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CONTINUOUS FLOW DRUG MANUFACTURING USED IN THE SYNTHESIS OF ARTEMISININ

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***Abstract*—*Artemisinin is an antimalarial drug that is important to artemisinin Combination Therapies (ACTs), which are the most effective treatments for malaria. A major problem is the scarcity and expensiveness of the main component of ACTs, artemisinin itself. This is due to the complexity of the molecule, which makes synthesis very difficult and not commercially viable. As a result, ACTs are in short supply and cannot keep up with demand, resulting in many fraudulent treatments being sold. By furthering the development of technologies used to manufacture artemisinin, global supply can increase, thus decreasing fraudulent treatments, and allowing for more lives to be saved.*

Continuous flow technology (CFT) is one of these technologies that is currently being explored for use in the manufacturing of pharmaceuticals. The process of CFT involves the mixing or separation of chemicals in small and precise amounts to limit the problems of safety and impurities found in the batch mixing of chemicals. Allowing the reactions to take place in a continuous manner eliminates the hazards of dangerous intermediates. The reaction also takes place in a closed system, eliminating impurities, side reactions, and human error. In CFT, the reagents can be mixed constantly, allowing the reaction to occur continuously, and the products can flow out of the system without stopping the reaction. The benefits of CFT can be applied to many major pharmaceuticals, artemisinin specifically. This allows for the production of more and purer products, in a safer and more efficient manner, which will reduce the cost of these life-saving medicines.

Key Words*—*Artemisinin, Batch Manufacturing, Continuous Flow Technology (CFT), Drug Manufacturing, Malaria, Pharmaceuticals

OVERVIEW OF CONTINUOUS FLOW TECHNOLOGY: PROCESS AND IMPACT

Continuous flow technology is the chemical process of performing reactions in a continuous manner, as reagents are fed into a reactor and then the finished products flow out. This process has several benefits over current methods used to perform chemical reactions in industrial settings. Some of these benefits include cost efficiency and a safer way to produce higher product yields [1]. Other benefits of continuous flow technology are speed of reaction, purity of product, and sustainability.

One of the main applications of the technology behind continuous flow technology is in the manufacturing of pharmaceuticals. The current process used in pharmaceutical manufacturing, batch manufacturing, involves the mixing of various reagents and catalysts in a large vat, then separating the desired intermediate from the byproducts, and purifying the product. This process is slow, not cost effective, and more dangerous than continuous flow technology. One example of the application of continuous flow technology to pharmaceutical manufacturing is the production of the antimalarial drug, artemisinin.

Artemisinin comes from the plant *Artemisia annua* and has been shown to provide a large variety of health benefits in different forms but is most commonly used as the main drug in the most effective type of malaria treatment, artemisinin combination therapies (ACTs). The current method of artemisinin production, a form of batch manufacturing using the extract from the plant leaf, produces very little product yield, with several dangers present in the reduction and purification process of the drug. By employing the use of continuous flow technology, not only can this reaction occur in a safer and better controlled way, but a byproduct of the batch manufacturing process can then be taken and also turned into artemisinin through a continuous flow reaction [2]. The increase in the production of artemisinin this would provide is a necessity, given the use of the artemisinin as the primary anti-malarial drug [3]. In addition, a higher production of artemisinin would allow for the drug to be studied more easily, potentially leading to more uses in medicine.

Malaria has negatively impacted our society as long as the disease has existed, and with half of the world's population reported to be at risk in 2016, the effects of this disease will only get worse if better methods to produce more and better medicines are not used [3]. Malaria is no longer a threat in the United States, but this is only because the medicine to treat malaria was readily available and affordable to U.S. citizens [4]. Locations in sub-Saharan

Africa, India and other locations where malaria poses its greatest threat are unable to afford medicine for all those who are at risk. By furthering the development and use of continuous flow technology in the production of artemisinin and other pharmaceuticals, availability of said drugs will increase, and the cost will decrease, allowing those affected by treatable diseases such as malaria to obtain a cure.

