Formulation and Optimization of Atovaquone Micronized Suspension by Top-down Method

Harsha Kathpalia, Sukanya Das, Supriya Shidhaye*

Department of Pharmaceutics, Vivekanand Education Society’s College of Pharmacy, Affiliated to University of Mumbai, Mumbai, Maharashtra, INDIA.

ABSTRACT

Aim: The present work aimed to tackle the solubility issue of a Biopharmaceutics Classification System (BCS) II drug, Atovaquone. Methods: Formulation of micronized suspension of atovaquone was optimized by employing a 3² full factorial design keeping poloxamer 188 (wetting agent) and phospholipon 90H (stabilizer) as the influential variables affecting the dependent variables viz. particle size and polydispersity index (PdI). Selected formulations from the optimized design space were further evaluated for dissolution and the formulation exhibiting maximum dissolution within 120 min was selected. The optimized batch consisting of atovaquone (15%), poloxamer 188 (2%), phospholipon 90H (1%), glycerin (10%) in the aqueous vehicle was microfluidized. Results: The particle size of resultant suspension was Z_{avg} = 1313 ± 40 nm and PdI = 0.1 ± 0.05. The zeta potential of the final micronized suspension was 0.0555 mV which indicated steric stabilization of the particles. The micronized suspension was adsorbed on a mixture of Kollidon CL SF and Aerosil 200 (2:1) and then dried and passed through 40# sieve. Conclusion: The solid-state characterization of the formulation revealed that the crystalline nature of the drug was retained after the milling process. The saturation solubility and in-vitro dissolution of adsorbed micronized suspension were 2.3-fold times enhanced as compared to the pure drug suspension due to a reduction in particle size. The top-down approach can be employed to improve the poor aqueous solubility of atovaquone. Key words: Atovaquone, Micronized suspension, Microfluidization, Full factorial design, Solubility enhancement.

INTRODUCTION

Enhancing the aqueous solubility is the most challenging phase of the drug development of a BCS class II drug. Atovaquone is a highly lipophilic (log \(p = 5.8\)) antiprotozoal agent. Although it is acidic, the high pKa (9.1) renders it essentially neutral at physiological pH. Atovaquone has extremely low aqueous solubility (less than 0.1 µg/ml). The adult dose of Atovaquone is 1000 mg/day for the treatment of malaria and 1500 mg/day for Pneumocystis pneumonia. In humans, the mean absolute bioavailability of atovaquone from Malarone tablets is merely 21% in the fed state and in the fasted state this is further reduced to 5–10%. The bioavailability of atovaquone suspension is approximately 47% with food and without food, it is reduced to 23%. \(^1\)\(^-\)\(^3\) The absorption of atovaquone is solubility dependent. The salt formation, solubilization using various surfactants and particle size reduction have commonly been used to increase the dissolution rate and thereby bioavailability of such drugs.\(^4\)\(^,\)\(^5\) Few approaches such as antisolvent precipitation based nanosuspension,\(^5\) solid lipid nanoparticles,\(^6\) Cyclodextrin complexation,\(^7\) liposomes,\(^8\) and nanocapsules\(^9\) have been successfully implemented to improve the solubility of atovaquone. However, all these researches suffer from a drawback of low drug loading. To overcome this drawback, the micronized suspension provides a means...
to increase the drug loading without the interference of toxic side effects caused by co-solvents. Micronized suspensions can be prepared by two methods namely, bottom-up technology and top-down technology. Bottom-up technologies include precipitation, microemulsion approach and melt emulsification. Top-down technology involves the fragmentation of larger particles into smaller, examples of which are high-pressure homogenization and milling methods.\textsuperscript{10} One such top-down method of size reduction is microfluidization. Particles dispersed in the suspension pass through the interaction chambers at high pressure as jet streams. The particle size reduction takes place when the particles flowing through this jet stream collide with each other. The top-down approach, unlike the bottom-up approach, does not require a solvent for processing of the formulation.\textsuperscript{11}

