Solubility enhancement of antiprotozoal agent by solid dispersion and herbal tablet method to improve its rate of dissolution

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Abstract-Drug dissolution is the rate limiting step for bioavailability of poor aqueous soluble drug that consequently affects the in vivo drug absorption. In the present study solid dispersion based drug delivery system of Atovaquone were successfully developed in the form of tablets with improved dissolution characteristic by forming solid dispersion with PEG 4000. For the Atovaquone formulation, F1 was chosen as it has % drug release about 46 % in 180 min. FTIR spectra of drug with other excipients have not shown any interaction and also selected formulation was stable after stability studies. The in-vitro dissolution studies revealed a considerable boost in dissolution rate of Solid dispersions of Atovaquone in contrast to pure drug. From FTIR spectroscopy, it was concluded that there was no well-defined chemical interaction between Atovaquone and PEG 4000 in Solid dispersions, as no important new peaks could be observed. The Atovaquone solid dispersion based tablet (F1) showed 30.33% drug release within first 20 min. and 46.45% drug release within 180 min.Thus from studies, it could be concluded that solid dispersion of poor aqueous soluble Atovaquone by solvent evaporation technique were effectively formulate during PEG-4000 and PVP-K 30 hydrophilic polymers. Thus, the statement can be given that the rate of dissolution and solubility of poor aqueous soluble Atovaquon can be appreciably improved by solid dispersion by use of water soluble carriers by solvent evaporation technique.

Keywords: Bioavailability; Dissolution Enhancement; In-Vitro Evaluation; Solid Dispersion; Atovaquone.

Introduction

Solid dispersion refers to a group of solid products consisting at least two components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline amorphous. The drug can be dispersed molecularly in amorphous particles (cluster) or in crystalline particles (Chion and Riegelman, 1971). Chiou and Rigelman in their classic review, defined these system as the dispersion of one or more active ingredients in an inert carrier matrix at solid state prepared by the melting (fusion), solvent or melting-solvent method (Craig, 2002).

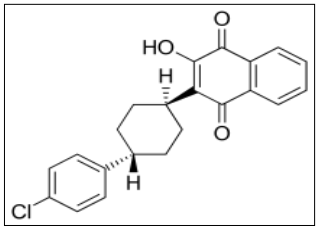
The concept of solid dispersion was originally proposed by Sekiguchi and Obi, who investigated the generation and dissolution performance of eutectic melts of sulfonamide drug and a water soluble carrier in early 1960s (Sekiguichi and Obi, 1961). Solid dispersion represents a useful pharmaceutical technique for increasing the dissolution, absorption and therapeutic efficacy of drugs in dosages forms. They may be also called as solid state dispersions as first used by Mayersohn and Gibaldi or as co-precipitates.

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 (Chawla & Bansal, 2008; Pathak *et al.*, 2008; Chiou & Riegel man, 1971). 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 (Vasconcelos *et al.*, 2007). Therefore, pharmaceutical researchers, focuses on two areas for improving the oral bioavailability of drugs include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs (Serajuddin *et al.*, 1990). It has been estimated that 40% of new chemical entities currently being discovered are poorly water soluble (Hao *et al.*, 2008; Liu, 2008). 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 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 (Dabbagh & Taghipour 2007; Sekiguchi & Obi 1961). The formulation of drugs having low aqueous solubility using solid dispersion technology has been an active area of research since 1960 (Goldberg *et al.*, 1966). Among the various approaches to improve solubility, the solid dispersion (SD) technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble drugs because it is simple, economic, and advantageous (Kaur & Grant 1980). Solid dispersion means a group of solid products consisting of at least two different components, generally a hydrophilic inert carrier or matrix and a hydrophobic drug. The carrier can be either crystalline or amorphous in nature. Most commonly used carriers for the preparation of SDs are different grade of polyethylene glycols (PEGs) and polyvinyl pyrollidine (PVPs), sugar etc.

Material and Method

Drug Profile

Selected Drug: Atovaquone



Molecular formula: $C_{22}H_{19}ClO_3$

Molecular weight: 366.8 g/mol

Chemical name: 3-[4-(4-chlorophenyl) cyclohexyl]-4-hydroxynaphthalene-1, 2-dione

Synonym: Mepron

Melting point: 216-219 °C

Solubility: Practically insoluble

Material and Chemical

Chemicals required for this research work were Atovaquone purchased from Matrix Lab Hyderabad India, Polyethylene glycol (PEG 4000), Polyvunyl Pyrrolidone, Talc, Magnesium stearate, Ethyl cellulose, Micro crystalline cellulose and Hydrochloric acid were purchased from S D fine Chemical Mumbai.

Preformulaion study

Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms.

Organoleptic Properties

Appearance

Transferred approximately 2 gm of the sample on a white paper spreaded uniformly and examined visually.

Colour

A small quantity of pure drug powder was taken in a butter paper and viewed in well illuminated place.

