



# International Journal of Pharmaceuticals and Health care Research (IJPHR)

IJPHR | Vol.12 | Issue 2 | Apr - June -2024

www.ijphr.com

DOI : <https://doi.org/10.61096/ijphr.v12.iss2.2024.96-106>

ISSN: 2306-6091

## Research

### Enhancement Of Solubility Dissolution Rate Of Atovaquone By Solid Dispersion Technique



**B. Ananya, Ch. Sudharani, N Sravani, E Laxman, M Saikrishna, K.Neelima Santhoshi\***

*Department Of Pharmaceutics, Svs Group Of Institutions (Autonomous) Bheemaram, Hanumakonda – 506015, Telangana. India.*

*Assistant Professor, Department of Pharmaceutics, SVS Group of Institutions (Autonomous), Bheemaram, Hanumakonda – 506015, Telangana. India.*

\* Author for Correspondence: K. Neelima Santhoshi

Email : neelimatatikonda89@gmail.com

	<b>Abstract</b>
Published on: 1 May 2024	<p>The present study was investigated that enhancement of dissolution rate of Atovaquone using solid dispersion method. For this study PVP- K30, Mannitol, PEG 20000 and Urea were used as carriers and Polyplasdone XL used as super disintegrate. Different ratios between drug and carriers were prepared. All formulations were evaluated for pre and post compression studies and those results were found to be within limits. Dissolution studies revealed that formulations F3 formulation was optimised formulation which contains Drug and Mannitol in the ratio of 1:1. FTIR studies revealed that no interactions between drug and excipients.</p>
Published by: DrSriram Publications	
2024  All rights reserved.	
 <a href="#">Creative Commons Attribution 4.0 International License.</a>	
	<b>Keywords:</b> Atovaquone, Solid dispersion , PVP- K30, Mannitol, PEG 20000,Urea, and Polyplasdone XL.

## INTRODUCTION

From the several previous years, the pharmaceutical scientists were working to enlarge patient compliance and secure dosage forms due to improved requirement in the market for them. As a result, developing the novel technologies has been growing annually because the growth of novel drug molecule requires high cost rather than novel technology. So the current trend in the greater part of pharmaceutical industries is development of dosage form with new formulation technology using old drug molecules to improve safety, efficacy and patient compliance<sup>1,2</sup>. Development of solid dispersion compacts is one such technology to enhance dissolution rate of poorly soluble drugs, thereby improving efficacy of drug molecules<sup>2</sup>.

The most convenient and commonly employed route of drug delivery has been by oral intake. The oral route is the preferred route of drug administration due to its convenience, better patient compliance and low medicinal production costs. In order for a drug to be absorbed into the systemic circulation after oral

administration, the drug must be dissolved in the gastric fluids<sup>2</sup>. It is well conventional that the active ingredient in a solid dosage form must undergo dissolution after it is available for absorption from the gastrointestinal tract. The absorption rate of poor water soluble drug, formulated as an orally administered solid dosage form, is controlled by its dissolution rate in the fluid present at the absorption site, i.e. the dissolution rate is the rate limiting step in drug absorption<sup>3</sup>. The poor dissolution rate of water insoluble drugs and poorly soluble drugs is still a significant problem confronting the pharmaceutical industry. Newly developed chemical entities do not reach the market because of their poor oral bioavailability due to inadequate dissolution in G.I fluids. The active ingredient must undergo dissolution before it is available for absorption from the gastrointestinal tract. The poor dissolution characteristics of water insoluble drugs are a major challenge for pharmaceutical industries. Accordingly, many hydrophobic drugs show erratic and partial absorption from the gastrointestinal tract.

One of the major challenges in drug development nowadays is poor solubility, as estimated 40% of all newly developed drugs are poorly soluble or insoluble in water. In addition, up to 50% of orally administered drug compounds suffer from formulation problems related to their low solubility and high lipophilicity.<sup>4,5</sup> Bioavailability of poorly water-soluble drugs is inadequate by their solubility and dissolution rate. Especially for class II substances according to the Biopharmaceutics Classification System (BCS), the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids. The term "water-insoluble drugs" includes those drugs that are "sparingly water-soluble" (1 part solute into 30 to 100 parts of water), "slightly water-soluble" (1 part solute into 100 to 1000 parts of water), "very slightly water-soluble" (1 part solute into 1000 to 10,000 parts of water), and "practically water-insoluble" or "insoluble" (1 part solute into 10,000 or more parts of water).

### BCS classification system

Based on the solubility and permeability, drugs are classified into four categories. Biopharmaceutics Classification System (BCS) was introduced by *Amidon et al.*, as a basis for predicting the possibility of *in vitro-in vivo* correlations for immediate release dosage forms, based on the detection that drug solubility/dissolution properties and gastrointestinal permeability are the fundamental parameters controlling the rate and extent of drug absorption.

The BCS was developed mainly in the situation of immediate release solid oral dosage forms. It is the scientific support for classifying drug substances based on their aqueous solubility and intestinal permeability. It is the drug development tool that allows estimation of the contributions of three major factors dissolution, solubility and intestinal permeability that affect oral drug absorption from immediate release solid oral dosage forms. It was first introduced into regulatory decision making process into guidance document of immediate release solid oral dosage forms:

#### Class

##### **Class I: High permeability and solubility.**

**Formulation independent:** The bioavailability of class I compounds is determined only by delivery of the drug solution to the intestine. Examples: Benzapril, Loxoprofen, Sumatriptan etc.