AN INTRODUCTION TO CONTINUOUS FLOW TECHNOLOGY

Continuous flow technology is one of the most important new advancements in manufacturing pharmaceuticals. In general, continuous flow technology refers to a new process by which the products are produced through a reaction that is run constantly, mixing a small amount of the reagents together continually. Currently, most pharmaceuticals are produced in large batches. However, batch manufacturing can have many hazards associated with it. First among these, some of the reagents used for the batch manufacturing are highly dangerous, toxic, or otherwise unsafe. This is particularly dangerous because, for batch manufacturing processes, a large amount of these reagents is required to produce each batch of products. In addition to the reagents being toxic or hazardous, the byproducts and leftover compounds from the reaction may also be toxic or dangerous. A third issue with batch manufacturing is that the large equipment used to manufacture these pharmaceuticals in batches is costly and cannot be disposed of easily, not that this happens often. More often, these large batch reactor setups are cleaned out and modified for use in producing other pharmaceuticals. This cleaning process is arduous and requires additional workers, which causes additional expenses. However, the ability to clean out the batch reactors to be used in a different reaction provides one potential benefit over continuous flow setups, which are tailored specifically for the production of a single compound. Additionally, traditional batch reactions often have many additional steps that are required to isolate the desired products and to purify them in order to move on to the next step of the synthesis. These additional steps also come with additional parameters that need to be monitored for batch manufacturing [5].

Continuous flow reactions have far fewer problems associated with them than batch reactions. A major benefit of continuous flow technology is that it is more sustainable. According to the Brundtland Report, a report on sustainability by the UN-appointed Brundtland Commission, this means that continuous flow chemistry will be capable of meeting the present [economic, social and environmental] needs of society, while not compromising the future generations' ability to meet their needs [5]. The technology is efficient, especially in its use of reagents, allowing for greater product yield, while wasting fewer reagents, making it profitable, which increases the economic stability. These improvements all help to improve the ability of continuous flow chemistry to meet environmental and economic needs. To keep many traditional batch reactions safe and producing a pure enough product, the reaction must be slowed down in some way. This method, although contributing to the safety, will slow production and increase cost, which reduces economic sustainability. Continuous flow technology can produce a pure and safe reaction at a much faster rate. These two benefits contribute to lowering the cost and improving the safety of process. The continuous flow reactor is also significantly smaller and has far fewer conditions to monitor than its batch manufacturing counterpart, which also directly contributes to benefitting the reaction process. Continuous flow technology also poses fewer social or ethical dilemmas, because it decreases waste and energy use, making the process more environmentally friendly as well [5]. While the reagents for the continuous flow process may be as dangerous as the ones used for batch processes, they are used in much smaller amounts and so can be used safely. This allows some reactions that would not be possible in traditional batch setups due to safety concerns to be performed. These benefits of continuous flow chemistry are what allows the process to be sustainable.

One example of the reactions that can't be performed in batch manufacturing is the photooxidation reaction. These types of reactions are very difficult to perform in batch setups because ensuring uniform irradiation is all but impossible. In this same vein, the conditions in continuous flow reactors are able to be more finely tuned, for example the temperature of each step can be optimized separately, or the pressure for different steps can be changed independently of the rest of the reactor, and exposure to light sources can be controlled and optimized, ensuring peak irradation. Doing so allows continuous flow reactors to use less energy than their batch counterparts, making them more economically and environmentally sustainable. Continuous flow setups are also much smaller than batch reactors and can be cleaned up and discarded more easily, if necessary. Continuous flow setups also allow for smaller amounts of dangerous reagents to be used, thus allowing the reactions to be carried out at higher temperatures and pressures. This is accomplished by generating dangerous intermediates in closed and pressurized systems and then converting them directly to less hazardous intermediates or final products by combining reaction streams. Continuous flow technology also eliminates a large issue with traditional batch methods: isolation and purification. Since continuous flow reactions are run in multi-step processes, the need for these steps is eliminated as each step is combined into one large uninterrupted reaction. This also eliminates the additional parameters that need monitoring in the batch production [5]. A key advantage of continuous flow technology is that it is much more easily scalable than traditional batch manufacturing. Another important advantage is that continuous flow technology can be used to produce more complicated molecules than traditional batch manufacturing.