Solubility

Aqueous solubility is an important physicochemical property of drug substance, which determines its systemic absorption and in turns its therapeutic efficacy. Solubility of Atovaquone was determined in water and methanol, ethanol, chloroform and ethyl acetate

Table -1 Solubility Specifications

Descriptive terms	Approximate volume of solvent in millilitres per gram of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	More than 10,000

Melting point determination

Melting point of Atovaquone was determined by Open capillary method.

Determination of partition coefficient

25 mg of Atovaquone with aqueous phase and n-octanol was taken in three separating funnels. The separating funnels were shaken for 2 hrs in a wrist action shaker for equilibration. Two phases were separated and the amount of the drug in aqueous phase was analyzed spectrophotometrically.

Determination of λ max

A solution of Atovaquone containing the concentration 10 µg/ ml was prepared in 0.1 N HCL and UV spectrum was taken using Shimadzu (UV-1800) double beam spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

Drug – Excipient Interaction Studies by FTIR

Infra-red spectra matching approach was used for the detection of any possible chemical reaction between the drug and

the excipients. A physical mixture (1:1) of drug and excipients was prepared and mixed with suitable quantity of potassium bromide. About 100 mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 10 tones pressure. It was scanned from 4000 to 150 cm-1 in a shimadzu FTIR spectro-photometer. The IR spectrum of the physical mixture was compared with those of pure drug and excipients and matching was done to detect any appearance or disappearance of peaks.

Preparation of standard calibration curve of Atovaquone in 0.1N HCl

100 mg of Atovaquone was accurately weighted into 100 ml volumetric flask, dissolved in 0.1N HCL and volume was made up with 0.1N HCL. Pipette 1ml of this solution into another 10 ml volumetric flask and the volume was made with 0.1N HCl and marked as Stock. From this Atovaquone standard stock solution (1000µg/ml), 1ml solution was diluted to 10 ml using 0.1N HCl solution to get concentrations of 100 µg/ml. from this solution, aliquots of, 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml, 1.0 ml, 1.2 ml and 1.4 ml from standard drug solution were diluted to 10 ml with 0.1M. The absorbance of these solutions was measured at 286 nm 0.1N HCL as a blank.

Preparation of Solid Dispersion

Atovaquone solid dispersion were prepared by using hydrophilic carriers like polyethylene glycol (PEG6000) and Polyvinyl Pyrrolidone (PVK 90) in proportions viz 1:1 (drug: carrier) (50mg:50mg), 1:2 (50mg: 100mg) and 1:1:1 (drug: carrier 1:carrier 2) (50mg: 50mg: 50mg) and (50mg: 100mg: 100 mg) were prepared by solvent evaporation method. Atovaquone and carriers were dissolved in methanol and mixed with magnetic stirring. Solvent was evaporated at reduced pressure at 40^{o}C in a rotatory evaporation apparatus. Subsequently solid dispersion was stored under vacuum over silica gel for 12 hrs. at room temperature. After drying the solid dispersion was passed through a 250µm sieve. Sample was stored in a desiccator and used for further investigation (Leuner & Dressman 2000).

Table-2 Composition of Different Solid Dispersion Preparations

Solid Dispersion (Code)	Atovaquone(mg)	PEG-4000 (mg)	PVP K90 (mg)	Ethanol (ml)
SDF1	50	50	--	30
SDF2	50	100	--	30
SDF3	50	--	50	30
SDF4	50	--	100	30
SDF5	50	50	50	30
SDF6	50	100	100	30

PVP – Poly Vinyl Pyrrolidine (K 90), PEG – Polyethylene Glycol

Evaluation of Solid Dispersion

The prepared formulations of solid dispersions were evaluated for the following Physico-chemical character-ization, *In-vitro* dissolution studies and

Compatibility study

Fourier transform infrared spectroscopy was employed to characterize the possible interactions between the Atovaquone and carriers. In this study pure drug, solid dispersions were studied by FTIR

spectrophotometer.

Drug content estimation

Solid dispersions equivalent to 10 mg of Atovaquone were weighed accurately and dissolved in the 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed by UV spectrophotometer. The Actual Drug Content was calculated using the following equation as follows

$$\% \textbf{ Drug Content} = \left(\frac{\textbf{Mact.}}{\textbf{Mss}}\right) \times \textbf{100}$$

Percentage Practical Yield

Percentage practical yield was calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation.

$$\textbf{Practical Yield } (\%) = \left(\frac{\textbf{Practical Mass (Solid Dispersion)}}{\textbf{Theoratical Mass (Drug + Carrier)}}\right) \times \textbf{100}$$

Determination of Solubility of Atovaquone Solid Dispersion

Drug solubility studies were performed in triplicate by adding excess amount of Atovaquone and solid dispersion to methanol and 0.1 N HCl pH (1.2). Solutions containing flasks were kept on a rotary Shaking Incubator for 24 hrs. After 24hrs, solutions were analyzed using UV spectrophotometer.