##### **Class II: High permeability but low solubility**

**Formulation dependent:** The bioavailability of class II compounds is limited by drug solubility/dissolution. Examples: Valsartan, Nimesulide, Loratadine, Aceclofenac etc.

##### **Class III: Low permeability but high solubility**

**Dependent on barrier properties:** The bioavailability of class III compounds is limited by intestinal permeability. Examples: Gabapentine, Topiramate, Atropine etc.

##### **Class IV: Low permeability and low solubility**

**Formulation and barrier properties dependent:** The bioavailability of class IV compounds is limited both by solubility/dissolution and intestinal permeability. Examples: Hydrochlorthiazide, Furosemide, Meloxicam etc.

### Techniques for Dissolution Enhancement

There are various techniques available to improve the solubility subsequently improves dissolution rate of poorly soluble drugs. Some of the approaches to improve the solubility and dissolution rate are

#### Micronization

Particle size reduction leads to increase in the effective surface area resulting in enhancement of solubility and dissolution velocity of the drug. Micronization is used to improve dissolution rates of drugs into the biological environment, in order to improve the oral bioavailability. Micronization of drugs is widely done by milling techniques using a jet mill, rotor stator, colloidal mill, and air attrition. But, the effect of micronization is often

unsatisfactory, particularly when the drugs are encapsulated or tablet. Micronized drugs also have the affinity to agglomerate as a result of their hydrophobicity, thus reducing their available surface area. A hydrophobic powder with small particle size leads to aggregation, making it difficult to disperse. The particles float on the dissolution medium because of entrapped air. It is difficult to remove or wet these particles. All these effects, in fact, reduce the rate of dissolution.<sup>5</sup>

### **Nanonization**

Recently, various nanonization strategies have emerged to increase the dissolution rates and bioavailability of several drugs that are poorly soluble in water. Nanonization broadly refers to the study and use of materials and structures at the nano scale level of approximately 100 nm or less. Nanonization can result in improved drug solubility and pharmacokinetics, and it may also decrease systemic side-effects.<sup>6</sup> There are different techniques used for nanonization of drug including Wet milling, Homogenization, Emulsification-solvent evaporation technique, Pear milling, Spray drying etc.

### **Salt form**

Salts have improved solubility and dissolution characteristics in comparison to the original drug. Example: Salt of basic drug like Atropine is more soluble than parent drug. Salt formation may increase hygroscopicity leading to stability problems. Solubilization technique lead to liquid formulations that is typically unattractive from patient acceptability and commercialization.

### **Use of surfactants**

Solubilization enhanced by using surfactants, to solubilize a poorly soluble substance is to reduce the interfacial tension between the surface of solute and solvent for better wetting and salvation interaction. Various surfactants like Polyglycolized glyceride (Labrasol), Tweens, Spans, Polyoxyethylene stearate and synthetic block copolymers like Poly (propylene oxide)-poly (ethylene oxide) – poly (propylene oxide), Poly (beta-benzyl-L-aspartate), b-poly (ethylene oxide) etc., used as carrier for solubility and dissolution enhancement. Improvement of drug solubility by using the amphiphilic surfactants is due to lowering of surface tension between drug and solvent, improvement of wetting characteristics and micellar solubilization of the drugs. To get some significant solubility enhancement, the surfactant concentration must be at least above the critical micelle concentration (CMC). The CMC will depend upon the surfactant itself and the ionic strength of the media. The amount of surfactant required depends on the CMC and the degree to which the compound partitions into the surfactant micelles but the solubilization of drugs in aqueous media by the use of surfactants leads to liquid formulations that are generally less patient acceptability and commercialization.

### **Use of Co-solvents**

Co-solvent is a highly effective technique for enhancement of solubility of poorly soluble drugs. It is well-known that the addition of an organic co-solvent to water can significantly change the solubility of drugs. Weak electrolytes and nonpolar molecules have poor water solubility and it can be enhanced by changing polarity of the solvent. This can be achieved by addition of another solvent. This process is known as co-solvency. Solvent used to increase solubility is known as co-solvent. Co-solvent system mechanism is reducing the interfacial tension between the aqueous solution and hydrophobic solute. The use of mixed solvent system is frequently necessary in pharmaceuticals when a drug is poorly soluble. Co-solvents such as ethanol, propylene glycol, glycerin, sorbitol and polyoxyethylene glycols, dimethylsulfoxide, ethanol and N, N dimethyl formamide can be used<sup>6</sup> but the solubilization of drugs in inorganic solvents or in aqueous media by the use of co solvents leads to liquid formulations that are generally less patient acceptability and commercialization.

### **Use of Metastable Polymorphs**

The presence of metastable, polymorphic crystalline forms can exert a great influence on the solubility, dissolution rate, and biological activity of medicaments. The separation and selective use of a definite polymorphic form to have the highest solubility, is a technique that can be useful in certain cases for the increase of dissolution rates. Melting followed by rapid cooling or recrystallization from different solvents can produce metastable forms of a drug. For example, a metastable form of chloramphenicol palmitate is more water-soluble than the A and C forms.