Taken together, these advantages and benefits of continuous flow chemistry lead to a process that is much more sustainable than traditional batch manufacturing, in every way. Economically, it costs less and can produce more of the drug, which brings prices of the final product down. Environmentally, it is more efficient in using reagents, which saves materials and waste, as well as producing less byproducts. The CFT process is also safer, which lessens the environmental impact. Socially, CFT is more sustainable because of the improvements that it brings to so many people's lives through the eradication of disease. This aspect of continuous flow technology proves especially useful in the semisynthesis of artemisinin.

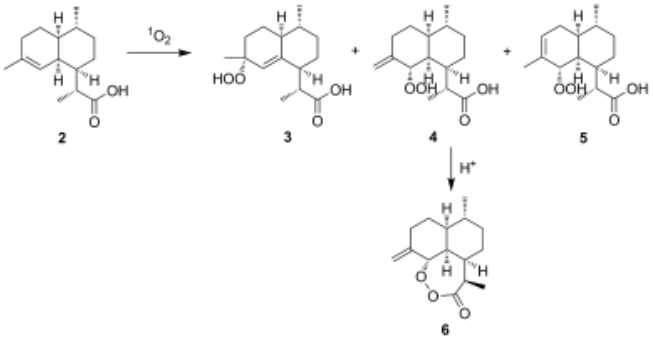
Currently, the total synthesis of artemisinin is not viable, due to the complexity of its structure. Due to the lack of a total synthesis process, artemisinin is currently only obtained by extraction from the leaf of *Artemisia annua*. This has led to the development of several semisynthesis processes, however, the key step in synthesizing artemisinin from dihydroartemisinic acid (DHAA) has proved to be extremely difficult to perform in a batch process.

USING CONTINUOUS FLOW TECHNOLOGY TO PRODUCE ARTEMISININ

To solve this problem, a semisynthesis was developed using continuous flow technology. To understand this process, it is necessary to understand the structure, the current batch processes, and the natural process for the synthesis of artemisinin. As mentioned before, artemisinin is exclusively obtained by extraction from the plant, *Artemisia annua*. This extraction is typically conducted by boiling the crushed leaves of the plant in organic solvents for up to 48 hours per batch [4]. The exclusive source for the drug and its long batch preparation times leads to an unstable supply and variation of the quality of the harvested artemisinin. Due to this scarcity of artemisinin, the prices are very high. In order to supplement the supply and bring the prices down, significant efforts are being directed towards developing the semisynthesis through advanced knowledge of the biosynthesis that occurs in the plant. It has been discovered that the plant produces dihydroartemisinic acid (DHAA), which is oxidized and then further reacts to give artemisinin. DHAA and its dehydrogenated precursor artemisinic acid (AA), which is also found in the plant, are potential starting materials for the semisynthesis of artemisinin. Developing a process for synthesis starting from DHAA is particularly attractive because this chemical is currently produced as a byproduct of traditional manufacturing of artemisinin. If a process with a reasonably high yield of artemisinin were developed, this would only increase the yearly yield of artemisinin.

To this end, a process was developed by a team led by Dr. Kopetzki, Dr. Francois Levesque, and Prof. Dr. Peter Seeberger. Starting from the idea that the key step in semisynthesis of artemisinin was an ene reaction involving singlet oxygen, the team was able to develop a continuous flow reactor setup and a process that produces artemisinin with great selectivity at a high efficiency. To accomplish this, each step in the reaction was optimized separately and then combined into a single stream continuous process.

The first step is the photooxidation of the DHAA, compound 2 in Figure 1. This ene reaction gives one hydroperoxide compound and two endoperoxide



compounds, shown in Figure 1 as compounds 3 (hydroperoxide), 4, and 5 (endoperoxides) [6]. Only one of these compounds, the hydroperoxide molecule 3, can be converted into artemisinin while the other two form side products.