Preparation of Solid Dispersion Based Formulation

Compressed tablets containing selected solid dispersed product with surfactants were prepared separately by direct compression method. Diluent lactose, dry binder polyvinyl pyrrolidone, and lubricants talc, magnesium stearate were used as excipients. All ingredients were sieved through 40 meshes and blended with lubricants and compressed in single station machine with flat punches.

Table- 3 Formulation of Solid Dispersion Based Tablets

Formulation Code	F1	F2	F3
SD - Formulation	--	SDF2	SDF6
Atovaquone	60	--	--
Poloxamer 407	30	--	--
Lactose	132	34.5	
PVP	5	5	5
Mg stearate	1	1	1
Talc	2	2	2
Total weight	230	230	230

Evaluation of Solid Dispersion Based Tablet Formulation (Pre-Compression)

Bulk density

It is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. It is expressed in gm/ml and is given by the formula:

Bulk density=M/Vo

Where,

M = mass of the powder

Vo = bulk volume of the powder

Angle of repose (θ)

It is defined as the maximum angle possible between the surface of the pile of the powder and the horizontal plane. Fixed

funnel method was used. The angle of repose was then calculated using following equation:

Angle of repose Ø = tan-1(h/r)

Where, h=height of the pile

r = radius of the pile

Table-4 Flow properties and corresponding angle of repose

Flow property	Angle of repose
Excellent	25-30
Good	31-35
Fair	36-40
Passaple	41-45
Poor	46-55
Very poor	56-65
Very very poor	>66

Tapped density

Ten gram of powder was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and the tapped volume was read. It is expressed in gm/ml and is given by:

Tapped density=M/Vt

Where, M = mass of the powder ,

Vt = final tapping volume of the powder

Compressibility index (Carr's index)

Compressibility index is used as an important parameter to determine the flow behavior of the powder. Carr's index can be represented by Equation:

Comprassibility Index

$$= \left(\frac{\mathbf{TD - BD}}{\mathbf{TD}}\right) \times \mathbf{100}$$

Hausner's ratio

Hausner's ratio is used to predict the flow ability of the powders. This method is similar tocompressibility index. Hausner's ratio can be represented by Equation:

$$\text{Hausner'Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Table-5 Scale of flow ability

Flow character	Compressibility index (%)	Hausner's ratio
Excellent	<10	1.00 – 1.11
Good	11 – 15	1.12 – 1.18
Fair	16 – 20	1.19 – 1.25
Passable	21 – 25	1.26 – 1.34
Poor	26 – 31	1.35 – 1.45
Very poor	32 – 37	1.46 – 1.59
Extremely poor	>38	>1.60

Evaluation of Solid Dispersion Based Tablet Formulation (Post-Compression)

The formulated tablets were evaluated for the following physicochemical characteristics:

General Appearance
The formulated tablets were assessed for its general appearance and observations were made for shape, color, texture and odor.

Weight variation
Randomly selected twenty tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablets pass the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double percentage limit.

PD = [(W_{avg} – $W_{initial}$) / (W_{avg})] x 100
Where,
PD = Percentage deviation
W_{avg} = Average weight of tablet
$W_{initial}$ = Individual weight of tablet

Thickness
The thickness and diameter of tablets was determined using Vernier Caliper. Twenty tablets from each batch were used and average values were calculated.

Hardness
The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between affixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of the hardness of the tablet. It is expressed in kg/cm2.

Drug content
Tablets were crushed and the powder equivalent to 100mg of drug were accurately weighed and transferred to 50 ml volumetric flask. To this flask, sufficient amount of distilled water was added to dissolve the tablets completely. Then, the volume of flask was made up to the mark with same solvent. From this solution, 1ml of the sample was pipette out and transferred to 10 ml volumetric flask. The volume in the second flask was made up to the mark with distilled water. From this 0.6ml, 0.8ml and 1ml samples were withdrawn and volume was made up to 10ml to maintain concentration within the beer's range. This final diluted solution was estimated UV spectrophotometrically (Goldberg, 1966).

Friability
Twenty tablets samples were weighed accurately and placed in friabilitor (Roche Friabilitor). After the given specification (4 min at 25 rpm), loose dust was removed from the tablets. Finally tablets were weighed. The loss in weight indicates the ability of the tablets to withstand this type of wear. The % friability was then calculated by:

% Friability = (Loss in weight / Initial weight) × 100

In-vitro Dissolution study
In-vitro dissolution studies of the prepared formulations were performed using USP type II (Paddle) apparatus with paddle rotating at 50 rpm in 900ml of 0.1 N HCl at 37 ± 0.5ºC. At fixed time intervals, 5ml samples were withdrawn, filtered and replaced with fresh dissolution media. Concentration of Atovaquone in each sample was determined by UV spectrophotometer.

Result and Discussion
Description
The colour, odour, nature and taste of the API were evaluated and were found to be as per the monograph.