### **Drug Dispersion in Carriers**

**Solid Solutions:** A solid solution is a binary system comprising a solid solute molecularly dispersed in a solid solvent. Since the two components crystallize together in a homogeneous one-phase system, solid solutions are also called molecular dispersions or mixed crystals. They are generally prepared by a fusion method, whereby a physical mixture of solute and solvent are melted together followed by rapid solidification. Ex; solid solution of griseofulvin–succinic acid dissolves 6–7 times faster than pure griseofulvin.<sup>8</sup>

**Eutectic Mixtures:** These systems are prepared by a fusion method. Eutectic melts differ from solid solutions in that the fused melt of solute and solvent show complete miscibility but negligible solid–solid solubility. When the binary mixture is exposed to water, the soluble carrier dissolves rapidly leaving the insoluble drug in a state of microcrystalline dispersion of very fine particles. Examples of eutectic mixtures include paracetamol–urea, griseofulvin–urea, and griseofulvin–succinic acid.<sup>8</sup>

The advantage with solid solutions and eutectics is that they are melts, are easy to prepare, and are economical because no solvent is used. Some limitations are that it cannot be applied to drugs that fail to crystallize from the mixed melt, thermolabile drugs, and carriers such as succinic acid that decompose at their melting points.

**Solute–Solvent Complexation Reactions:** Molecular complexation between molecules of dissolving solutes and certain solvents have been known to affect dissolution rates. The major complexation mechanism in these systems is hydrogen bonding.

**Solid dispersion:** The dispersion method allows the preparation of physically modified forms of the drug that are much more rapidly soluble in water than the pure compound. The most regularly used hydrophilic carriers for solid dispersions include polyvinyl pyrrolidone, polyethylene glycols, and pladone-S630. Surfactants may also be used in the formation of solid dispersions. Surfactants like Tween-80, Myrj-52, Pluronic-F68 and sodium lauryl sulfate are used as water-soluble polymer, as an excellent universal carrier for improving the dissolution rate and oral absorption of water-insoluble drugs. Various methods are used in preparation of solid dispersion like fusion (melting), solvent evaporation, lyophilization (freeze drying), melt agglomeration, extrusion, spray drying, surfactant use, electrostatic spinning, and super critical fluid technology. In the preparation, the use of vast amount of organic solvent may cause environment and safety concern. The surface solid dispersions were introduced to overcome this limitation. But still there are limitations for this technique which be positioned with the use of solvents for preparation of surface solid dispersions. Finding an appropriate solvent to dissolve the drug and carrier is difficult. Complete removal of solvent is complicated and residual solvent cause toxicity.

**Sonocrystallisation:** This technique is successfully employed to reduce particle size by using ultrasound, is sonocrystallisation which is a novel approach by use of anti-solvents and liquid solvents. By adding these anti-solvents and liquid solvents, recrystallization of poorly water soluble drugs occurs.

**High pressure homogenization:** It is basically involves the use of high pressure with very high velocity by passing the crystalline drug aqueous dispersion through a narrow gap. The proposed mechanism for this process is by shear forces and cavitations due to which particles get disintegrated. In this homogenization process drug particle which are obtained is dependent on directly pressure, nature of drug substance and number of homogenization cycles undergone. It can be performed in two ways: either in water (that is in disso cubes) or in water reduced media (nanopure).

**Nanomorph technology (NT):** By use of NT low water soluble drug substances are converted into amorphous nanomorph from crystalline state. In this suspension of drug substance is prepared in a solvent which is mixed with other solvent in a chamber, due to this a conversion of drug suspension into a true molecular solution occur. Precipitation of drug substance is induced by the aqueous solution of polymer. These polymers play an important role in preventing of aggregation or growth and maintain their nanoparticulate state. The example is CAP, Calcium-phosphate based nanoparticles which improve the oral bioavailability of hormones and proteins.

**Evaporative precipitation:** In this technique there is a rapid phase separation for nucleation and growth of microparticles and nanoparticles of water insoluble drugs. In this low boiling solvent is selected and a suitable amount of drug is added to it and the resultant solution is passed and pumped through a inert tube which is heated to a temperature under pressure above the selected organic solvent boiling point and sprayed into the heated aqueous solution through a fine atomizing nozzle. Further the surfactants are added so as to optimize the particle size.

## Methods for preparing solid dispersion

### Simple physical mixture

This method is simple and it was earlier used. Solid dispersion can be prepared by simple mixing of the drug and carrier in mortar-pestle.

### Fusion method

In fusion method first mix the drug and carrier in require proportion. Then melt the resultant mixture in china dish by giving of heat up to melting point. Cool the melted mixture in ice bath and convert in solid. Afterward pass the prepared solid dispersion through small size screen. Sekiguchi and Obi used a fusion method

to prepare simple eutectic mixtures. They use Sulphathiazole and urea (carrier) melted together at a temperature above the eutectic point and then cooled in an ice bath. Molecular dispersion can be depends on the degree of supersaturation and rate of cooling in the process.

