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Formulation And Evaluation Of Solid Dispersion For Enhance The Solubility Of Atovaquone

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ABSTRACT
The aim and objectives of this present work are based on application of various nanotechnology based strategies to achieve the objectives of improved solubility, dissolution rate and oral bioavailability. Atovaquone is an anti-malarial agent and belongs to biopharmaceutical classification system class IV. The polymers like PEG 4000, PVP K30 were used for solid dispersion. For preparation of solid dispersions, various solid dispersion methods (Solvent evaporation, Fusion method) were used. The effect of several variables to both solid dispersion preparations was investigated. IR and UV spectral analysis, Differential 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. Optimized solid dispersions were further evaluated by XRD, DSC, and SEM.
KEYWORDS: Atovaquone, Solid Dispersion, Solubility enhancement, Bioavailability, Fusion method

INTRODUCTION
The most popular and recommended way of medicine delivery is via the oral route because it is convenient and simple to consume. From the standpoint of the patient, taking medication via swallowing a dose form is a cosy and familiar experience. Therefore, compared to alternative modes of administration, such as parenteral, patient compliance and, consequently, drug therapy, is often higher with drugs delivered orally. [2]
The biopharmaceutical classification system (BCS) class IV drug Atovaquone is a unique naphthoquinone with a broad-spectrum antiprotozoal agent. It has a low and variable oral bioavailability (46%) due to its poor water solubility (less than 0.25 µg/ml).[1] Atovaquone oral medication delivery calls for improving solubility and, consequently, bioavailability. The solubility of drugs that are poorly soluble in water has been improved using a variety of technologies, including micronization, salt creation, solid dispersion, complexation, etc. [3]
Atovaquone is a naphthoquinone compound having a 4-(4-chlorophenyl)cyclohexyl group at

the 2-position and a hydroxy substituent at the 3-position. It has a role as an antimalarial, an antifungal agent, an EC 1.3. 5.2 [dihydroorotate dehydrogenase (quinine)] inhibitor, an EC 1.6. [4]

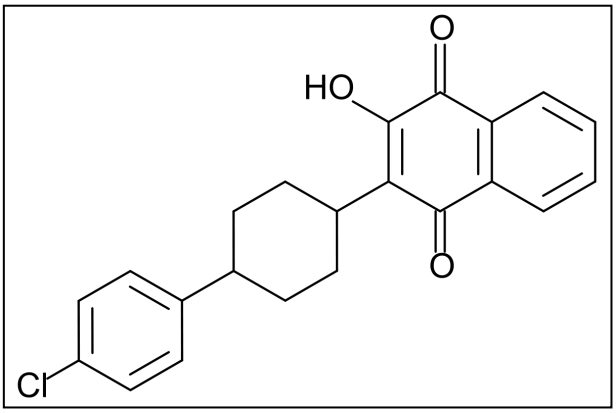

Figure No: Structure of Atovaquone

MATERIALS AND METHODS

Materials

Atovaquone was gifted by Cure Pharma Pune, India. Polyvinyl pyrrolidone K30 and Polyethylene Glycol 4000 was also purchased from Anand agencies, Pune, India.

Methods

Phase Solubility Studies Phase solubility studies were done by taking different concentrations of Polyvinyl pyrrolidone K30 and Polyethylene Glycol 4000, in distilled water [5-8]. 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 dissolved. Three determinations were carried out for each sample to calculate the solubility of each drug.

Preparation of solid dispersion of Atovaquone by fusion method:

Atovaquone the drug with PEG-4000 and PVPK30 were prepared by separately at three different ratios 1:1, 1:2, 1:3. The polymer has been taken in china disc and kept in a mantle for a melting for drug. After reaching melting point than add the drug with continuous stirring with a glass rod. After taking it out from the mantle, kept immediate for cooling in an ice bath, after cooling take it out and kept in desiccators separately.