Description of Atovaquone
Atovaquone was dark yellow color and order less.

Solubility study
Solubility study of Atovaquone is reported in table-6.

Table-6 Solubility Study of Atovaquone

S.No.	Solvent	Solubility
1.	Water	+ - - -
2.	0.1N HCl	+ - - -
3.	Mathanol	++++
4.	Ethanol	++++

Melting point determination

The melting point of Atovaquone was found to be 220.5° C.

Determination of λ max

Solution was scanned under UV-Vis Spectrophotometer and λ max was determined. It was found to be as per the monograph.

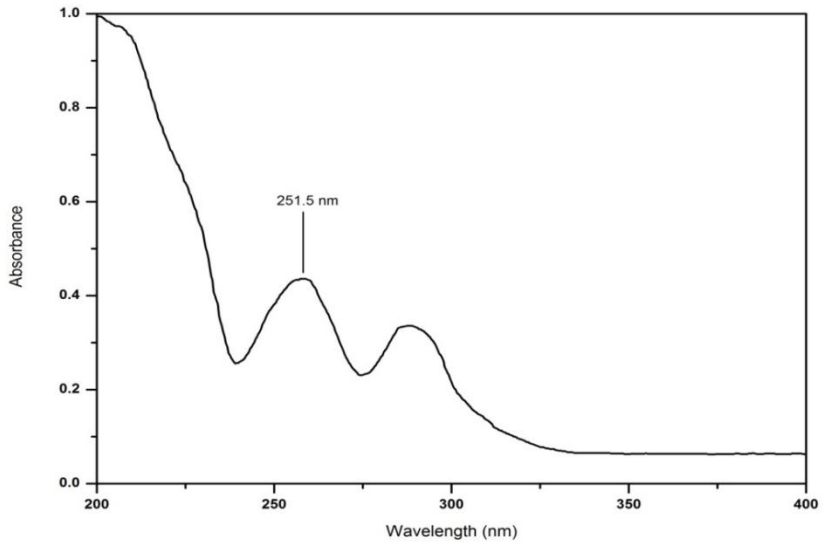


Figure-1 UV spectra of Atovaquone

Wavelength

Wavelength of maximum absorption of Atovaquone in 0.1N HCL was found to be 251.5 nm

Partition coefficient

Partition coefficient of Atovaquone inn-octanol was found to be 0.23

Table-7 Standard calibration Curve data of Atovaquone in 0.1N HCL

S. No	Concentration(µg/ml)	Absorbance at λ max 251.5 nm
1	0	0
2	2	0.184
3	4	0.425
4	6	0.678
5	8	0.896
6	10	1.163

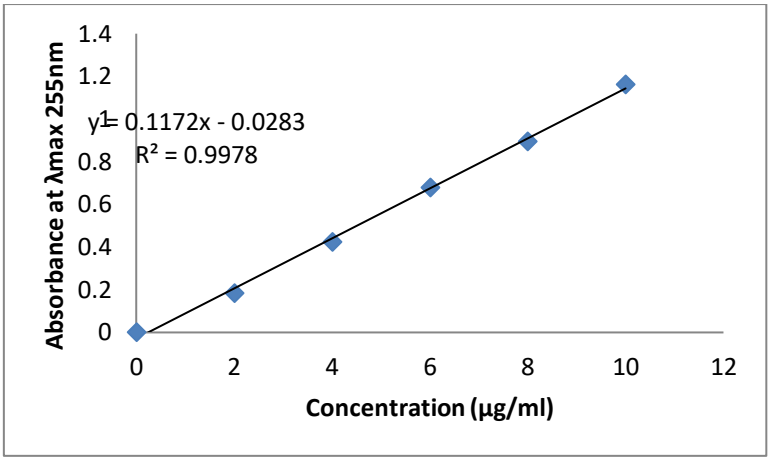


Figure-2 Standard calibration curve of Atovaquone in 0.1N HCL

Evaluation of Solid Dispersion

FTIR study

The FTIR spectra of pure Atovaquone, carriers and solid dispersion of drug with carrier are shown in Tables and Figures. (Figure 3-4 and Table 8)

