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Additively Manufactured Continuous Processing Reactor System for Producing Liquid-Based Pharmaceutical Substances

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Abstract: In this study, an AM-based continuous processing reactor system was designed, manufactured, and assembled on a laboratory scale for the generation of pharmaceutical substances with an improved process control. The developed AM-based (additively manufactured) continuous pharmaceutical reactor system for the synthesis of metronidazole derivatives aimed to optimize both the physical and the chemical processes with time savings. Using AM, we were able to build reactor subcomponents with complex designs and precise dimensions, which facilitated the precise control of the reaction parameters and reduced the amount of chemicals required compared to macroscale reactors. The assembly of the whole reactor system consisted of main reactor bodies, mixers, valves, heat exchangers, electrical motors, and a microcontroller system. The assembled reactor system revealed a continuous flow of reagents and ensured uniform mixing and reaction conditions, thereby increasing the process efficiency and product quality. Five metronidazole derivatives were synthesized via two continuous processes, involving metronidazole reduction and its subsequent reactions with terephthalic aldehyde and anthracen-9(10*H*)-one to form Schiff bases. The optimal conditions were determined as follows: compound **A** (72% yield, 120 min, 55 °C), compounds **B** and **C** (63% and 68% yield, respectively, 8 h, 65 °C), and compounds **D** and **E** (74% and 85% yield, respectively, 8 h, 45 °C).

Keywords: reactor systems; chemical processes; additive manufacturing; metronidazole derivatives; continuous processing reactor

Citation: Khabiyev, A.; Dilibal, S.; Mussulmanbekova, A.; Kanapiya, M.; Kerimkulov, D. Additively Manufactured Continuous Processing Reactor System for Producing Liquid-Based Pharmaceutical Substances. *Appl. Sci.* **2024**, *14*, 6853. https://doi.org/10.3390/app14166853

Academic Editor: Qi-Huang Zheng

Received: 19 June 2024
Revised: 31 July 2024
Accepted: 31 July 2024
Published: 6 August 2024

1. Introduction

Continuous processing reactors are essential for optimizing pharmaceutical synthesis by offering continuous flow, real-time monitoring, and a modular design. They enable control over reaction parameters and reduce waste generation. Their automation capabilities and scalability further enhance their efficiency and flexibility in pharmaceutical manufacturing [1]. Additionally, the integration of AM technology improves the potential of continuous processing by facilitating the fabrication of customized reactors with complex designs [2]. These AM-based reactors facilitate enhanced regulation over the reaction parameters, resulting in optimized operational processes, lower manufacturing expenditures, and elevated product standards [3].

Pharmaceutical companies are under growing demands to streamline their operations, minimize expenses, and elevate the caliber of their products. In the pharmaceutical industry, AM technology offers transformative solutions for drug development and personalized medicine. It allows for the fabrication of precise dosage forms with tailored drug release profiles, improving patient adherence and efficacy [4]. AM enables the production of complex drug delivery systems, such as implants and transdermal patches, as well as

patient-specific medications, enhancing treatment outcomes. Moreover, it enables the swift creation of prototype pharmaceutical formulations, expediting the drug development lifecycle and diminishing the associated expenditures. Furthermore, it offers innovative approaches for personalized healthcare and drug delivery.

The integration of continuous processing reactors and AM technology opens up a promising avenue for the synthesis of pharmaceutical intermediates, particularly Schiff base compounds and metronidazole derivatives. These compounds have garnered significant attention due to their diverse biological activities and potential therapeutic applications. By leveraging the advantages of continuous flow and the design flexibility offered by AM, researchers can optimize reaction conditions, increase product yield, and improve the overall efficiency of pharmaceutical synthesis. This synergistic approach not only addresses the challenges faced by the pharmaceutical industry but also paves the way for the development of novel drug candidates with improved efficacy and reduced side effects.