FIGURE 1 [6]
Diagram of the reaction

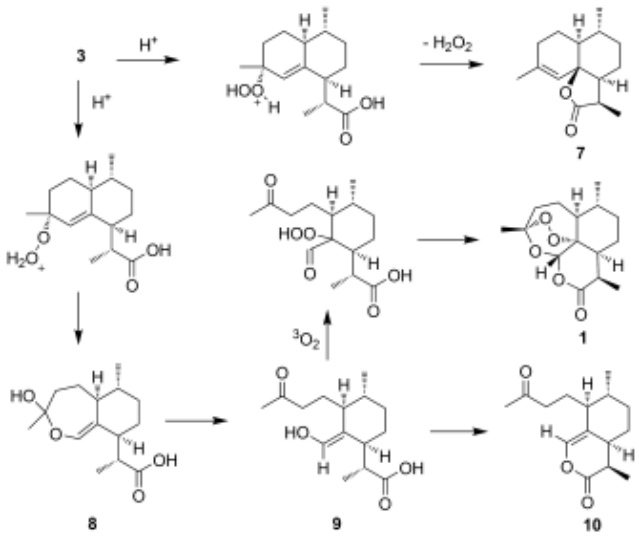
For the light source in the photooxidation, LEDs were chosen because they are monochromatic, highly efficient, have a long lifetime, and are available in various wavelengths, making them ideal for photochemical applications [6]. This illustrates another advantage that continuous flow reactions have over traditional batch reactions. In traditional batch reactions, attaining uniform irradiation is nearly impossible because of the decay of light intensity as distance from the source increases.

Once the light source for this step was chosen, the other reaction conditions were determined. The first of these conditions was temperature. At all the temperatures, DHAA was almost entirely consumed, and the desired hydroperoxide, compound 3, was the major product, however, it was found that lower temperatures shifted the ratio more towards compound 3. Based on the data gathered and shown in Figure 2, the best yield of hydroperoxide 3 was obtained by running this step at a temperature of -20℃ [6].

Temp. [°C]	Conv. [%]	**3** [%]	**4** [%]	**5** [%]	Other by-products [%]
~75[a]	86	62	10	5	24
60	99	70	11	5	14
40	99	73	12	4	11
20	99	78	11	4	8
0	99	81	11	3	5
−20	98	84	10	3	3

FIGURE 2 [6]
Artemisinin yield by temperature

The other part of this step to optimize is the sensitizer that is used to kick off the photooxidation reaction. The sensitizer does this by absorbing a light of a specific wavelength and entering an excited state. The excited sensitizer then reacts with the DHAA to form the hydroperoxide products shown in Figure 1 [6]. The step was tested with three different sensitizers: tetraphenylporphyrin (TPP), zinc tetraphenylporphyrin (ZnTPP), and 9-10 dicyanoanthracene (DCA). The DCA and TPP were found to promote good selectivity at low concentrations, while ZnTPP did not promote the same high selectivity. As the concentration was increased, the DCA increased in selectivity, while the TPP decreased. In addition, DCA is resistant to the acid that is required in the next synthesis steps, whereas the TPP will have much lower yields due to the presence of basic parts of the molecule [6]. This means that the acid solution required for the next steps, which are acid catalyzed, can be added to the reaction mixture in the beginning, improving efficiency.



The acid-catalyzed steps are the next steps in the continuous flow semisynthesis process for artemisinin. In this step, acid is added to the mixture of hydroperoxides that was created in the previous photooxidation step, where it can react with compound 3 in two different ways to product artemisinin or one of two other byproducts [6]. The first reaction path can come from the hydroperoxide being protonated proximally, as shown in Figure 3.

FIGURE 3 [6]
Illustrated ene reaction

This results in the formation of a lactone (compound 7), and hydrogen peroxide. The second reaction path that can be followed is when the original hydroperoxide is protonated terminally, which the forms the enol intermediate, compound 9 [6]. This enol intermediate can either react with triplet oxygen to form another hydroperoxide intermediate before ultimately forming artemisinin, or it can isomerize to an aldehyde that then cyclizes to compound 10. For this step, several acids had been analyzed previously and it was found that trifluoroacetic acid (TFA) worked best to perform the proper protonation and form the intermediate. Acetic acid was found to decrease selectivity and increase production of by byproducts. Stronger acids were found to convert most of the hydroperoxide into the cyclic aldehyde. Based on these observations, TFA was chosen as the acid to be added to perform the acid catalyzed steps [6].

