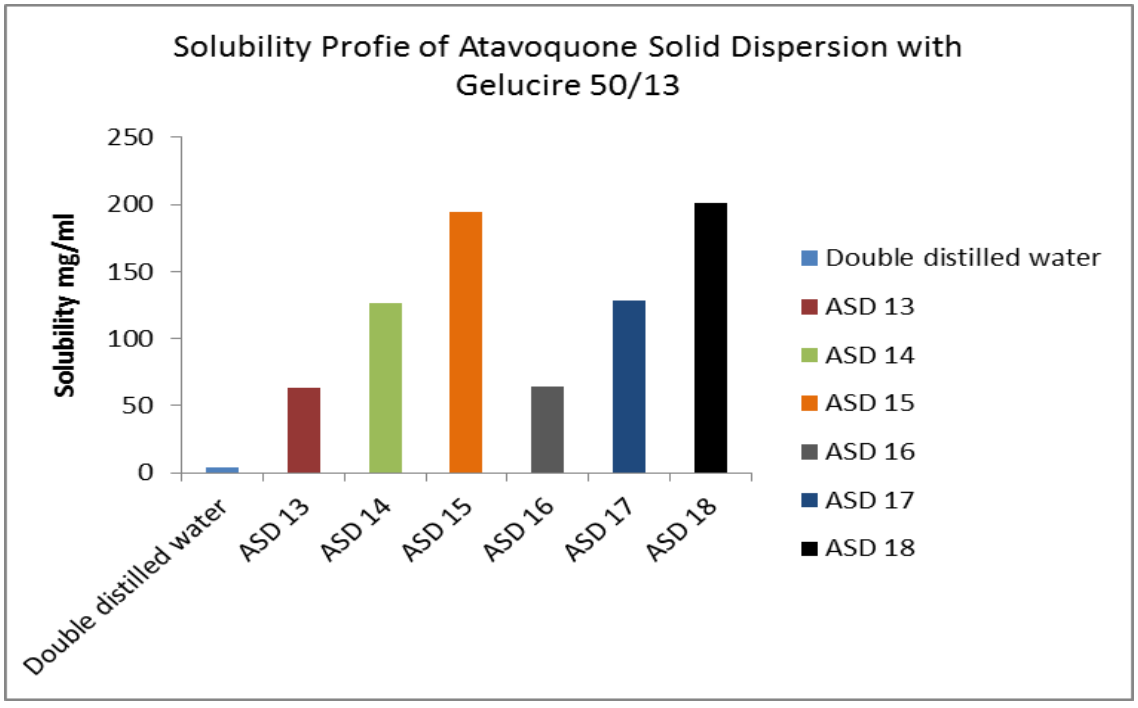

Fig 10: Solubility Profile of Atovaquone Solid Dispersions prepared with Gelucire 50/13

Dissolution studies of Atovaquone Solid Dispersions

Dissolution studies were conducted for all the prepared formulations in 500ml of PBS of pH7.4 +30% IPA using USP XXII (Type- II) dissolution test apparatus (100 rpm, and 37^0C). Each formulation was tested in triplicate. % Drug release values at various time intervals were calculated and results obtained are shown in Table 15. Graphs were plotted for each carrier (Figures11-14)by taking % drug release on Y-Axis and time on X-Axis.

Out of all the formulations, Gelucire 44/14 has shown greater drug release than the remaining carriers. This might be due to the greater solubility of the drug in presence of gelucire 44/14. And formulation ASD 12 containing gelucire 44/14 as carrier and Aerosil 380 as inert carrier prepared by solvent evaporation method has shown greater drug release than the remaining carriers and hence chosen for *ex vivo* and *in vivo* studies.

Comparative dissolution was done with pure drug, marketed formulation and best formulation (MSD12). Results are given in table 16 and graph is shown in figure--. Various dissolution parameters like Q_{10}, Q_{60}, DE_{10}, DE_{60}, MDT, MDR, IDR & t_{50} were calculated for pure drug, marketed and best formulation. Obtained values are given in table-16. It was observed that all the parameters were improved significantly for best formulation than pure drug and marketed formulation.