The important limitation of this method is the thermostability of the drug and the carrier. If temperature required to high, the drug may decompose or evaporate.

### Complexation with Cyclodextrins

Complexation is the association between two or more molecules to form a non bonded entity with a well-defined stoichiometry. The beta and gamma cyclodextrins and several of their derivatives are unique in having the ability to form molecular inclusion with hydrophobic drugs having poor aqueous solubility. The two types of complexation that are most useful for increasing the solubility of drugs in aqueous media are stacking and inclusion. Stacking complexes are formed by the overlap of the planar regions of aromatic molecules, while inclusion complexes are formed by the insertion of the nonpolar region of one molecule into the cavity of another molecule (or group of molecules).

The  $\alpha$ -,  $\beta$ - and  $\gamma$ -cyclodextrins are cyclic oligosaccharides consisting of six, seven, and eight glucose units respectively. One of the important properties of these naturally occurring cyclodextrins is their ability to form inclusion complexes with smaller molecules that fit into the hydrophobic cavity of the cyclodextrin. The formation of inclusion complexes alters a variety of the physicochemical properties of the drug molecule such as solubility, dissolution rate, membrane permeability, chemical reactivity, and dissociation constant. In some cases, as the concentration of cyclodextrin increases, the solubility increases initially, levels off, and then decreases.

Among them, liquisolid compacts is one of the most promising and new technique which promotes dissolution rate of water insoluble drugs.<sup>9</sup> The term liquisolid compact refers to immediate release or sustained release tablets or capsules, combined with the inclusion of appropriate adjuvant required for tablets or encapsulating.

**Sublimation** is the transition of a substance directly from the solid to the gas phase without passing through an intermediate liquid phase. Sublimation is an endothermic phase transition that occurs at temperatures and pressures below a substance's triple point in its phase diagram. The reverse process of sublimation is desublimation, or deposition.

At normal pressures, most chemical compounds and elements possess three different states at different temperatures. In these cases, the transition from the solid to the gaseous state requires an intermediate liquid state. Note, however, that the pressure referred to here is the partial pressure of the substance, not the total (e.g., atmospheric) pressure of the entire system. So, all solids that possess an appreciable vapor pressure at a certain temperature usually can sublime in air (e.g., water ice just below 0 °C). For some substances, such as carbon and arsenic, sublimation is much easier than evaporation from the melt, because the pressure of their triple point is very high, and it is difficult to obtain them as liquids.

When change of a solid substance directly to a vapor without first passing through the liquid state. The term is also used to describe the reverse process of the gas changing directly to the solid again upon cooling. An example of sublimation is seen when iodine, on being heated, changes from a dark solid to a purplish vapor that condenses directly to a crystalline solid upon striking a cool surface. In this way pure crystals of iodine are prepared. Some other substances, e.g., mercuric chloride, can be prepared by sublimation. Solid carbon dioxide, commonly known as dry ice, sublimates at -78.5°C (-109.3°F). Sublimation also occurs when air saturated with water vapor is suddenly cooled below the freezing point of water. Frost and snowflakes are thus formed by water changing directly from the gaseous to the solid state. Sublimation requires additional energy and is an endothermic change. The enthalpy of sublimation (also called heat of sublimation) can be calculated as the enthalpy of fusion plus the enthalpy of vaporization.

## MATERIALS

Atovaquone-Procured from Matrix Lab Ltd, Hyderabad., India. Provided by SURA LABS, Dilsukhnagar, PVP- K30-Merck Specialities Pvt Ltd, Mumbai, India, Mannitol-Merck Specialities Pvt Ltd, Mumbai, India, PEG 20000-Merck Specialities Pvt Ltd, Mumbai, India, Urea-Merck Specialities Pvt Ltd, Mumbai, India, Polyplasdone XL-Merck Specialities Pvt Ltd, Mumbai, India, Mg.stearate-Merck Specialities Pvt Ltd, Mumbai, India, Talc-Merck Specialities Pvt Ltd, Mumbai, India, MCC-Merck Specialities Pvt Ltd, Mumbai, India.

## METHODOLOGY

### Preformulation Studies

Pre formulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system.

### Analytical method development for Atovaquone

#### Determination of Absorption maxima

A spectrum of the working standards was obtained by scanning from 200-400nm against the reagent blank to fix absorption maxima. The  $\lambda_{\text{max}}$  was found to be 251 nm. Hence all further investigations were carried out at the same wavelength.

#### Preparation of standard graph in pH 6.8 medium

10 mg of Atovaquone was dissolved in 10 ml methanol (Primary stock). From this primary stock 1 ml was transferred to another volumetric flask made up to 10ml with Phosphate buffer of pH 6.8 (Secondary stock). From this secondary stock was taken to produce 2, 4, 6, 8 and 10  $\mu\text{g/ml}$  respectively. The absorbance was measured at 251 nm by using a UV spectrophotometer.

### Formulation Development

Solid dispersions were prepared by solvent evaporation method. Methanol was used as solvent. Water soluble polymers such as PVP- K30, Mannitol, PEG 20000 and Urea were selected as carriers. Drug and Carriers were taken in different ratios stated in the formulation chart (Table 7.1). The prepared solid dispersions were passed through the sieve no 20 to get uniform sized particles. The solid dispersions were mixed with required quantities of super disintegrate, diluent, lubricant and glidant. (Table 7.2) The blend was evaluated for precompression parameters.