The final component of the continuous flow process to be determined was the solvent. Several solvents were each tested by bubbling oxygen through a solution of the products formed during the initial photooxidation step, using the acid catalyst determined in the last step, TFA, and measuring the conversion and % yield of artemisinin compared to the other products, the results shown in Figure 4.

Solvent	Artemisinin Yield [%]	Dihydro-*epi*-deoxyarteannuin B Yield [%]
acetonitrile	39	36
dichloromethane	69	17
cyclohexane	76	6
toluene	81	7
perfluorooctane[a]	40	0
benzotrifluoride	78	11
hexafluorobenzene	81	6
1,3-bis(trifluoromethyl)benzene	82	8

[a] Phase separation occurred.

FIGURE 4 [6]
Artemisinin yield by solvent

Full conversion of compound 3 was observed in all solutions, however, the artemisinin yield was substantially better in nonpolar solvents. In an attempt to extend lifetimes of the singlet oxygen, several fluorinated solvents were tested because of the high solubility of oxygen in these solvents. However, while these solvents prevented the formation of side products, they also decreased the yield of artemisinin [6]. These expensive fluorinated solvents would also have to be recycled. This led to the solvent toluene being selected due to its high artemisinin yield as well as its low side product formation, despite the safety concerns about flammability typically associated with using toluene and oxygen together in a reaction. This is a concrete example of one of the benefits of continuous flow technology -- only small amounts of oxygen are present in the continuous flow reactor setup, whereas, in the batch process, the amount would be much higher.

Once all the components of the acid catalyzed step were determined, the last thing to optimize in this step was the temperature of the reaction. To do this, the acid that was determined to be the most effective in the last step, was added to the solution used for photooxidation in the solvent, toluene, chosen for its high selectivity and low cost. This mixture was stirred, and then oxygen was bubbled through the solution for 20 minutes each time, and then the concentration of artemisinin and the side products was determined. The highest yield occurred at 25℃ while increasing or decreasing the temperature decreased the yield, as shown in Figure 5 [6].

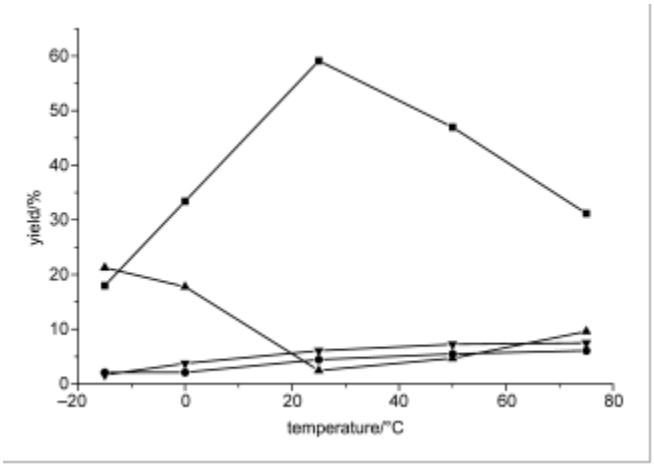
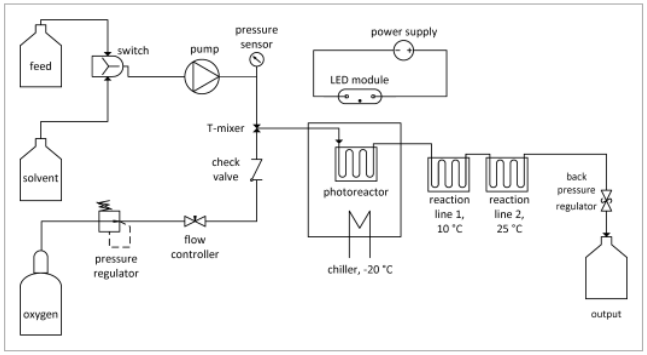