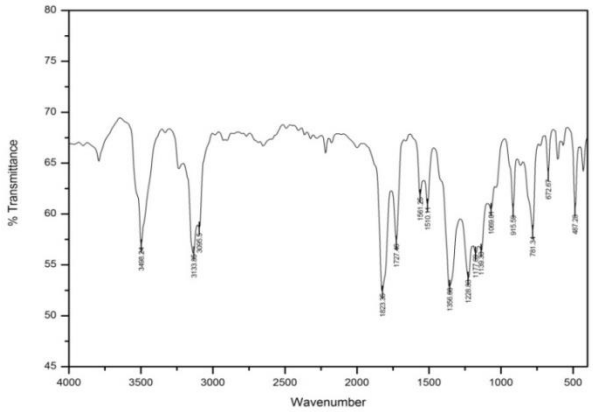


Figure-3 Standard FTIR spectra of Atovaquone

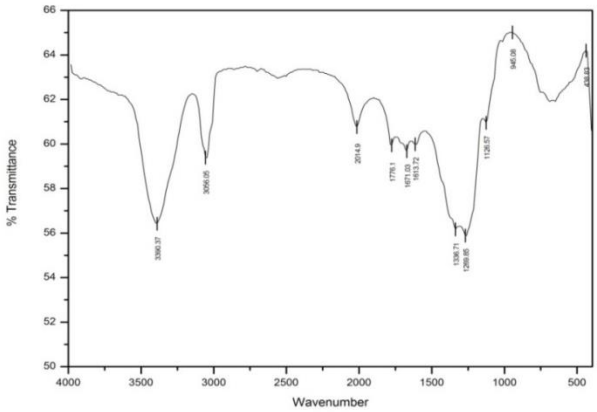


Figure-4 Standard FTIR spectra of PVP K 90

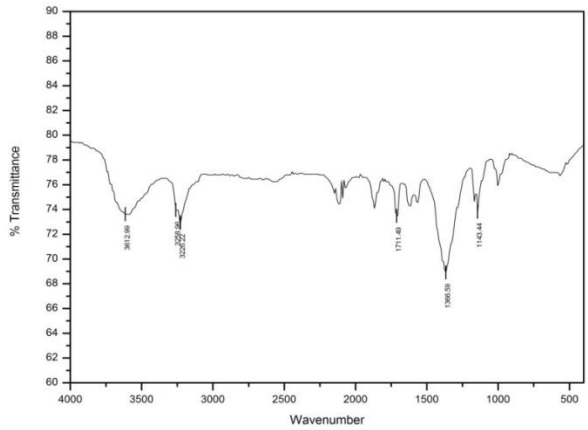


Figure-5 Standard FTIR spectra of PEG 4000

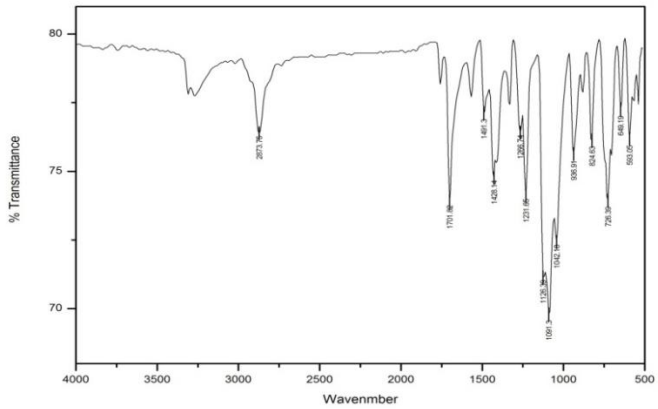


Figure6: Standard FTIR spectra of Solid Dispersion (SD-2)

Table-8 FTIR Spectral Data of Atovaquone, PV K90, PEG 4000 and Solid Dispersion Formulation.

S.No.	IR Spectrum	Peaks(cm-1)	Groups	Stretching /Deformation
1	**Atovaquone**	3483.99	O-H (Alcohol)	Stretching
		1823.24	C=O (Aromatic)	Stretching
		781.36	C-Cl (Alkyl halide)	Stretching
		3095.42	C-H (Aromatic)	Stretching
2	**PVP K90**	3463.99	O-H(Alcohol)	Stretching
		1674.24	C=C(Alkene)	Stretching
		1062.36	C-F(Alkyl halide)	Stretching
		573.42	C-Br(Alkyl halide)	Stretching
3	**PEG4000**	3446.54	O-H(Alcohol)	Stretching
		2889.37	C-H(Alkane)	Stretching
		1640.10	C=O(Amide)	Stretching
		542.79	C-BR (Alkyl halide)	Stretching
4	**Solid Dispersion ()**	3270.38	O-H (Alcohol)	Stretching
		1711.50	C=o (Carbonyl)	Stretching
		1138.58	C-F(Alkyl halide)	Stretching
		744.83	C-Cl(Alkyl halide)	Stretching

Drug Content

Drug content uniformity of Atovaquone solid dispersion in all the formulations (SD1 to SD 6) was shown from 92.56±1.25 to 98.16±1.53 respectively. As shown in Table-9 and Figure-7.