**Table 1: Formulation of solid dispersion showing various compositions**

Ingredients	SD1	SD2	SD3	SD4	SD5	SD6	SD7	SD8
Atovaquone	1	1	1	1	1	1	1	1
PVP- K30	1	2	-	-	-	-	-	-
Mannitol	-	-	1	2	-	-	-	-
PEG 20000	-	-	-	-	1	2	-	-
Urea	-	-	-	-	-	-	1	2

**Table 2: Formulation of fast dissolving tablet by using solid dispersion**

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Atovaquone	500	750	500	750	500	750	500	750
equivalent to 250mg	SD1	SD2	SD3	SD4	SD5	SD6	SD7	SD8
Polyplasdone XL	20	20	20	20	20	20	20	20
Mg.stearate	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3
MCC	QS	QS	QS	QS	QS	QS	QS	QS
Total weight	1000	1000	1000	1000	1000	1000	1000	1000

## RESULTS AND DISCUSSION

### Determination of $\lambda_{\text{max}}$

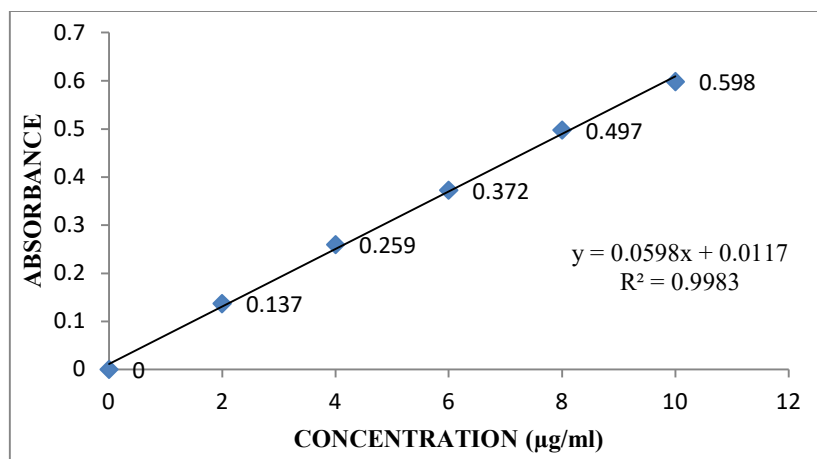
The prepared stock solution was scanned between 200-400 nm to determine the absorption maxima. It was found to be 251 nm.

### Calibration curve of Atovaquone

The standard graph of Atovaquone was obtained and good correlation was obtained with  $R^2$  value of 0.998. The medium selected was pH 6.8 phosphate buffer. The standard graph values of Atovaquone are tabulated as below.

**Table 3: values of Atovaquone at 251 nm in pH 6.8 phosphate buffer**

Concentration (µg/ml)	Absorbance
0	0
2	0.137
4	0.259
6	0.372
8	0.497
10	0.598

**Fig 1: Standard Curve of Atovaquone****Characterization of Precompression Blend**

The precompression blend of Atovaquone solid dispersions were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Angle of repose was less than  $35.23^\circ$ , Carr's index values were less than 20.01 for the precompression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.26 for all the batches indicating good flow properties.

**Table 4: Physical properties of precompression blend**

Formulation Code	Angle of repose (°)	Bulk density (gm/cm <sup>3</sup> )	Tapped density (gm/cm <sup>3</sup> )	Carr's Index (%)	Hausner's ratio
F1	35.12±0.019	0.3823±0.0032	0.4852±0.0044	20.01±0.0848	1.26±0.0000
F2	34.99±0.003	0.3910±0.0014	0.4650±0.0036	15.90±0.3040	1.16±0.0070
F3	33.86±0.002	0.2896±0.0014	0.3449±0.0013	16.04±0.3676	1.18±0.0424
F4	35.23±0.001	0.3100±0.0035	0.3655±0.0031	15.19±0.2969	1.17±0.0070
F5	32.61±0.001	0.3925±0.0026	0.4614±0.0028	14.93±0.9545	1.16±0.0070
F6	31.60±0.017	0.4082±0.0071	0.4808±0.0020	15.09±1.4495	1.17±0.0141
F7	34.21±0.006	0.3683±0.0009	0.4473±0.0002	17.66±0.0212	1.21±0.0212
F8	34.75±0.003	0.4214±0.0068	0.5245±0.0013	19.64±0.5020	1.24±0.0070

**Evaluation of Tablets****Physical Evaluation of Atovaquone solid dispersion tablets**

The results of the weight variation, hardness, thickness, friability, and drug content of the tablets are given in Table 7. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from  $2.2 \pm 0.31$  to  $2.8 \pm 0.26$  kg/cm<sup>2</sup> and the friability values were less than 1% indicating that the tablets were compact and hard. The thickness of the tablets ranged from  $2.1 \pm 0.15$  to  $2.4 \pm 0.16$  mm. All the formulations satisfied the content of the drug as they contained 95-100% of Atovaquone and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically within control limits.