The major advantage of micronized suspension is the enhanced dissolution achieved due to reduced particle size and increased specific surface area of the drug particles. A reduction in particle size affects the stability of the drug by particle agglomeration upon storage. Hence their transformation into solid products is often required to maintain its physical stability. This can be achieved by techniques such as freeze-drying, spray-drying, pelletization, or granulation. Recently adsorption onto silicates in amorphous forms or as solutions has gained substantial importance in pharmaceutical research. Silicates can absorb liquids as much as thrice their weight. Some of the examples of silicates are Aerosil\textsuperscript{®} 200, Neusilin\textsuperscript{®} UFL2, Neusilin\textsuperscript{®} US2, SiperNat\textsuperscript{®} 22, Sylsia\textsuperscript{®} 350, Zeopharm\textsuperscript{®} 600.\textsuperscript{12,13}

In the present study, atovaquone micronized suspension was prepared by a three-stage top-down processing

- Wet milling using trituration method
- Probe sonication
- Microfluidization

This three-stage processing was used to reduce the particle size of atovaquone from 9 microns to a particle size range of 1200-1400 nm. To maintain this particle size and prevent particle size growth, the micronized suspension was further adsorbed on a substrate to convert it into a solid dosage form. Poloxamer 188 was used as a wetting agent and Phospholipon 90H as a stabilizer. Phospholipon is a phospholipid that has been studied to have an impact on solubility of water-insoluble drugs.\textsuperscript{14}

**MATERIALS AND METHODS**

**Materials**

Atovaquone was received as a gift sample from Glenmark Pharmaceuticals Ltd., Mumbai, India. Poloxamer (Kolliphor\textsuperscript{®} P188), crospondione (Kollidon\textsuperscript{®} CL SF) and polyethoxylated castor oil (Kolliphor\textsuperscript{®} EL) were received from BASF, Navi Mumbai, India. Hydrogenated phospholipid (Phospholipon\textsuperscript{®} 90H) was obtained as a gift sample from Lipoid GmbH, Germany. Colloidal silicon dioxide (Aerosil\textsuperscript{®} 200) was obtained from Evonik, India. All other chemicals and reagents were purchased from LobaChemie, India.

**Pre-formulation studies and screening of excipients**

Equilibrium solubility studies of atovaquone were carried out employing water, various buffer solutions and solutions of surfactants like tween 80, sodium lauryl sulphate, Kolliphor EL buffered at different pH values. The equilibrium solubility studies were also carried out in a 10% surfactant solution in water with surfactants like poloxamer, Solutol HS 15, Phospholipon 90H, d-α-Tocopheryl polyethylene glycol 1000 succinate (Kolliphor\textsuperscript{®} TPGS), polyvinyl pyrrolidone (Kolliphor\textsuperscript{®} K30) and tween 80. The excess amount of the drug was added to 10 ml of each solution in screw-capped vials and vortex mixed for 30 s (Vortex mixer, Remi, Mumbai, India). The sealed vials were shaken in an orbital shaker incubator (Hally Instruments, India) at 37°C at 200 rpm for 48 hr. The samples were centrifuged (REMI 120C, REMI Labs, India) at 15,000 rpm for 5 min and then filtered through a 0.22 µm nylon syringe filter. The filtrates were assayed in triplicates by validated HPLC method.

**Selection of thickener/stabilizer**

Kolliphor K 30, d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS), Phospholipon 90H were evaluated as stabilizers/thickeners at 1% concentration to keep the drug particles suspended in aqueous medium after wetting with poloxamer P188. Micronized suspensions at 15% atovaquone concentration with these stabilizers were prepared in presence of poloxamer P188 and evaluated for sedimentation behavior and ease of redispersibility.

**Preparation of atovaquone suspension**

The drug concentration in all formulations was kept constant at 15% w/w. The drug was dispersed in an aqueous solution of 2-10% poloxamer 188 and 1-5% Phospholipon 90 H with trituration. Glycerine (10%) was added as viscosity building agent and volume was made up with purified water. This suspension was homogenized at 10,000 rpm for 10min (Ultraturrax T25 with S25N-10G dispersing element, IKA-Werke GmbH and Co.KG, Staufen, Germany) and then probe sonicated for 10 min (Oscar Ultrasonic Processor)
Sonapros PR-250, Mumbai, India) using 3mm horn at 30% variac for further particle size reduction.