Table-9 Drug content, % Practical Yield and Solubility of Atovaquone in Solid Dispersion formulations

Formulation code	Drug content (in %)	% Practical Yield	Solubility (µg/ml)
SD-(Drug)	-	-	4.84±1.15
SD-1	95.83±2.14	82.17±2.53	22.45±2.09
SD-2	96.28±2.42	84.56±1.19	45.86±2.53
SD-3	92.56±1.25	75.86±1.23	8.53±1.21
SD-4	94.72±1.43	78.54±1.52	12.34±2.34
SD-5	98.16±1.53	81.92±2.53	19.34±3.09
SD-6	96.27±2.20	80.50±1.19	33.95±1.83

* All the values are expressed as mean ± SD; n=3

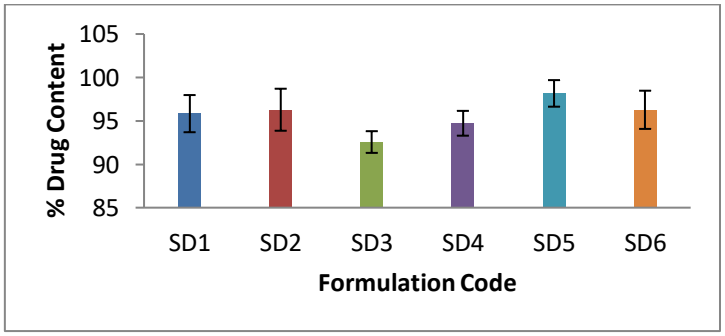


Figure-7 % Drug content of Atovaquone in Solid Dispersion formulations

% Practical Yield and Solidity Estimation

% Practical Yield of Atovaquone solid dispersion in all the formulations (SD1 to SD 6) was shown n Table 6.7 and Figure 6.8. Higher practical yield was found for formulation SD-2 and lowest for SD-3. Solidity study was also performed and results show good improvement in solubility enhancement and was found higher for formulation SD-2. Table 9 and Figure 8 & 9.

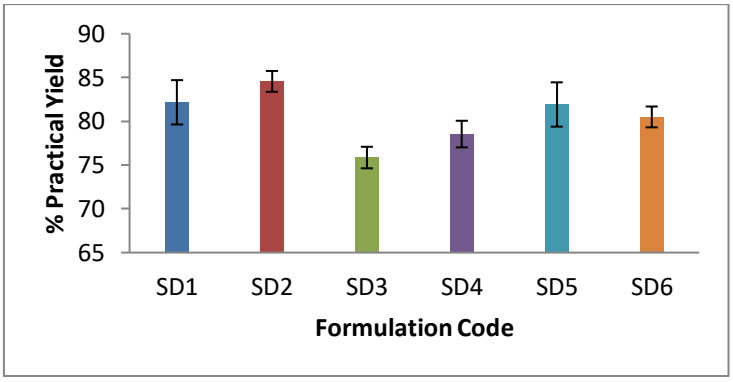


Figure-8 % Practical Yield of Atovaquone in Solid Dispersion formulations

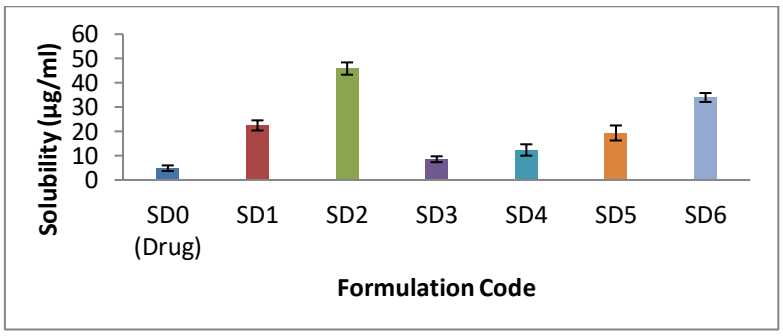


Figure-9 Solubility of Atovaquone in all Solid Dispersion formulations

Pre-Compression Study of Atovaquone Solid Dispersion Formulations

Precompression studies of powdered blend were performed on parameters like bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose as shown in the table below. Angle of repose was found to be 26.09±2.17, 26.51±2.65, and 26.71±3.09. Bulk density 0.53±0.10, 0.52±0.11 and 0.53±0.07g/cm3, tapped density 0.63±0.08, 0.59±0.07 and 0.59±0.05g/cm3, Hausner's ratio 1.07±0.11, 1.09±0.15 and 1.09±0.10,Carrs index 12.58±1.64, 12.32±1.35 and 12.51±1.47were found for F1, F2 and F3 solid dispersion formulations respectively and reported in Table 10 and Figure 10-11.

Table-10 Pre Compression Study of Atovaquone Solid Dispersion Formulations

Formulation Code	Angle of repose (o)	Bulk density (g/ml)	Tapped bulk density (g/ml)	Hausner ratio	Carr's index (%)
F1	26.09±2.17	0.53±0.10	0.63±0.08	1.07±0.11	12.58±1.64
F2	26.51±2.65	0.52±0.11	0.59±0.07	1.09±0.15	12.32±1.35
F3	26.71±3.09	0.53±0.07	0.59±0.05	1.09±0.10	12.51±1.47

* All the values are expressed as mean ± SD; n=3

Post-Compression Study of Atovaquone Solid Dispersion Formulations

The formulated tablets were evaluated for their organoleptic characters. The tablets are round in shape and white in colour. All the tablets showed elegance in appearance. The hardness of the tablets was measured by Monsonto hardness tester. The hardness of all the formulations was found to be in the range of 7.12 to 7.45 kg/cm2. It indicates all the tablets have adequate mechanical strength. Twenty tablets of each formulation were selected for weight variation test. The accepted percentage deviation was ±7.5 for 130-324mg weight tablets. It was within the I.P. limit and all the tablets passed the weight variation test. Friability test was carried out by Roche friabilitor. The maximum weight loss should be not more than 1%. All thetablets passed the friability test. All formulations were exhibited good drug content. Table11 and Figure 12-15.