**Table 5: Physical Evaluation of Atovaquone tablets**

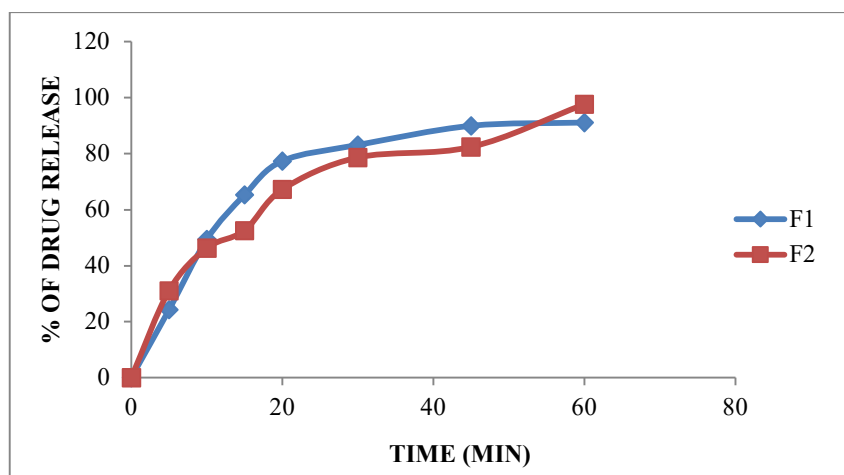
Formulation code	Average Weight (mg)	Thickness (mm)	Hardness (Kg/cm <sup>2</sup> )	Friability (%)	Content uniformity (%)
F1	998.12	6.56	4.3	0.35	98.36
F2	997.65	6.31	4.9	0.48	97.12
F3	999.14	6.82	4.7	0.62	95.24
F4	997.29	6.48	4.1	0.72	97.83
F5	995.82	6.91	4.5	0.49	96.28
F6	996.47	6.72	4.7	0.68	99.57
F7	998.75	6.14	4.5	0.31	97.36
F8	997.56	6.94	4.0	0.75	98.33

***In vitro* release studies**

The drug release rate was studied using the USP type II dissolution test apparatus. The dissolution medium was 900 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of  $37 \pm 0.5$  °C. Samples of 5 ml were collected at different time intervals up to 1 hr and analysed after appropriate dilution by using UV Spectrophotometer at 251 nm.

**Table 6: *In vitro* drug release results for all formulations**

TIME(Min)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
5	24.31	31.10	19.59	17.81	26.46	15.84	11.25	20.92
10	49.40	46.34	32.14	30.65	35.91	21.63	19.71	27.87
15	65.34	52.58	37.79	44.73	55.69	29.32	26.31	33.66
20	77.37	67.26	44.52	52.14	78.37	35.18	38.10	40.45
30	83.12	78.65	57.91	66.43	93.81	53.26	47.57	53.63
45	89.92	82.39	73.50	76.15	96.14	68.72	59.20	72.48
60	91.14	97.67	98.41	89.61	96.14	89.54	66.46	91.54

**Fig 2: *In vitro* dissolution data for formulations F1-F2 containing PVP- K30 as carrier.**



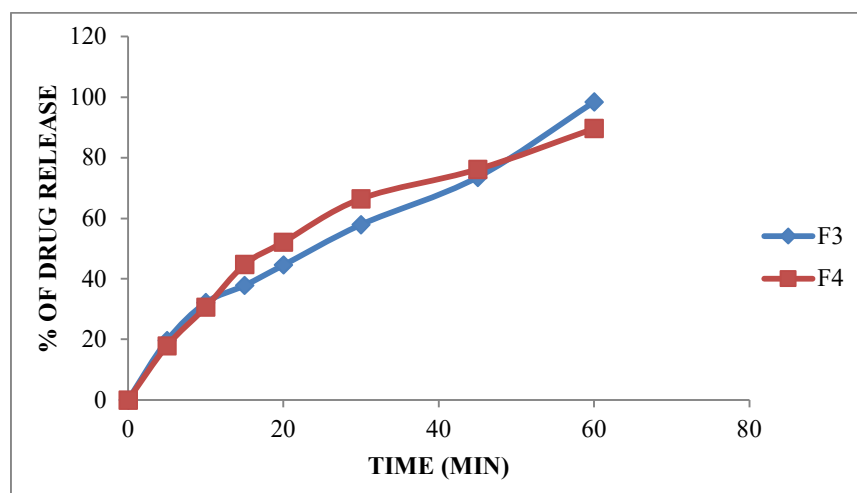


Fig 3: *In vitro* dissolution data for formulations F3-F4 containing Mannitol as carrier.