Table 15: *In Vitro* Drug Release Data of Atovaquone Solid Dispersion Formulations (n=3)

Formulations	% Drug Released within (MEAN ± SD)					
	5 min	10 min	20 min	30 min	45 min	60 min
ASD1	13.41± 1.31	22.15± 1.18	35.49± 2.51	49.89± 1.73	69.24 ± 1.04	93.04 ± 1.10
ASD2	32.71 ± 1.51	42.59 ± 1.91	78.34± 2.34	95.26± 2.31	99.34± 1.51	99.91± 1.62
ASD3	40.71± 1.47	52.71± 1.24	80.93± 1.91	97.48± 2.17	100.19± 1.63	--
ASD4	16.78± 1.81	25.14± 1.19	40.52± 2.62	52.56± 1.79	73.02 ± 1.10	95.12 ± 1.09
ASD5	34.69 ± 1.54	44.61 ± 1.91	80.24± 2.30	97.45± 2.30	99.68± 1.49	100.91± 1.55
ASD6	42.61± 1.42	54.70± 1.22	82.89± 1.91	99.25± 1.08	100.42± 1.71	--
ASD7	13.69± 1.51	21.17± 1.21	32.54± 2.51	47.36± 1.81	67.10 ± 1.09	92.08 ± 1.10
ASD8	25.37 ± 1.54	39.61 ± 1.91	58.31± 2.33	75.1± 2.31	90.41± 1.41	100.88± 1.55
ASD9	37.65± 1.41	49.61± 1.31	66.87± 1.78	83.45± 2.56	92.35± 1.54	100.67± 2.35

Formulations	% Drug Released within (MEAN ± SD)					
	5 min	10 min	20 min	30 min	45 min	60 min
ASD10	16.45± 1.51	24.19± 1.19	32.48± 2.51	50.31± 1.67	72.31 ± 3.29	97.23 ± 3.56
ASD11	27.27 ± 1.59	44.71 ± 2.18	63.39± 2.67	80.15± 2.43	93.45± 3.26	101.91± 2.34
ASD12	39.47± 2.45	50.81± 1.53	72.89± 1.91	93.44± 2.13	100.24± 2.15	100.45± 2.24
ASD13	22.67 ± 1.51	35.65 ± 1.67	47.28± 2.31	62.16± 2.32	79.34± 1.56	93.87± 1.56
ASD14	32.64 ± 2.51	43.76 ± 1.90	60.43± 2.34	78.18± 2.35	92.34± 3.43	100.67± 1.34
ASD15	37.61± 1.41	50.65± 1.31	67.89± 1.88	84.34± 2.09	93.18± 1.56	100.55± 2.35
ASD16	22.63 ± 1.49	35.65 ± 1.90	46.41± 2.34	61.21± 2.32	80.32± 1.50	96.78± 1.53
ASD17	34.59 ± 2.51	45.59 ± 2.01	62.34± 2.53	80.21± 2.45	95.18± 3.23	98.45± 3.65
ASD18	40.34± 1.56	52.56± 2.38	69.81± 2.96	82.46± 2.31	95.26± 1.34	99.46± 1.35