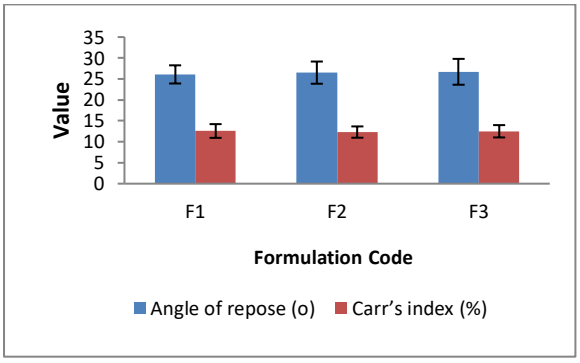


Figure-10 Pre Compression Study of Atovaquone Solid Dispersion Formulation (Angle of repose (⁰) and Carr's index (%))

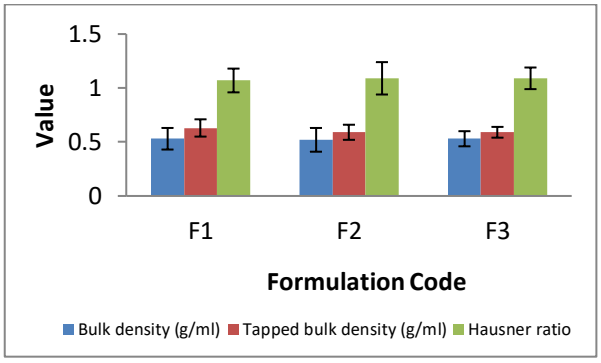


Figure-11 Pre Compression Study of Atovaquone Solid Dispersion Formulations (Bulk density (gm/mL), Tapped density (gm/mL) and Hausner's ratio)

Table-11 Post Compression Study of Atovaquone Solid Dispersion Formulations

Formulation Code	Average Weight	Hardness (kg/cm2)	Friability	% Drug content
F1	351.77±1.26	7.12±0.22	0.53±0.014	99.64±1.27
F2	348.65±1.69	7.35±0.28	0.55±0.018	99.25±1.45
F3	352.12±1.38	7.45±0.14	0.54±0.012	98.76±1.36