FIGURE 5 [6]
Artemisinin yield by temperature of acid catalyzed step

Once each of the steps was optimized individually, it was time to combine the steps into one continuous process that would take DHAA and turn it into artemisinin. Based on the optimizations made to the individual steps, the setup that was expected to generate that best yield and efficiency was to conduct the photooxidation step at -20 degrees Celsius using the sensitizer DCA, in a solution with a nonpolar solvent, toluene. Due to the acid insensitive nature of DCA, it can be added to the mixture during the initial step with no loss of efficacy. This allows the continuous process to only



use one pump which can deliver the solution used in the photooxidation step that also contains the acid catalyst, TFA [6]. To carry out the photooxidation, two equivalents of oxygen are added to the solution, which is then raised to room temperature. This solution then goes through reaction line 1 where it is cooled down to 10 degrees Celsius, and then through reaction line 2 where it is reacted at 25 degrees Celsius, to perform the acid catalyzed step, as shown in Figure 4.

FIGURE 6 [6]
Continuous Flow Reactor Setup

After this step, the output is then collected and purified, resulting in a yield of artemisinin of approximately 65% based on DHAA content. This reactor setup is capable of producing 165 g of artemisinin daily [6]. While this method may not produce a commercially viable amount of artemisinin as it is, this process was designed with the ability to be scaled up in mind.

The final and most important point about the synthesis method detailed here is that it uses DHAA as the feed solution. During the current commercial practice of extracting artemisinin from the plant leaves, the final purification of artemisinin leaves a solution that was found to contain low amounts of both AA and DHAA. This is treated as a waste product by those manufacturers, but it was found that using this solution as feed stock for the semisynthesis process yielded 57% artemisinin based on DHAA content [6]. This shows that the continuous flow process can use the current plant waste create artemisinin, thus supplementing current production, which will help to use the plants we do grow more efficiently.

This method for producing artemisinin is additionally beneficial because the reduction of artemisinin from DHAA, which is needed for the purification of the drug, uses sodium borohydride. Sodium borohydride is a potentially explosive compound, but, with the application of continuous flow technology, the compound can be used in large quantities safely. Another benefit of this method is that the DHAA is a byproduct of artemisinin production and is produced in amounts up to ten times more than artemisinin is itself. By

finding a method to produce artemisinin from DHAA through continuous flow technology, this byproduct will not be wasted. In addition to artemisinin, this process also produces several other medically useful artemisinin derivatives [2].

ANALYZING THE IMPACT OF CONTINUOUS FLOW TECHNOLOGY

As previously mentioned, the current rate at which artemisinin is being produced has not been able to match the need for the medicine, specifically for its applications as a combined therapy against malaria. The combination therapy of artemisinin-based medicines is recommended by the World Health Organization (WHO) as the most effective medication for malaria, especially strains that have become resistant to other drugs [4]. From 1986 to 1992, clinical trials for the use of artemisinin in curing malaria expressed an efficacy of 100% in alcohol and oil based preparations of the drug [4]. With this great of an efficiency at curing malaria, artemisinin and artemisinin-based combination therapies (ACTs) became the obvious choice as an anti-malarial drug. The crop that artemisinin is derived from, *Artemisia annua*, is a resilient plant with high yields of the needed biomass to produce artemisinin [4]. This suggests that the limited and unstable supply of artemisinin is due to the inability to produce high yields from batch manufacturing. With the application of continuous flow technology significantly increasing product yield for artemisinin, the present supply could become stable and increase, leading to a lower cost and greater availability of the medicine to people who need it. This ability to meet the current demand for the medicine further expresses the social sustainability of continuous flow technologies. Artemisinin has been shown to present antibacterial properties, as well as being a strong immunity stimulant, and has been long used in traditional Chinese culture to cure various illnesses, making it no surprise that the drug was later found to kill the malaria parasite [4].