Optimization of atovaquone suspension

Risk assessment was carried out for screening the critical formulation variables and it was observed that levels of both surfactants (poloxamer 188), as well as a stabilizer (phospholipon 90H), were critical. A 3² full factorial design was used to statistically optimize the formulation factors in the development of micronized suspension and for quantitatively expressing the effect of influential formulation variables viz. surfactant and stabilizer concentration on the response variables viz the critical quality attributes like particle size expressed as Z-average diameter of the particles in nm and polydispersity index (PdI). Table 1 presents the description of a total of 9 experimental runs at various levels of formulation variables and the design matrix as per full factorial design. All the prepared formulations were characterized for the envisioned critical quality attributes, viz. particle size (Z_avg, nm) and polydispersity index and optimized formulations were selected.

Statistical analysis was performed using Design Expert (Version 8.1, Stat-EASE INC., Minneapolis, MN, USA) software. For this study, the multiple linear regression analysis was applied to fit the model with a full second-order quadratic polynomial equation with added interaction terms to correlate the response variables with the evaluated variables using Design-Expert software. One-way ANOVA was carried out by analyzing the model parameters like model p-value, coefficient of correlation and predicted error sum of squares. The response surface analysis was carried out using the 3D-response surface plots and contour plots. The optimized formulation was selected from the design space overlay plot based on the minimum particle size and polydispersity index and optimized formulations were selected.

The optimized composition of various micronized formulations prepared as per the 3² full factorial design is given in Table 1.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poloxamer 188 (%)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Phospholipon 90H (%)</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

Adsorption studies

Adsorption studies were carried out using Kollidon CL SF and Aerosil 200 as the adsorbent, in the ratio 2:1. The required amount of adsorbent was spread in a porcelain dish and the microfluidized micronized suspension was poured over the adsorbent uniformly to saturate it till wet (mixing was done as required to ensure uniform adsorption). After partial drying remaining micronized suspension was added and allowed to air dry. The dried adsorbed suspension was passed through 40# sieve.

Characterization of micronized suspension

The micronized suspension was diluted 10 times with Millipore water, filled in the cuvette and analyzed. The adsorbed micronized suspension was diluted in water to achieve a concentration of 150 mg/ml. This reconstituted suspension was checked for ease of redispersibility. The particle size, PdI and zeta potential were determined by diluting the reconstituted suspension 10 times with Millipore water and analyzing it using Malvern Zeta sizer (Nano ZS90, Malvern Instruments, Malvern, UK).

The adsorbed powder was dissolved in methanolic sodium hydroxide and further diluted with methanol:water (50:50). The solution was analyzed for drug content using HPLC at 220 nm. The saturated solution of adsorbed micronized suspension in water was shaken for 48 hr. to determine the solubility. The solution was centrifuged, filtered and analyzed using HPLC at 220 nm.

The powdered X-ray Diffraction (XRD) pattern was recorded using an X-ray diffractometer (X’PertPRO MPD, PANalytical, Netherland) at 40kV, 30mA at a scanning rate of 0.02°/min at the diffraction angle 2θ over the range 10-80 using copper (as an anode) radiation of wavelength 1.5405 Å. The thermal characteristics of adsorbed nanosuspension and pure drug samples were evaluated using differential scanning calorimeter (DSC 6220, SHI Nanotechnology, SEIKO). Alumina was used as a reference and the thermogram
Results and Discussion

Equilibrium Solubility Studies

Among various mediums explored for equilibrium solubility studies, the maximum solubility for atovaquone was observed in 40% IPA in phosphate buffer pH 8 (Figure 1), which is the official medium as per OGD guidelines of the US FDA for atovaquone tablets. But it is not a discriminatory medium for dissolution; hence 2% Kolliphor EL solution in water showing significant solubility of atovaquone (50 µg/mL) was selected as a discriminatory organic solvent-free medium for dissolution studies. Similarly, amongst various surfactants employed, the minimum solubility and maximum wettability was obtained in poloxamer 188 (Figure 2) and it was selected as the wetting agent (Table 2). Poloxamer 188 has been used in marketed suspension (Mepron) as a wetting agent in 0.5% concentration and is also listed as one of the inactive ingredients in Malarone tablets. Poloxamer 188 is an amphiphilic nonionic block polymer and its hydrophobic polypropylene oxide segment adsorbs on the surface of the drug and its hydrophilic polyethylene oxide segment provides steric hindrance to prevent particle aggregation. The hydrophobicity of atovaquone molecules affects its dispersibility, poloxamer act as a wetting agent and assist in dispersion. Thereafter, it acts as a non-ionic stabilizer.