Preparation of solid dispersion of Atovaquone by solvent evaporation method:

Atovaquone drug with PEG-4000 and PVPK30 were prepared by separately at three different ratios 1:1, 1:2 and 1:3. Accurately weighed 100mg drug was taken and mixed with 100, 200 and 300mg of PEG- 4000 and PVPK30. This drug was dissolved in methanol and constant stirring. Solution was evaporated under low pressure to get the solid dispersion for both drugs.[1]

Preparation of calibration curve of Atovaquone:

The Atovaquone drug 10 mg was weighed accurately and then it dissolve in the 10 ml phosphate buffer of pH 6.8 in the 10 ml of volumetric flask, then to make (1000 µg/ml) standard stock solution. Then from it take 1 ml of stock solution was taken from the 10 ml volumetric flask, to make (100 µg/ml) standard stock solution. 1 ml stock solution was taken in another 10 ml volumetric flask and then final concentration were prepared 2-10 µg/ml with phosphate buffer 6.8 pH. The absorbance of standard solution was determined using UV/ VIS

spectrophotometer at 254 nm. Absorbance values obtained are given in table 1 and calibration curve plotted is shown in figure 2. Regression equation obtained was used to estimate the Atovaquone from in vitro samples.

Table 1: Absorbance values obtained for Atovaquone

Sr. No	Concentration (µg/ml)	Absorbance (λmax = 254 nm)
1	0	0
2.	2	0.186
3.	4	0.382
4.	6	0.573
5.	8	0.752
6.	10	0.982

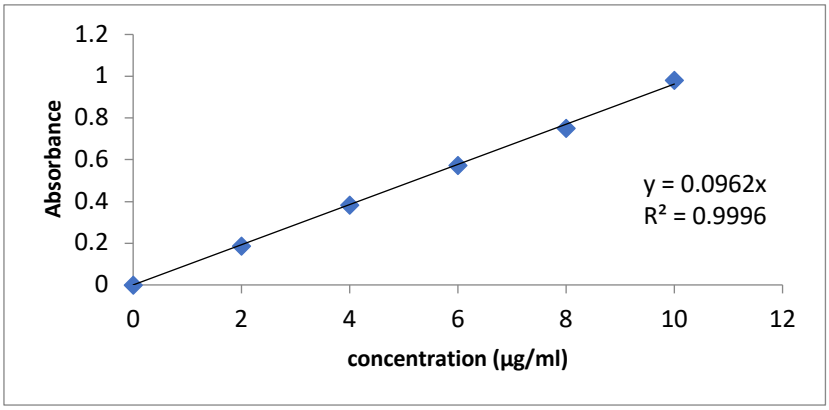

Figure No 2: Standard Graph of Atovaquone

Micromeritic/preformulation studies of Atovaquone solid dispersion

All the formulation of Atovaquone lubricated powder blends was subjected for Micromeritics properties using conventional methods. Bulk density and tapped density was determined by using measuring cylinder method. Hausner's ratios, Carr's index, were determined using the bulk density and tapped density data. An angle of repose was determined by conventional funnel method [9-12].

Percentage yield (i.e. recovery) of solid dispersion formed

The % recovery of formulated solid dispersion was resolute after complete removal of moisture. Thus % recovery calculation involves the weight of dried Solid dispersion to sum of the weight of drug and pharmaceuticals required for the formulation.

$$\% \text{ Yield} = \frac{\text{Prepared actual weight of SD}}{\text{Excipients and drug total weight}} \text{X100}$$

Evaluation of Solid dispersion

IR Spectral analysis

To know about the interaction between the drug and carriers used in the formulation, the IR analysis was carried out. The IR spectra of pure Atovaquone and solid dispersions were studied

by FTIR. It is scanned over the Frequency range of 4000-400 cm^{-1}.[13-15]

X-ray powder diffraction (XRDP)

The X-ray powder diffraction pattern for each sample was analyzed using a Diffractometer equipped with a mounting for Bragg-Brentano reflection that was connected to a Monochromator and a DIFFRAC plus channel program. Dimensions were carry out at room temperature using Cu K radiation at 40 mA and 40 kV, with an angular 2 increment of 0.02◦/s and a counting speed of 1.2 s per step. A rotation of 15 rpm was applied to the samples. .[13-15]

DSC Studies

Differential scanning calorimetry (DSC) Thermal analysis was conceded out using TA SDT 2960 DSC differential scanning calorimeter. 3 – 5 mg amount of sample was sealed in an aluminum pan while an empty aluminum pan was exploited as a reference. And then the sample heated in the range of 30 to 450 ° C with an underlying heating rate of 10°C/min. Dry nitrogen at flow rate of 40 ml/min was used to cleanse DSC cell. . [13-15]

SEM Studies

By using the Model-JEM-100S, Jeol, Tokyo Japan SEM, observed pure drugItraconazole and Atovaquone their solid dispersion surface characteristics. [13-15]

Drug Content

The entire prepared solid dispersions formulations equivalent to 100 mg of Atovaquone were weighed accurately and dissolved in 100 ml of phosphate buffer pH 6.8 in a separate volumetric flask. The solution was filtered, diluted suitably with same solvent and drug content is analyzed at 254 nm respectively by UV-spectrophotometer.