Various reaction types are used to synthesize pharmaceutical intermediates, including the formation of Schiff base compounds through condensation reactions. Schiff bases constitute a significant category of organic compounds that possess a diverse array of applications [5]. They have been extensively used as ligands for forming transition metal complexes [6]. Furthermore, Schiff bases have demonstrated a wide range of biological effects, including antibacterial, antifungal, and anti-inflammatory capabilities [7]. Schiff bases incorporating heterocyclic components have attracted substantial interest owing to their multifaceted biological activities, encompassing anticancer, antiviral, fungicidal, bactericidal, and anti-HIV properties [8]. Developing new chemotherapeutic Schiff bases has become an area of focus for medicinal chemists [9]. Numerous research teams have dedicated their efforts to the synthesis and biological evaluation of Schiff base compounds [10]. As an example, scientists have made different Schiff base compounds from 2-aminothiazoles and substituted benzaldehydes and then tested how well they fight three types of human tumor cells in the lab [11]. Other research groups have also made Schiff bases from 7-amino-4-methylcoumarin and benzaldehydes, studying their pain-relieving and anti-inflammatory effects. Their findings revealed that certain prepared Schiff base compounds have comparable or even superior potency compared to reference drugs used for these therapeutic applications [12]. Moreover, scientists have prepared Schiff base compounds via the condensation of aromatic and heteroaromatic aldehydes with coumarin acetohydrazides, employing both conventional and microwave-assisted techniques. A subsequent evaluation of their antimicrobial efficacy revealed a range of moderate to potent activity against various bacterial strains [13]. In recent times, researchers have reported on the synthesis and antiglycation activity of bis-Schiff bases derived from isatins. Their findings demonstrate that the presence of electron-withdrawing groups on the isatin moiety enhances these compounds' antiglycation activity significantly [14]. Quite recently, scientists have documented their work on the synthesis and antimicrobial properties of novel optically active Schiff base compounds derived from substituted benzaldehydes and various amines. Their research showed that adding nitro, methoxy, and halogen substituents to the phenyl ring made the compounds they made more effective against different types of bacteria [15]. In a comparable manner, metronidazole and its derivative compounds exhibit a vast array of biological activities [16]. These metronidazole-based compounds are excellent at fighting trichomoniasis, different types of amoebiasis, and infections caused by anaerobic bacteria and protozoan pathogens [17]. Azomycin, a 2-nitroimidazole compound, is the sole approved antibiotic based on the nitroimidazole structure. Both Actinobacteria species, including Streptomyces eurocidicus and Nocardia mesenterica, and Proteobacteria, including Pseudomonas fluorescens, produce it [18]. As a result, azomycin has served as a crucial synthetic precursor for the development of numerous nitroimidazole-based pharmaceutical drugs. From azomycin, the following nitroimidazole compounds are made: metronidazole (Figure 1a), secnidazole (Figure 1b), tinidazole (Figure 1c), and ornidazole (Figure 1d).

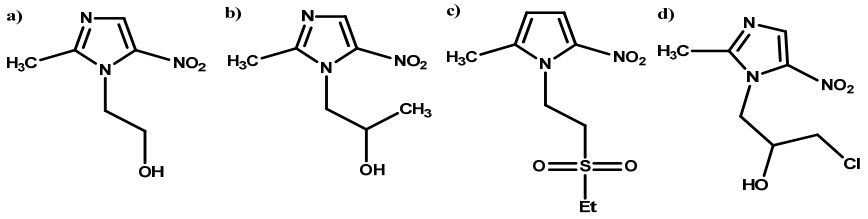

Figure 1. The structure of metronidazole (**a**) and its derivatives: secnidazole (**b**), tinidazole (**c**), and ornidazole (**d**).

Continuous processing offers several advantages, including reduced reaction times, improved process control, and enhanced safety [19]. Despite the aforementioned benefits, the widespread implementation of continuous processing in pharmaceutical manufacturing has been impeded by several technical and practical hurdles. These obstacles encompass the necessity for specialized equipment and infrastructure, regulatory considerations that must be addressed, and challenges associated with scalability when transitioning from batch to continuous operations [20,21]. Designing AM-based continuous processing reactors for pharmaceutical applications requires a multidimensional approach that considers various factors to ensure optimal performance, safety, and regulatory compliance. The key considerations include selecting biocompatible and chemically resistant materials suitable for pharmaceutical use, optimizing the reactor design for continuous flow to facilitate uniform mixing and reaction kinetics, and incorporating precise temperature control mechanisms to maintain optimal reaction conditions [22]. Modularity and scalability are essential for accommodating different production scales and process requirements, while integration with downstream processes, such as purification and analyses, streamlines manufacturing workflows. Safety features, including pressure relief valves and leak detection systems, are crucial for preventing accidents and ensuring safe operation. Regulatory compliance with pharmaceutical manufacturing standards, such as GMPs, and cost-efficiency considerations, such as material costs and energy consumption, must also be carefully addressed [23]. By meticulously evaluating these design factors, additive manufacturing-based continuous processing reactors can be customized to cater to the distinct requirements of pharmaceutical applications. This approach facilitates the efficient, secure, and cost-effective production of pharmaceutical products while enhancing their quality and consistency attributes [24].