Selection of Thickener/Stabilizer

Several batches were prepared using the standard preparation method (containing only the atovaquone and poloxamer) in the absence of stabilizer. From microscopic views (not shown), agglomeration of nanoparticles was observed without the addition of stabilizer. Based on sedimentation behavior and ease of redispersibility, Phospholipon 90H was selected as the stabilizer. The suspension showed a thick floc
without any sign of sedimentation and was easily redispersed in a single stroke. Thus, Phospholipon 90H was found to be an indispensable dispersing agent required in the preparation of well-dispersed homogenous suspension. Phospholipon 90H provides the phospholipid network to entrap the drug particles without forming strong bonds. The phospholipid offers steric hindrance that prevents particle size growth and even after sedimentation, the flocs easily redisperse on shaking. The concentration of Phospholipon is critical as higher concentration may affect the release of drug entrapped in the phospholipids. Non-ionic surfactants like Phospholipon 90H and Poloxamer tend to increase the solution viscosity, which in turn provides a barrier against aggregation.

**Preparation and optimization of atovaquone suspension**

With the consideration of the concentration Phospholipon 90H and Poloxamer 188 as the critical formulation parameter that will have an impact on the properties of the micronized suspension, a polynomial was fitted based on the difference in the values of predicted and adjusted $r^2$. On comparing with other models, it was suggested that the quadratic model for the particle size and 2F model for PdI is best suited due to the largest values of $r^2$ for all the responses. The results of the experimental design for particle size showed that the upward trend of wire mesh in the 3D surface plot was at a higher concentration of poloxamer 188 whereas phospholipon 90H did not have any effect on the particle size. On the contrary, the interaction of poloxamer 188 and phospholipon 90H had a significant effect on particle size. The factors B, AB, B$^2$ are significant terms in this model, B (phospholipon 90H), AB (Interaction of A and B) and B$^2$ (phospholipon 90H) are significant model terms considering the $p<0.05$. The final mathematical equation of the fitted model for particle size is as follows

$$\text{Particle size} = 20.53 + 1.55A - 8.25B + 7.18AB - 0.62A^2 + 10.74B^2$$

where A is Poloxamer 188 and B is Phospholipon 90H

The results of the experimental design for PdI showed that the upward trend of the mesh of the 3D surface plot was at a high level of phospholipon 90H and low level of poloxamer 188. A relatively lower trend of mesh is seen at a higher level of Poloxamer 188 and a lower level of phospholipon 90H. The interaction of poloxamer 188 and phospholipon 90H also has a significant effect on PdI. In this model, B (phospholipon 90H), AB (Interaction of A and B) and B$^2$ (phospholipon 90H) are significant model terms. The final mathematical equation of the fitted model for PdI is as follows

$$\text{PdI} = 26.13 -2.0A + 2.47B + 12.3AB$$

Where A is Poloxamer 188 and B is Phospholipon 90H

Three-dimensional response surface plots and two-dimensional contour plots are shown in Figure 3. To optimize all the responses with different targets, a graphical optimization technique by the overlay plot was used. The optimized formulation was obtained by applying constraints on dependent variable responses and independent variables. An overlay contour plot was plotted between two excipients, X1 and X2 which showed the region between the two set criteria, i.e. particle size which should be between 1000 nm to 2500nm and polydispersity index which should be between 0.1 and 0.3. The yellow region in Figure 4 indicates the region of successful operating ranges.

Two batches were selected from the optimized region of the overlay plot (i) 2% poloxamer, 5% phospholipon 90H and (ii) 2% poloxamer, 1% phospholipon 90H. These batches were prepared and studied for dissolution behavior. It was observed that a maximum 15.5% drug was dissolved in 2h with 5% phospholipon 90H whereas 18.8% of the drug was dissolved in 2h with 1% phospholipon 90H. Hence formulation with 2% poloxamer and 1% phospholipon 90H was the optimized batch. Excess of phospholipon interfered with the drug release by forming a dense network in the aqueous medium. The formula for final optimized suspension is shown in Table 3.