Dissolution studies of Atovaquone

Firstly the pure drug, developed solid dispersions were tested for In-Vitro dissolution study by utilizing USP type-2 Dissolutions Testing Apparatus (6 vessel assembly, Paddle-type II) at 100 rpm. 900ml of 0.1N HCL solution was used as dissolving media. Temperature was kept 37±0.50C. Samples of 5ml were taken at 5 minute time intervals and same amount of pure dissolution fluid preserved at identical temperatures was reinstated to maintain sink conditions. Samples were passed from a whatman filter-paper, suitably diluted using 0.1N HCL solutions and examined spectrophotometrically at 254 nm.

Curve fitting analysis (Kinetics of drug Release)

Atovaquone sustain release tablets were done by studying the release information with zero order, first order kinetics, Higuchi and Korsemeyer equation. The release mechanism was understood by fitting the data to Korsmeyer Peppas model.

RESULT AND DISCUSSION

Micromeritic/preformulation studies of Atovaquone solid dispersion

The results of Micromeritics properties of solid dispersion of Itraconazole formulations were as below

Table No 2: Micromeritic studies of Atovaquone solid dispersion

Parameters	Bulk Density (g/cm3) ±S.E.M.	Tapped Density(g/cm3) ±S.E.M.	% Compressibility index	Hausers ratio	Angle of repose
Formulation code					
AKF1	0.323± 0.005	0.348 ± 0.004	13.6	1.12	30°37'
AKF2	0.286 ± 0.008	0.344 ± 0.006	12.67	1.14	30°56'
AKF3	0.324 ± 0.007	0.345 ± 0.005	12.93	1.16	27°28'
APF1	0.336± 0.004	0.349 ± 0.004	13.15	1.14	31°17'
APF2	0.278 ± 0.006	0.336 ± 0.005	12.34	1.12	30°47'
APF3	0.335± 0.004	0.372 ± 0.004	11.56	1.13	27°21'
AKS1	0.333± 0.006	0.352 ± 0.005	12.34	1.11	31°57'
AKS2	0.282 ± 0.007	0.348 ± 0.007	11.78	1.13	32°46'
AKS3	0.335± 0.008	0.379 ± 0.006	12.45	1.14	28°67'
APS1	0.337± 0.005	0.367 ± 0.004	13.5	1.12	31°52'
APS2	0.282 ± 0.007	0.348 ± 0.008	12.78	1.14	31°56'
APS3	0.329 ± 0.006	0.359 ± 0.007	12.37	1.13	29°28'

Atovaquone were found to be identical with standards given in analytical profile of drug substances.

Percentage yield

The results of percentage yield of solid dispersion of Atovaquone formulations were as below

Table No 3: Percentage yield of solid dispersion of Atovaquone

Sr. No.	Formulation code	% yield
1	AKF1	82.14
2	AKF2	86.65
3	AKF3	91.75
4	APF1	96.16
5	APF2	93.46
6	APF3	94.27
7	AKS1	89.65
8	AKS2	96.36

9	AKS3	91.24
10	APS1	90.88
11	APS2	94.35
12	APS3	93.23

The % yield was found good with formulated SD. The Batch AKS2 has showed maximum yield of 95.45 and 96.36%.

FTIR spectroscopy

Analysis of FTIR result ensuring that absence of interface among polymer with drug Atovaquone. Thus, carriers such as PVP K30 and PEG 400 used in formulation were compatible with drug. As shown in figure 3.