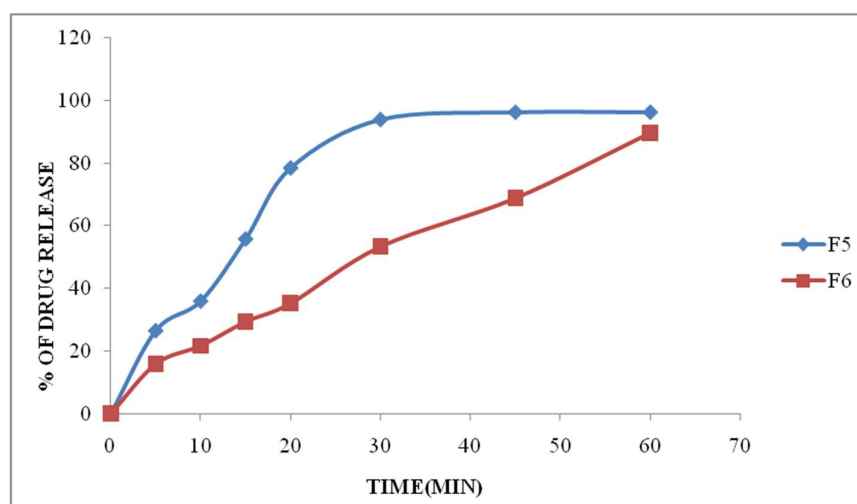


Fig 4: *In vitro* dissolution data for formulations F5 and F6 containing PEG 20000 as carrier

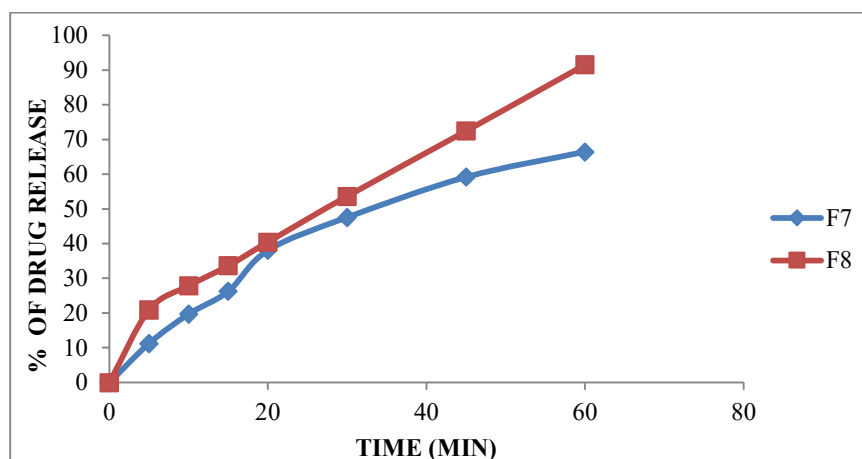
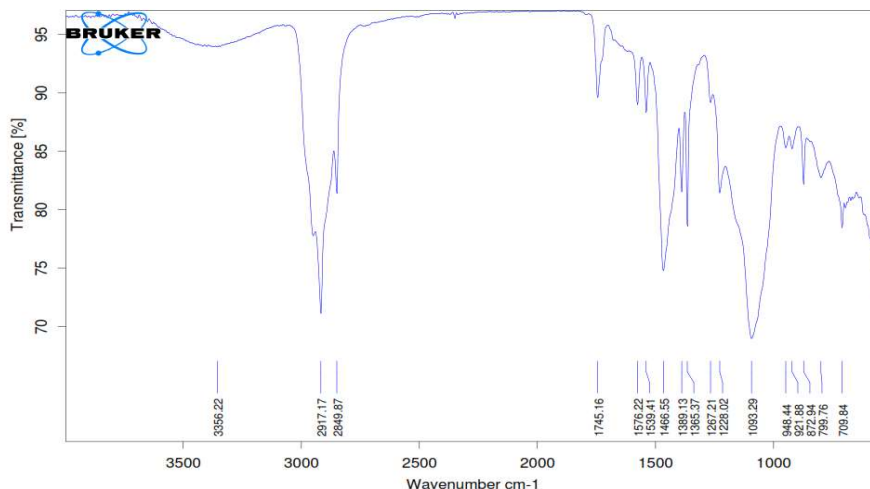


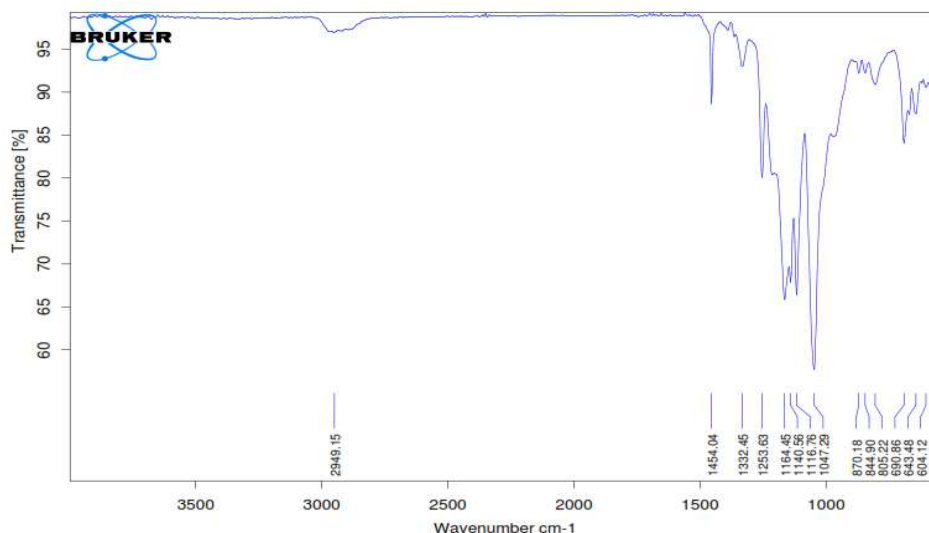
Fig 5: *In vitro* dissolution data for formulations F7 and F8 containing Urea as carrier