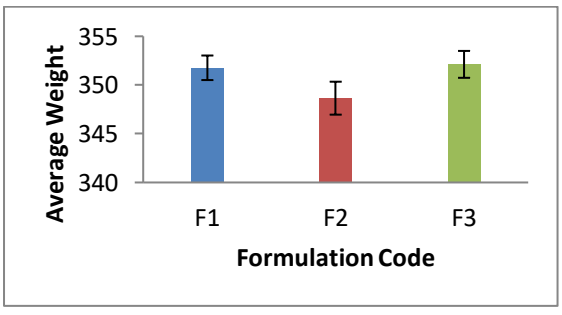


Figure-12 Average Weight of Designed Solid Dispersion Formulations

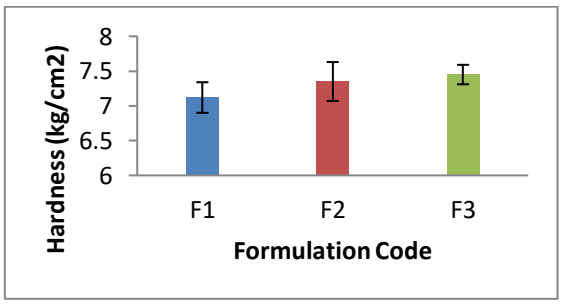


Figure-13 Hardness of Solid Dispersion Formulations

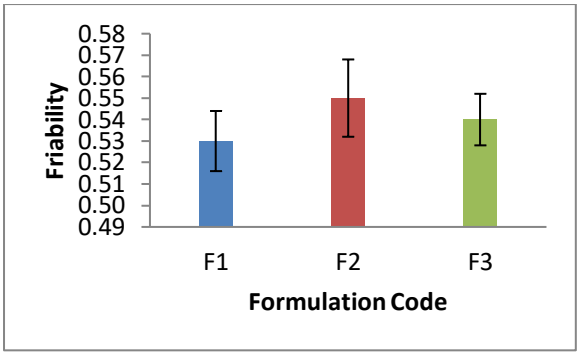


Figure-14 Friability of Solid Dispersion Formulations

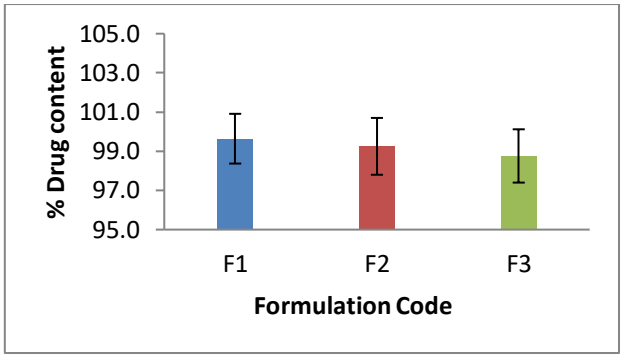


Figure-15 % Drug Content of Solid Dispersion Formulations

In- Vitro Drug Release Study of Atovaquone Solid Dispersion Formulations

In-vitro drug release studies were done for optimized formulations. The drug release was found to show maximum in case of F1 with 46.45% in 180min..as shown in table and figure.

Table-12 % Drug Release Studies of Solid Dispersion Formulations and Marketed Preparations of Atovaquone (Marketed Suspension-Mepron, Tablet-Malarone)

S.No.	Time (Min.)	F1	F2	F3	Marketed Suspension (Mepron)	Marketed Tablet (Malarone)
1.	0	--	--	--	--	--
2.	10	12.04±0.11	7.46±1.54	4.27±2.55	4.11±2.15	4.17±0.11
3.	20	15.95±1.55	12.68±3.55	11.36±2.23	6.25±3.52	8.66±2.23
4.	30	21.67±1.45	14.95±2.23	13.81±1.25	8.98±2.23	10.81±1.25
5.	40	30.33±2.78	16.67±1.45	14.09±1.56	10.47±1.56	12.16±3.55
6.	50	36.19±1.65	18.32±2.53	17.46±3.45	12.42±0.11	13.49±1.54
7.	80	38.49±3.51	20.43±1.22	19.64±1.21	14.96±1.53	15.66±3.55
8.	120	39.47±2.25	23.12±2.55	22.26±1.54	15.81±2.07	17.28±1.61
9.	150	42.13±1.55	26.97±1.45	23.23±2.61	17.43±3.49	19.25±1.52
10.	180	46.45±1.23	28.85±1.56	24.71±2.52	19.13±1.23	21.74±1.47

* All the values are expressed as mean ± SD; n=3

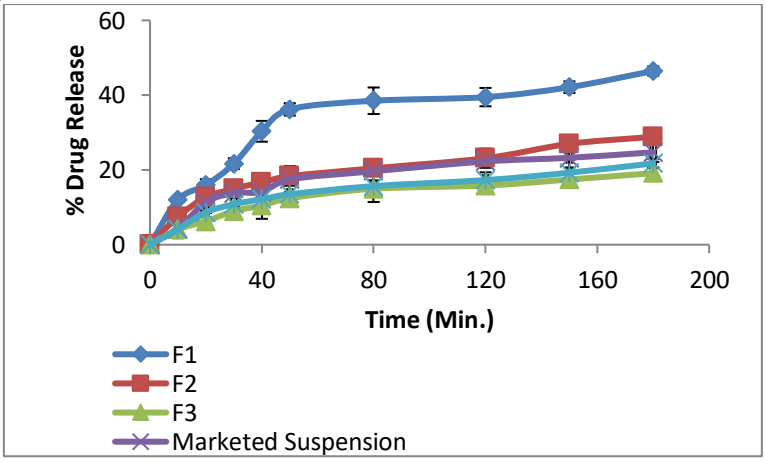


Figure-16 % Drug Release Studies of Solid Dispersion Formulations and Marketed Preparations of Atovaquone(Marketed Suspension-Mepron, Tablet-Malarone)

Conclusion

Thus from studies, it could be concluded that solid dispersion of poor aqueous soluble Atovaquone by solvent evaporation technique were effectively formulated using PEG-4000 and PVP-K 30 hydrophilic polymers. thus, the statement can be given that the rate of dissolution and solubility of poor aqueous soluble Atovaquone can be appreciably improved by solid dispersion by use of water soluble carriers by solvent evaporation technique.

The solubility and dissolution rate of Atovaquone can be enhanced by formulating Solid dispersions of Atovaquone with PEG 4000. The solubilisation effect of PEG 4000, reduction of particle aggregation of the drug, formation of microcrystalline or amorphous drug, increased wet ability and dispersibility, and alteration of the surface properties of the drug particles might be responsible for the enhanced solubility and dissolution rate of Atovaquone from its Solid dispersion. The results showed that the formulation satisfied the objective of enhancement of dissolution, ease of administration and safety. Success of the present study recommends a detailed investigation in to in-vivo studies for its effective use in clinical practice.

Disclaimer Statement

Authors declare that no competing interest exists. The products used for this research are commonly used products in research. There is no conflict of interest between authors and producers of the products.

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