**Microfluidization**

Microfluidization has tremendous potential to produce commercially viable products due to its ease of scalability. A patent of Glaxo Wellcome Inc., mentions the use of microfluidization technique to bring the down the particle size of atovaquone in the range of 0.1 to 2µm. It is important for the formulation to pass through high shear homogenization using Ultra-Turrax and probe sonication to avoid jamming

---

**Table 3: Optimized formulation of ATQ micronized suspension.**

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Components</th>
<th>Quantity</th>
<th>Role of excipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Atovaquone</td>
<td>15%</td>
<td>API</td>
</tr>
<tr>
<td>2</td>
<td>Poloxamer 188</td>
<td>2%</td>
<td>Wetting agent</td>
</tr>
<tr>
<td>3</td>
<td>Phospholipon 90H</td>
<td>1%</td>
<td>Stabilizer</td>
</tr>
<tr>
<td>4</td>
<td>Glycerine</td>
<td>10%</td>
<td>Wetting and suspending agent</td>
</tr>
<tr>
<td>5</td>
<td>Purified water</td>
<td>q.s 100%</td>
<td>Vehicle</td>
</tr>
</tbody>
</table>
in the valve openings of microfluidizers.\textsuperscript{18} The final optimized batch was microfluidized after exposing it to high shear homogenization with Ultra-Turrax at 10,000 rpm for 10 min and probe sonication for 10 min. Microfluidized samples were observed under a microscope at various steps of the microfluidization process as shown in Figure 5. Reduction in particle size was observed up to a limiting number of cycles and pressure and then further increase caused aggregation.

**Adsorption study**

The microfluidized micronized suspension was found to show aggregation after two days even at refrigerated conditions, hence the suspension was adsorbed onto the Aerosil-Kollidon CL SF mixture to prevent an increase in particle size. Air drying was the preferred method to avoid aggregation of particles. For example, if the nanoparticles are coated with polymeric surfactants such as poloxamers, drying at elevated temperature may lead to crystallization of the polymer, thereby compromising their ability to prevent aggregation. Drying can also create additional thermal stresses that may destabilize the particles.\textsuperscript{19}

**Characterization of micronized suspension**

The particle size of the pure drug was 8-9 microns. Table 4 depicts the particle size of the suspension at various stages of preparation showing a progressive decrease in particle size with an increase in shear. The zeta potential value was 0.0555 mV which indicates that the micronized suspension has steric stability and aggregation did not occur.

The adsorbed micronized suspension was easily and uniformly re-dispersed in water. A slight shift in the particle distribution to the higher particle size was observed. The mean particle size of the reconstituted powder particles was typically 30% higher than the mean

<table>
<thead>
<tr>
<th>Stage of preparation</th>
<th>Particle size Z\textsubscript{avg}, nm</th>
<th>Polydispersity index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probe sonication</td>
<td>1900±100</td>
<td>0.500±0.05</td>
</tr>
<tr>
<td>Microfluidization</td>
<td>1313 ± 40</td>
<td>0.100±0.05</td>
</tr>
<tr>
<td>Adsorption</td>
<td>1700 ± 200</td>
<td>0.400±0.10</td>
</tr>
</tbody>
</table>

**Table 4: Particle size and polydispersity index.**

Figure 3: Contour plots for Particle size and PdI.

Figure 4: Overlay plot for Particle size and PdI.

Figure 5: Microscopy images (45x) of size reduction of particles after processing through microfluidizer.

Figure 6: Comparative X-ray diffractogram of adsorbed submicron suspension.
of the original micronized suspension. Hence although polymeric surfactants can stabilize nanoparticles in an aqueous environment, their stabilization ability is compromised in the dehydrated state. It should be noted that there was an absence of larger particle aggregates after redispersion. The XRD data of the drug was compared with the formulation containing only poloxamer 188 and poloxamer 188 with phospholipon 90H (Figure 6). The intensity of the peaks of non-microfluidized suspension (subjected to Ultra-Turrax and probe sonication) was lesser than the pure drug powder. The intensity of the peaks of adsorbed microfluidized micronized formulation was significantly reduced compared to that of the pure drug due to the dilution effect though there was no major change in the crystallinity of the drug. The DSC thermogram of atovaquone after microfluidization and adsorption as shown in Figure 7 revealed an endothermic peak at 214.6°C while the pure drug shows a sharp endothermic peak at 222.8°C. The slight reduction in melting endotherm temperature, \( T_m \) compared with untreated drug suggests a decrease in crystallinity; however, the reduction was very small, which agreed with XRD analysis. The assay of the adsorbed powder was found to be 358.82 mg/g.