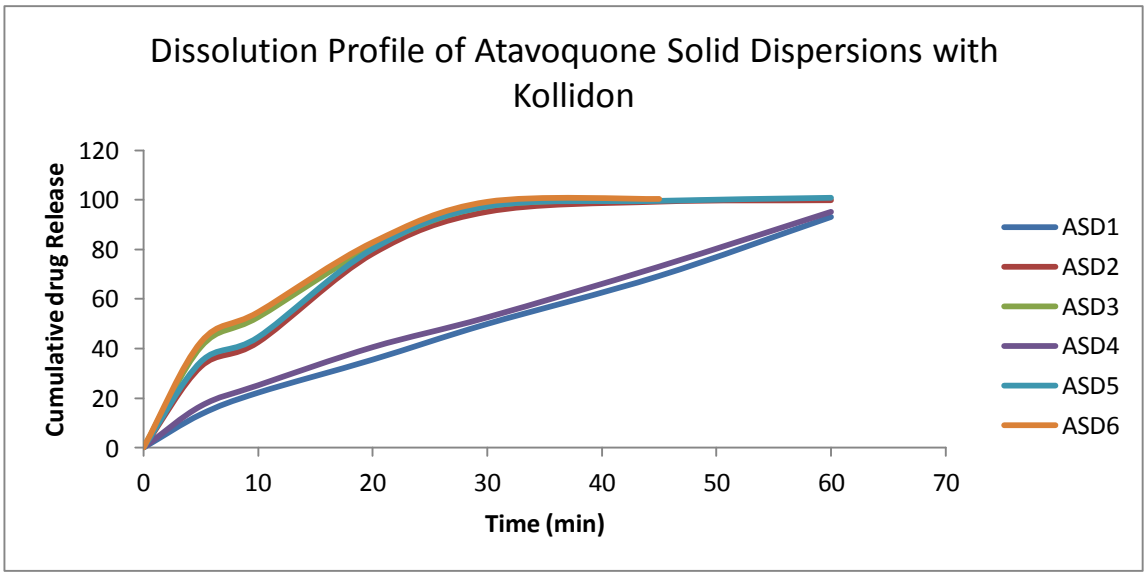

Fig 11: Dissolution profile of Atovaquone Solid Dispersions with Kollidon

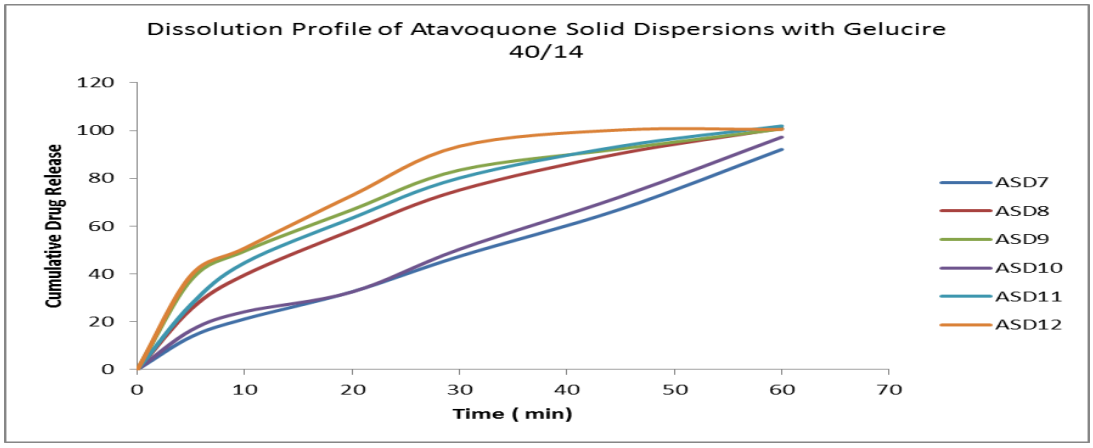

Fig 12: Dissolution profile of Atovaquone Solid Dispersions with Gelucire 40/14

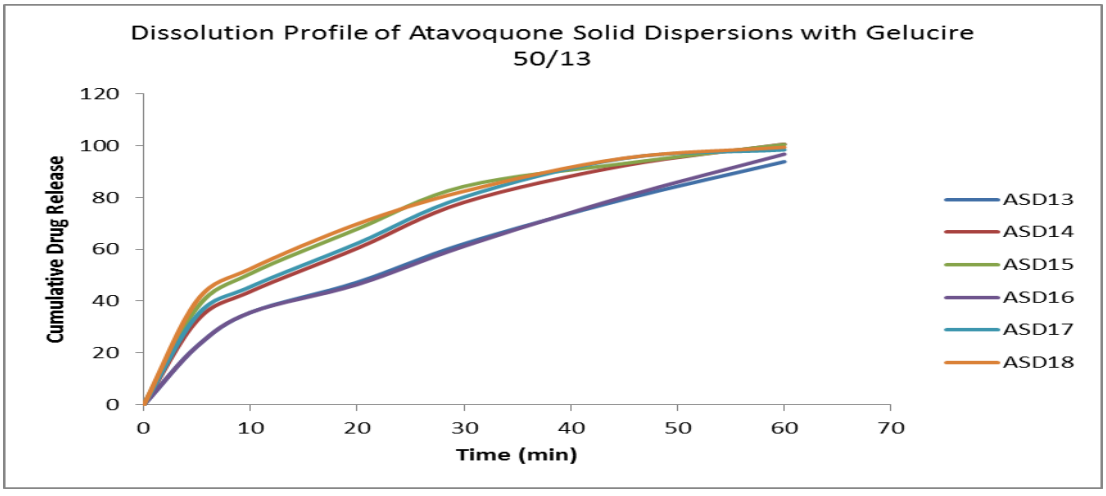

Fig 13: Dissolution profile of Atovaquone Solid Dispersions with Gelucire 50/13

Table 16: Comparative dissolution profile of pure drug, marketed and best formulation (ASD12)