This study aimed to explore the potential applications of AM-based continuous processing reactors in the pharmaceutical synthesis of metronidazole derivatives. Considering the extensive interest in the biological activity and profile of Schiff bases and metronidazole, and as part of our ongoing research endeavors focused on synthesizing novel compounds with pharmacological relevance, we hereby present the synthesis of two metronidazole derivatives. The first derivative was obtained through the reduction of the nitro group present in metronidazole, while the second compound was synthesized by facilitating a reaction between this reduced metronidazole derivative and terephthalic aldehyde within an additive manufacturing-based continuous processing reactor system. Furthermore, we propose the development of a continuous processing pharmaceutical reactor system that employs AM technology, with the objective of expediting the production of metronidazole-based pharmaceutical substances within an optimized development time.

2. Materials and Methods for Production of Pharmaceutical Ingredients

2.1. Materials and Methods

The reagents and chemical substances employed were of analytical grade and were procured from commercial suppliers Sigma-Aldrich (Saint Louis, MO, USA), Fluka (Old Brickyard, UK), and Merck (Darmstadt, Germany). The progression of the reactions was monitored through thin-layer chromatography (TLC) techniques. This process involved the utilization of pre-coated glass plates containing a layer of silica gel (E. Merck Kiesegel 60 F254, with a layer thickness of 0.25 mm). A solvent system comprising chloroform and methanol was employed as the eluent. The visualization of the TLC plates was facilitated

either through exposure to iodine vapor within an iodine chamber or by illumination under ultraviolet (UV) light. The formation of the final compounds was confirmed by HPLC analysis, which proved to be >95% pure.

The melting points of the synthesized compounds were determined using Stuart Scientific melting point equipment, namely the SMP 10 Fascia model (Cole-Parmer Ltd., Staffordshire, UK). The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were acquired using a JNM-ECA 400 spectrometer (JEOL Ltd., Tokyo, Japan), with deuterated dimethyl sulfoxide (DMSO-d6) serving as the solvent (refer to Table 1 for data) and tetramethylsilane (TMS) employed as an internal standard. The compounds 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)acetic acid (compound **A** with chemical formula: $C_6H_{11}N_3O$), 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)acetyl chloride (compound **B** with chemical formula: $C_{20}H_{24}N_6O_2$), and 2-(5-(anthracen-9(10*H*)-ylideneamino)-2-methyl-1*H*-imidazol-1-yl)ethan-1-ol (compound **C** with chemical formula: $C_{20}H_{19}N_3O$) were synthesized by following the literature procedures outlined in reference [25], with minor adjustments or modifications to the original methods described therein [25]. The synthesis of ((((1Z,1′Z)-1,4-phenylenebis(methaneylylidene))bis(azaneylylidene))bis(2-methyl-1*H*-imidazole-5,1-diyl))bis(ethane-2,1-diyl) bis(4-methyl benzenesulfonate) (compound **D** with chemical formula: $C_{34}H_{36}N_6O_6S_2$) and 2-(5-(anthracen-9(10*H*)-ylideneamino)-2-methyl-1*H*-imidazol-1-yl)ethyl 4-methylbenzene-sulfonate (compound **E** with chemical formula: $C_{27}H_{25}N_3O_3S$) was accomplished by introducing slight alterations or changes to the procedures reported in the literature reference [26]. The infrared (IR) spectra were acquired using the potassium bromide (KBr) disc method on an Analytical Technologies FT-IR spectrophotometer (Analytical Technologies Limited, Gujarat, India), model 2202 (refer to Table 2 for data). The purity assessment of the compounds was conducted through thin-layer chromatography (TLC) on pre-coated Merck silica gel 60 F254 plates, employing a solvent system that comprised a mixture of chloroform and methanol. The visualization of the spots was facilitated either by exposure to iodine vapor within an iodine chamber or by illumination under ultraviolet (UV) light.

Table 1. ^{1}H-NMR signals of groups used for identification of metronidazole and compounds **A**–**D**.