The saturation solubility of atovaquone in water was found to be 0.2 \( \mu g/ml \) and saturation solubility of adsorbed micronized suspension was found to be 10.7 \( \mu g/ml \). From the saturation solubility, it was seen that there was a drastic improvement in the solubility of the drug in micronized suspension as compared to the pure drug (\( p<0.05 \)).

**In vitro dissolution studies**

The dissolution profile of the adsorbed microfluidized micronized suspension was compared to the unmilled pure drug suspension as shown in Figure 8. The adsorbed micronized suspension showed a release of around 30% drug in 2 h. The release showed a 2.3-fold times increase in the dissolution of the drug compared to suspension and drug (\( p<0.05 \)). Atovaquone in its crude unprocessed form is present as aggregates, which when processed through the three-stage top-down processing offers distinctly separated particles. Furthermore, the decrease in particle size increases the surface area of the particle and thus the dissolution. Poloxamer acts as a wetting agent which aids the drug to easily disperse in the media. It is postulated that further reduction in particle size of the micronized suspension will improve the dissolution.

**CONCLUSION**

Adsorbed micronized suspension of atovaquone was successfully optimized using 3\(^2\) full factorial design utilizing three concentrations of surfactant and three concentrations of stabilizer. The final optimized formulation containing 2% poloxamer 188 and 1% phospholipon 90H was microfluidized which successfully yielded micronized suspension. The stabilizers and the microfluidization process appeared to have the most significant impact on the quality of the micronized suspension. The adsorbed micronized suspension exhibited enhanced saturation solubility and in vitro dissolution as compared to untreated drug suspension. The micronized suspension was converted into solid by adsorption which can further be given as a dry syrup formulation with added sweeteners and flavors. The idea of size reduction of a rigid molecule like Atovaquone using microfluidization to improve its
solubility provides a novel insight for the development of nanosuspension of atovaquone.\textsuperscript{30}

**ACKNOWLEDGEMENT**

The authors are grateful to Glenmark Pharmaceuticals (Mumbai, India) for providing atovaquone and Lipoid GmbH (Germany) for providing Phospholipids 90H. The authors further thank BASF Fine Chemicals (Mumbai, India) for providing gift samples of Kolliphor\textsuperscript{®} P188, Kollidon\textsuperscript{®} CL SF and Kolliphor\textsuperscript{®} EL. We thank Trident Equipments Pvt. Ltd., Mumbai for providing the facility for microfluidization of our samples. The authors also express their gratitude towards the management of Vivekanand Education Society’s College of Pharmacy to provide the facility to conduct this research work.

**CONFLICT OF INTEREST**

The authors declare there is no conflict of interest.

**ABBREVIATIONS**

BCS: Biopharmaceutical Classification System; nm: nanometer; rpm: rotations per minute; PdI: Polydispersity index; HPLC: High Performance Liquid Chromatography; ANOVA: Analysis of Variance; USP: United States Pharmacopoeia; XRD: X-ray Diffraction; IPA: Isopropyl alcohol; OGD: Office of Generic Drugs; US FDA: United States Food and Drug Administration; DSC: Differential Scanning Calorimeter

**REFERENCES**

3. Product Monograph: PMalARONE\textsuperscript{®} PMALARONE\textsuperscript{®} PEDIATRIC [Internet]. Glaxo Smith Kline Inc. 2015/47. Available from: https://ca.gsk.com/media/591413/malarone.pdf
SUMMARY

Atovaquone is currently available as a tablet and oral suspension, both of which are required in large doses due to bioavailability constraints. The developed formulation highlights the efficiency of processes like sonication and microfluidization to reduce the particle size and improve the dissolution characteristics of Atovaquone.