Time (min)	% Drug Released		
	Pure drug	Marketed	ASD12
0	0	0	0
5	7.21±0.34	30.34±1.56	39.47± 2.45
10	12.45±1.12	46.34±1.04	50.81± 1.53
20	15.75±1.18	63.24±1.69	72.89± 1.91
30	18.36±0.91	77.56±1.85	93.44± 2.13
45	21.24±0.83	86.81±1.07	100.24± 2.15
60	23.54±0.45	97.45±1.36	100.45± 2.24

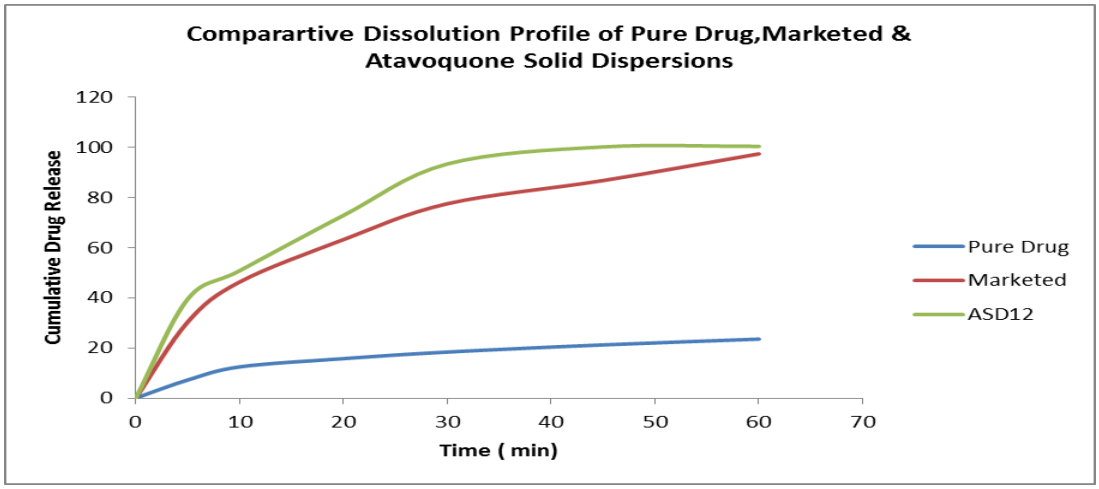

Fig 14: Comparative dissolution profile of Atovaquone solid dispersion, pure drug and marketed

Drug Excipient Compatibility Studies:

Infrared Spectroscopy:

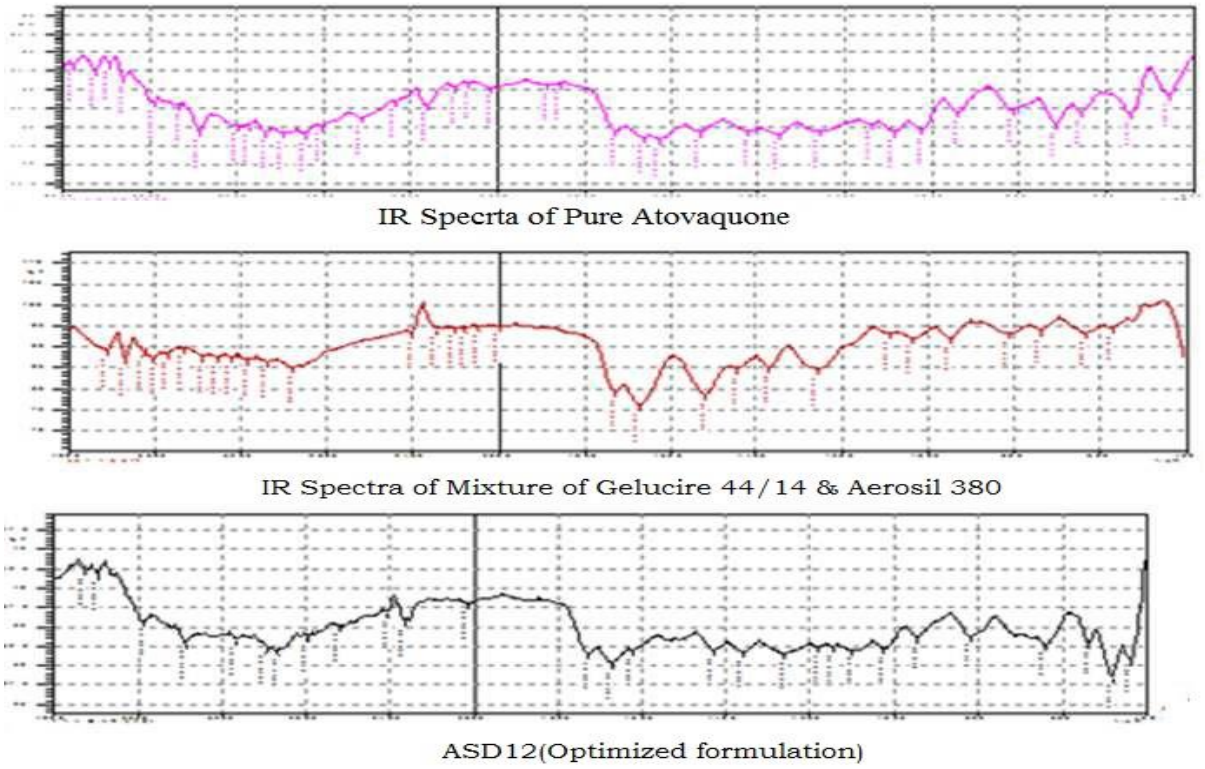

Fig 15: FTIR spectra

Differential Scanning Calorimetry:
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 100 C/min in the range 400C to 3000C. Nitrogen gas was purged at the rate of 30 ml/min to maintain inert atmosphere.

X-Ray Powder Diffractometry (XRD):
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 3-500 with reproducibility of ±0.001 on a diffractometer.