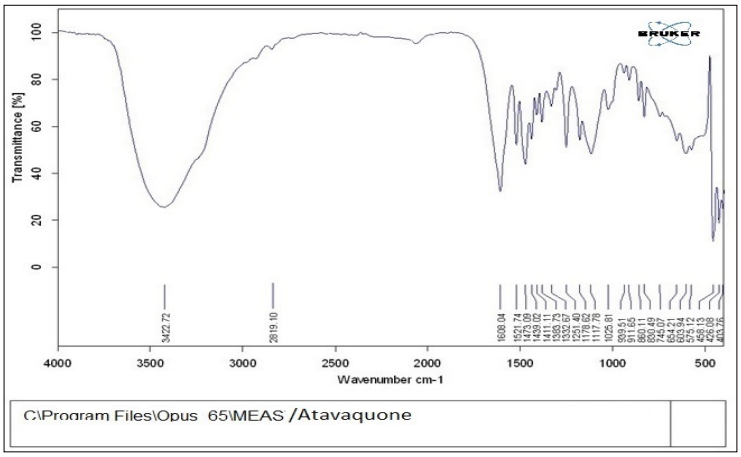

Figure No 3: FTIR spectrum of Atovaquone

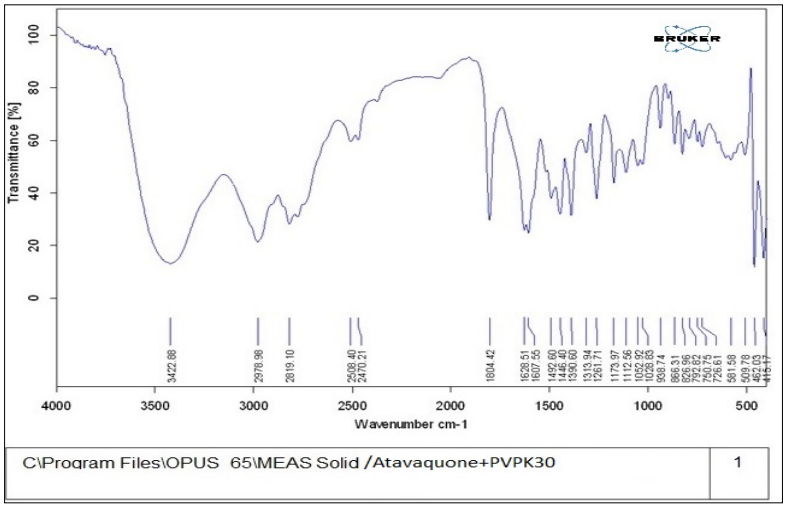

Figure No 4: FTIR spectra of Atovaquone with PVPK 30

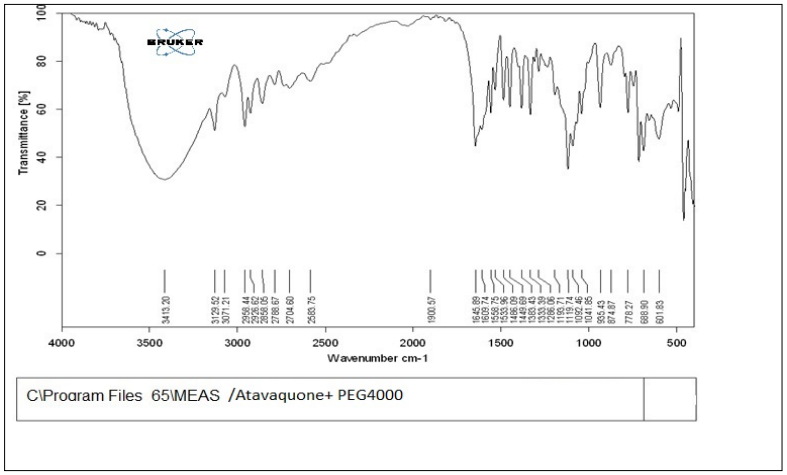

Figure No. 5: FTIR Spectra of Atovaquone with PEG 4000

X-ray diffraction analysis

Pure Atovaquone showed the characteristic peaks in the 2θ range of 15-30^0,which indicates that, the unprocessed Atovaquone was a crystalline material. As shown in figure 4.