From the dissolution data, Formulations containing Mannitol as carrier was shown good drug release compared to formulations containing PVP- K30, PEG 20000 and Urea as carrier. F5 to F8 formulations were not shown maximum drug release. Hence those formulations were not taken into consideration. Among all formulations F3 formulations containing Drug and Mannitol in the ratio of 1:2 was shown maximum drug release at 60 min. Hence F3 formulation was concluded as optimised formulation. From the comparison graphs revealed that Formulation F3 was shown maximum drug release at 60 min. Hence Among all formulations F3 was considered as optimised formulation.

#### Drug – Excipient Compatibility Studies By FTIR Studies



**Fig 6: Ftir Spectra Of Pure Drug**



**Fig 7: Ftir Spectra Of Optimised Formula**

From the above graphs it was showed no interactions between drug and excipients. Both API and excipients compatibility with each other.

## CONCLUSION

Atovaquone is an treatment or prevention of *Pneumocystis carinii* pneumonia in patients who are intolerant to trimethoprim-sulfamethoxazole (TMP-SMX). Also indicated for the acute oral treatment of mild to moderate PCP in patients who are intolerant to TMP-SMX. The standard curve of Atovaquone was obtained and

good correlation was obtained with  $R^2$  value of 0.998. The medium selected was pH 6.8 phosphate buffer. FTIR studies revealed that no interactions between drug and excipients. The pre compression blend of Atovaquone solid dispersions were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. The precompression blend of all the batches indicating good to fair flowability and compressibility. Solid dispersions were prepared with various concentrations of carriers, the prepared solid dispersions were compressed into tablets. The formulated tablets were evaluated for various quality control parameters. The tablets were passed all the tests. Among all the formulations F3 formulation containing, Drug and Mannitol in the ratio of 1:1 showed good result that is 98.41 % in 60 minutes.

## REFERENCES

1. Jaysweh J Harani, Dhaval A Rathod, Kantilal R Vadila, Orally disintegrating tablets, A review, *Tropical Journal of Pharm.Sciences*, 2009, 8(2), 161-172.
2. V.B.Yadav, A.V.Yadav, Lquisolid granulation technique for tablet manufacturing, an overview, *Journal of Pharmacy Research*, 2009, 2(4), 670-674.
3. Spireas S, Bolton M, Lquisolid systems and methods of preparing same, U.S. Patent 5,968,550, 1999.
4. Ellsworth AJ, Witt DM, Dugdale DC, Medical Drug Reference, Elsevier science, Missouri, 2003, 610-612.
5. Subrahmanyam, C. V. S. Dissolution. In *Textbook of Physical Pharmaceutics*, 2nd ed.; Jain, M. K., Ed.; Vallabh Prakashan: Delhi, India, 2000; pp 1, 92.
6. Ahmad Zaheer et al., Solubility enhancement of poorly water soluble drugs, a review *IJPT*, 2011, 3(1), 807-82.
7. Brahamankar D. M; Jaiswal S. B; Bioavailability and Bioequivalence, In *Biopharmaceutics and Pharmacokinetics*, A Treatise, 1st edition, Vallabh Prakashan: Delhi, India, 1995, 298-299.
8. Sekiguchi K, Obi N, Studies on absorption of eutectic mixtures, I. A comparison of the behavior of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man, *Chem. Pharm. Bull*, 1961, 9, 866–872.
9. Fahmy RH, Kassem MA, Enhancement of famotidine dissolution rate through lquisolid tablet formulation: In vitro and In vivo evaluation, *Eur. J. Pharm. Biopharm*, 2008, 69, 993-1003.
10. Spiras S, Lquisolid systems and methods for preparing same, United States patent, 6,423,339 B1, (2002).
11. Ajit S. Kulkarni, Nagesh H. et al., Lquisolid Systems: A Review. *International Journal of Pharmaceutical Sciences and Nanotechnology*, 2010, 3(1), 795-802.
12. Spireas SS, Jarowski CI, Rohera BD. Powder Solution technology, Principles and Mechanism, *Pharma Research*, 1992, 9, 1351 – 1358.
13. Kiranbabu, N.Tharun, formulation and evaluation of Rosuvastatin immediate release tablets. An embase, encase covered journal 2014, 5(2), 1924- 1928.
14. Frizon Fernando, Josimar de Oliveira Eloy, Carmen Maria Donaduzzi, Márcia Lina Mitsui, and Juliana Maldonado Marchetti. "Dissolution rate enhancement of loratadine in polyvinylpyrrolidone K-30 solid dispersions by solvent methods." *Powder Technology* 235 (2013): 532-539.
15. Hafsa Mohammadi, V Hemanath Kumar. Formulation and Evaluation of Solid Dispersion Incorporated Fast Disintegrating Tablets of Tenoxicam Using Design of Experiment. *International Journal of Pharmaceutical Sciences and Drug Research* 2019; 11(1): 35-44.