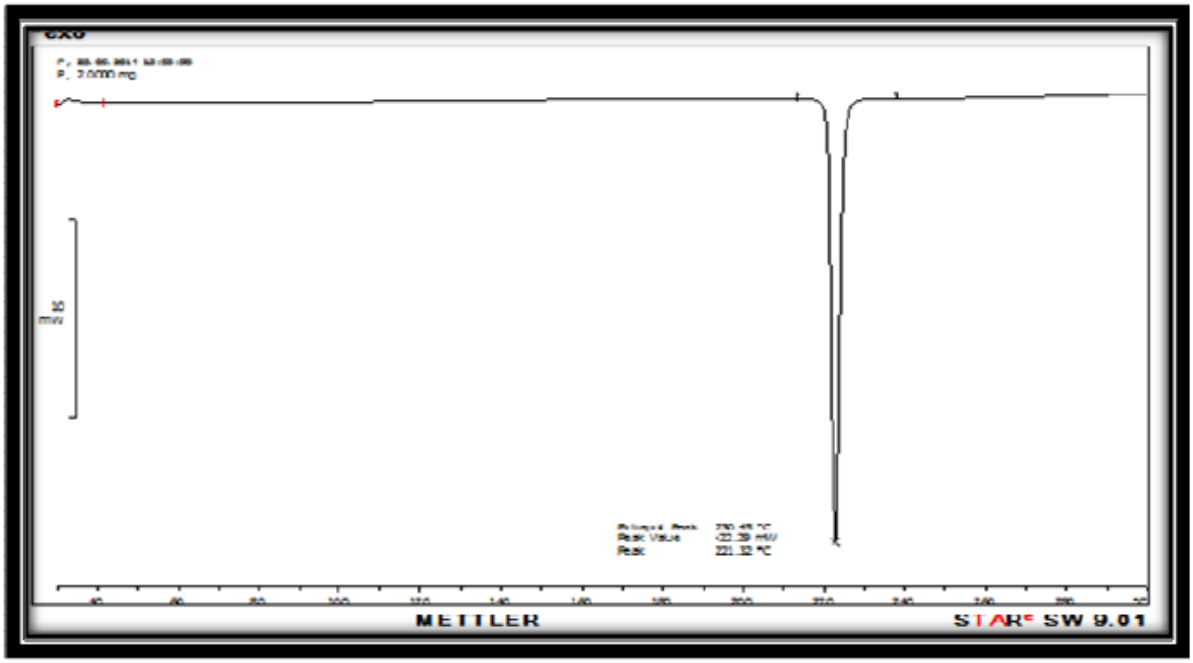

Fig 16:DSC of Pure Atovaquone

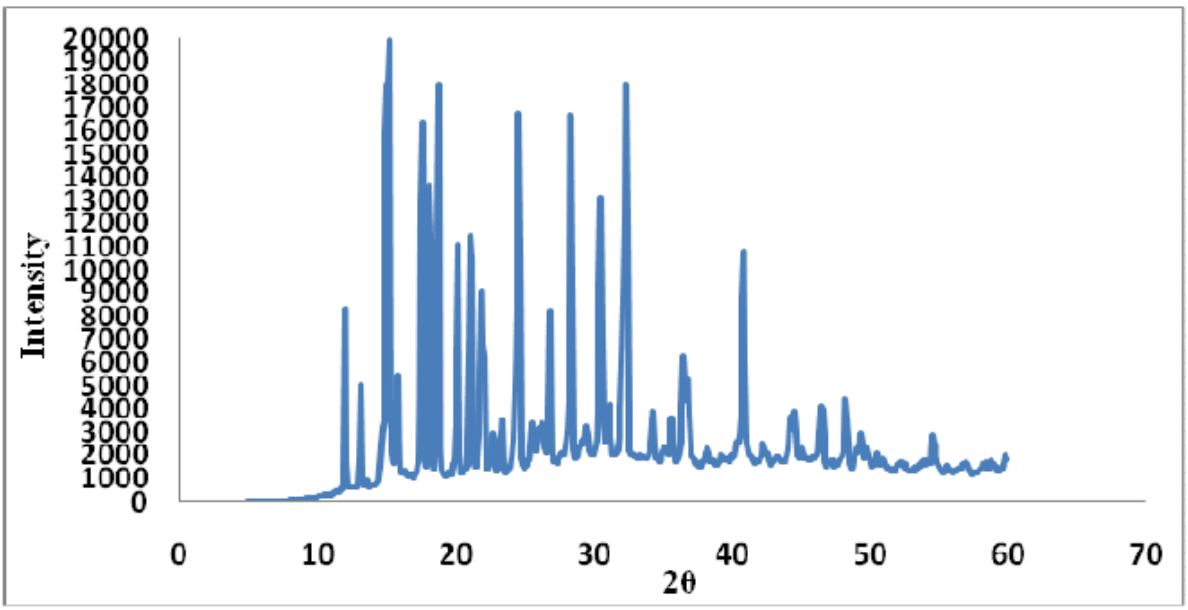

Fig 17: XRD spectra of Atovaquone Pure Drug

SUMMARY AND 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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