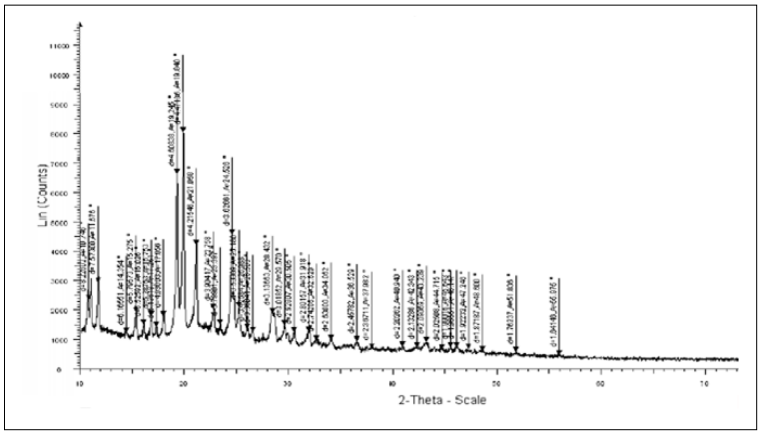

Figure No 4 : XRD of Atovaquone SD

DSC Thermogram

The DSC curve of solid dispersion of Atovaquone with PVP K30 shows reduced in the intensity of the endothermic peak to 192°c.It shows compatibility with the drug. As shown in figure 5.

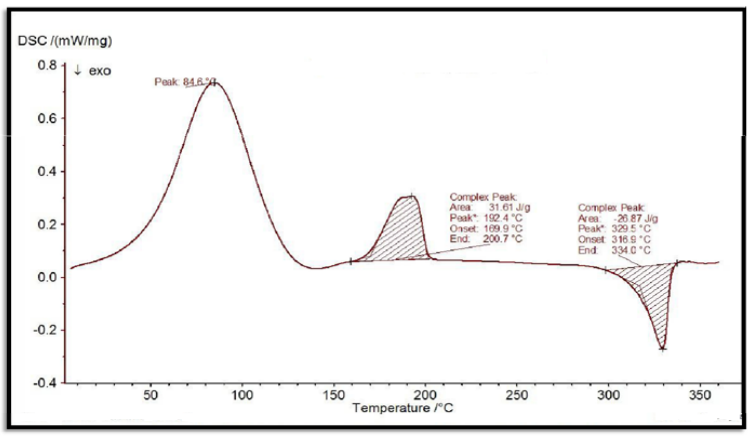

Figure No 5: DSC of Atovaquone SD

SEM Studies

The result of for Atovaquone SEM of SD formulation with PVPK30 .The study clearly reveals the difference between SEM of Atovaquone and its SD formulation. Also observed definite morphological changes in crystal of drug. As shown in figure 6.

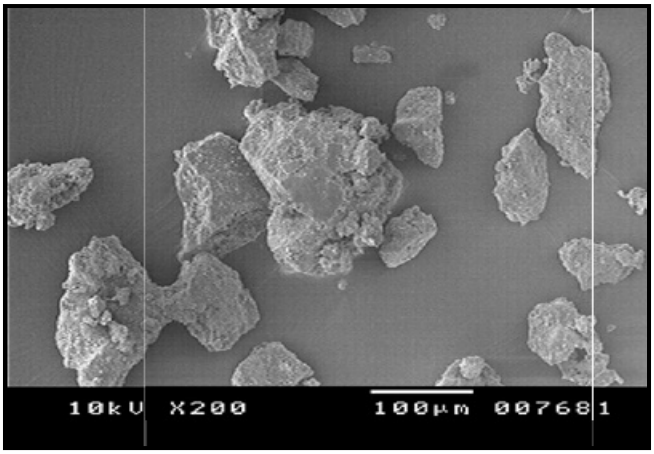

Figure No. 6: SEM of Atovaquone SD

Dissolution studies of Atovaquone

Solid dispersions were tested for In-Vitro dissolution study by utilizing USP type-2 Dissolutions Testing Apparatus (6 vessel assembly, Paddle-type II) at 100 rpm. 900ml of 0.1N HCL solution was used as dissolving media. Results are interpreted in the table 4 and drug release showed in figure 7.