Malaria, as the author Tariq Aftab described it, "Is a major scourge of humankind, which still continues to confront medical science and technology" [4]. Malaria, although considered eliminated from the United States and Europe, has been steadily coming back, and the parasite has been developing a resistance to two of the more common malaria drugs [4]. The disease was successfully eliminated from the United States because the medicines were readily available and much less expensive, allowing widespread access. The lack of access to available and effective medicines has allowed the disease to continue in locations like sub-Saharan Africa and India [3]. Malaria cases are estimated to be greater than two hundred million yearly, with nearly half a million deaths occurring every year [3]. With this strong of a reach and with many of the cases being in children, the need for a better method of medicine production is evident. In addition to this, the burden of malaria forms a negative economic cycle, where due to low income and capital, the countries that malaria severely damages are unable to invest in health care for their citizens. When the nation is unable to invest in health care, citizens are less likely to obtain the care they need. This increase in sickness in turn negatively influences income and capital [4]. If a stable supply of artemisinin is reached and the cost of ACTs decrease, both the number of cases and the number of deaths every year could see a significant decrease. The use of continuous flow technology in the synthesis of artemisinin would not only go towards fixing the problem of an unstable supply, but also allow for a decrease in cost.

In addition to the antimalarial benefits of artemisinin, the drug also has several other health benefits. One of these health benefits includes the antibacterial properties of artemisinin that can help with problems such as fevers, colds and diarrhea, and a weak immune system [4]. Another health benefit of artemisinin is its use in cancer therapies. Artemisinin has been found to have anti-proliferative and anti-metastatic effects on cancerous cells, as well as having the ability to induce apoptosis and inhibiting angiogenesis in cancer cells [4]. Several cases have been reported where the use of artemisinin and its derivatives have reduced the size and density of tumors, as well as beneficial in prolonging and improving the patients' quality of life [4]. In addition to having benefits to cancer patients, artemisinin has also shown antiviral properties, most notably against herpes simplex 1 and HIV-1 protease [4]. Although these benefits are not as extreme as the drug's ability to cure malaria, they are benefits that if an increase in artemisinin yield and a decrease in cost of manufacturing occurred, further study and application of the use of artemisinin in these situations could occur easier.

CONTINUOUS FLOW TECHNOLOGY: A TOOL FOR THE FUTURE

Continuous flow technology will have a huge impact on many of the current and future pharmaceuticals on the market. However, the benefit will not be immediately realized because of the complexity of the reactions used to produce them. One of the reasons for the success of the semisynthesis of artemisinin is that the natural process for producing artemisinin is so well understood, and it is simple, only involving a few steps. The continuous flow process can and most likely will be developed for every reaction, however most of the industry is much more accustomed to planning and working with the batch manufacturing process, making it likely that new drugs will first be produced in the more 'traditional' way before the process to produce them with continuous flow technology is realized. This will occur until the continuous flow technology can supplant the traditional batch manufacturing process, likely following the example set by artemisinin.

Continuous flow technology is a safer, less expensive, and more sustainable alternative to vat and batch manufacturing for performing chemical reactions. The isolated and small reactor, being constantly fed the correct amounts of each needed reagent reduces the likelihood of wasting reagents and maximizes product. In addition, because of the size, reactions that would be seen as unsafe to occur in large batches can be performed safely at varying temperatures and pressures. This versatile technology, when applied to the manufacturing of pharmaceuticals, is capable of producing better medicines than those produced through batch manufacturing. Considering the specific case of the manufacturing of artemisinin, continuous flow technology significantly increases product yield and allows for cheaper and more available supplies. The need for these supplies is evident when considering the use of artemisinin as the primary medicine used for the treatment and curing of malaria. The drug has been proven to be one of the most effective pharmaceuticals used in combating malaria. In addition to malaria, artemisinin has shown promise as a treatment for various other diseases and common ailments. The primary use of the drug, however, is for treating malaria, and the medicine needs to see an increase and stabilization of supply, while costs decrease. Malaria is an extremely widespread and dangerous disease, and as every year many more cases and deaths occur, the need for a widespread and available cure increases. Artemisinin and artemisinin-based combination therapies can be the needed cure, but only if the technology we have available can increase production, lowering costs, and providing a stable supply. Continuous flow technology is fully capable of accomplishing all of these tasks.

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