Table No. 4: In Vitro Drug Release of Atovaquone Solid Dispersion by Solvent Evaporation method by using PVPK30

Time in (min)	% Drug Release			
	Atovaquone	AKS1 (1:1)	AKS2 (1:2)	AKS3 (1:3)
0	0	0	0	0
10	10.30±1.6	25.8± 1.03	28.4± 1.12	27.9± 1.12
20	17.27±1.8	39.6± 1.12	45.3± 1.01	48.7± 1.02
30	24.12±1.2	56.6± 1.11	61.4± 1.14	59.8± 1.7
40	29.35±1.5	75.8± 1.32	75.5± 1.10	73.4± 1.13
50	32.11±1.8	86.7± 1.12	87.9± 1.3	81.5± 1.08
60	36.10±1.1	95.5± 1.08	98.2± 1.05	94.2± 1.13

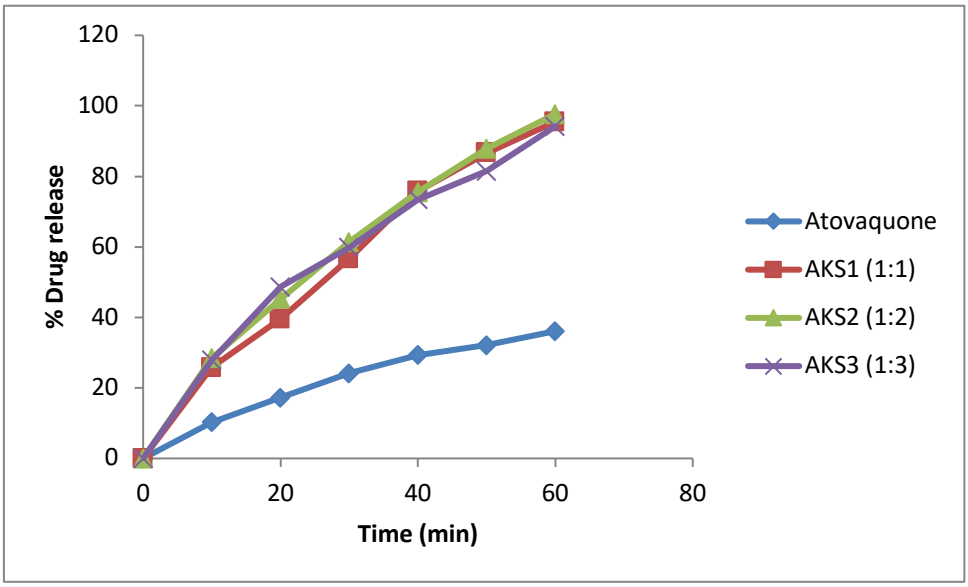

Figure No 7: In Vitro Drug Release of Atovaquone Solid Dispersion by Solvent Evaporation method by using PVPK30

The invitro dispersion studies of pure drug and all solid dispersion formulation with different ratios 1:1, 1:2, 1:3 by using two different carrier PVPK30. The prepared solid dispersions of Atovaquone equivalent to 100 mg of pure drug and dissolution studies were carried out in dissolution USP Type II apparatus (LABINDIA, DISSO 2000) containing 900ml of 0.1N HCL solution was used as dissolving media. Temperature was kept 37±0.50C. The samples were taken at different interval of time. 0 min, 10 min, 20 min, 30 min, 40 min, 50 min, 60min. also absorbance were recorded at 252 nm. From this invitro studies the solid dispersion containing drug and PVPK30 (1:2) released maximum 98.2% W/V (Solvent evaporation method). From this invitro studies it conclude that the solid dispersion containing Atovaquone and PVPK30 (1:2) (Solvent evaporation method) showed high release. The studies proved that one of the fast releasing dosage form for poorly water soluble Atovaquone by using solid dispersion technology.

Kinetics Release studies of Atovaquone

By fitting the experimental data to models such as zero-order, first-order, Hixson-Crowell, Higuchi and Korsmeyer-Peppas best fitted model is evaluated for solid dispersion.

Table No 5: Release kinetics of Atovaquone solid dispersion by solvent evaporation method by using PVP K30

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer R^2
AKF1 (1:1)	0.982	0.959	0.978	0.987
AKF2 (1:2)	0.984	0.975	0.968	0.981
AKF3 (1:3)	0.998	0.966	0.981	0.999

Table 5 represents the values of the best-fit parameters of the Krosmeyer-Peppas model. Which provided the best adjustment curves for the kinetics of drug release for created solid dispersion tablets.

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 PVP K30 and PEG 4000. From this invitro studies the solid dispersion containing drug and PVPK30 (1:2) released maximum 98.2% W/V (Solvent evaporation method). Solid dispersions prepared by solvent evaporation 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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