Compound Name	Group	Shift	Compound Name	Group	Shift
MNZ ($C_6H_9N_3O_3$)	NH_2-	6.27	**C** ($C_{20}H_{19}N_3O$)	CH_2- (of 9,10-dihydroanthracene)	4.35
	HO-	4.96	**D** ($C_{34}H_{36}N_6O_6S_2$)	CH_3- (bonded to benzene ring)	2.43
	CH_3-	2.53		CH_3- (bonded to benzene ring)	2.53
A ($C_6H_{11}N_3O$)	HO-	4.96		CH- (of a benzene ring)	7.45, 7.75
	CH_3-	2.53	**E** ($C_{27}H_{25}N_3O_3S$)	CH_3- (bonded to benzene ring)	2.43
B ($C_{20}H_{19}N_3O$)	CH- (of the benzene ring)	8.02		CH_3- (of a benzene ring)	2.53
	H-	8.99		CH- (of a benzene ring)	7.45, 7.75

Table 2. Infrared absorption results for Schiff base compounds **A**, **B**, and **C**.

Compound Name	I.R. (KBr) cm^{-1}				
	υ (O-H)	**υ (C-H) Arom. and Aliph.**	**υ (C=N)**	**υ (C-O)**	**Others**
Metronidazole ($C_6H_9N_3O_3$)		CH_2: 1466–1452 CH_3: 1387 CH: 711	1070	1275–1096	NO_2: 1536, 1369 C=C: 1600 C=N: 1523 N=O: 1479, 1356 (asym) N=O: 1371 (sym) C-C: 1425–1426
A ($C_6H_{11}N_3O$)	-	2950.07	1537	1075	NH_2: 3590–3518

Table 2. *Cont.*

Compound Name	I.R. (KBr) cm^{-1}				
	υ (O-H)	υ (C-H) Arom. and Aliph.	υ (C=N)	υ (C-O)	Others
B ($C_{20}H_{19}N_3O$)	3448	3100 2886	1620	1199	
C ($C_{20}H_{19}N_3O$)	3454	2866	1650	1199	
D ($C_{34}H_{36}N_6O_6S_2$)	-	3076 2953, 2916	1262		$S=O_2$: 1378 (asym) $S=O_2$: 1173 (sym)
E ($C_{27}H_{25}N_3O_3S$)	-	3075 2950, 2911	1262		$S=O_2$: 1382 (asym) $S=O_2$: 1170 (sym)

2.2. Continuous Processes 1 and 2

The reduction process employing sodium dithionite ($Na_2S_2O_4$) as the reducing agent proved to be the most efficacious methodology, yielding the highest product percentage and facilitating the isolation of compound **A** as a solid precipitate. Further, in continuous processes 1 and 2, the Schiff base compounds **B** and **C** were successfully obtained from the interaction of compound **A** with terephthalic aldehyde and anthracen-9(10*H*)-one, respectively, with a good yield (Figure 2).

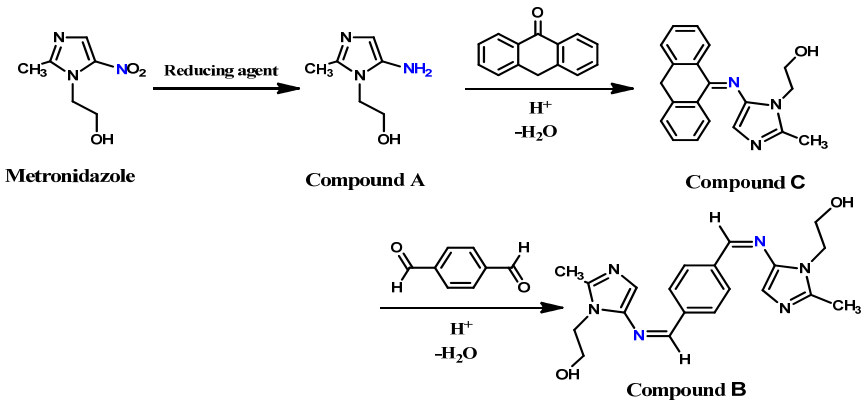

Figure 2. Synthesis scheme of compounds **A**, **B**, and **C**.

The subsequent scheme outlines the synthetic pathway for obtaining compounds **B** and **C** through the reaction of precursors **D** and **E** with the reagent 4-methylbenzenesulfonyl chloride (Figure 3).

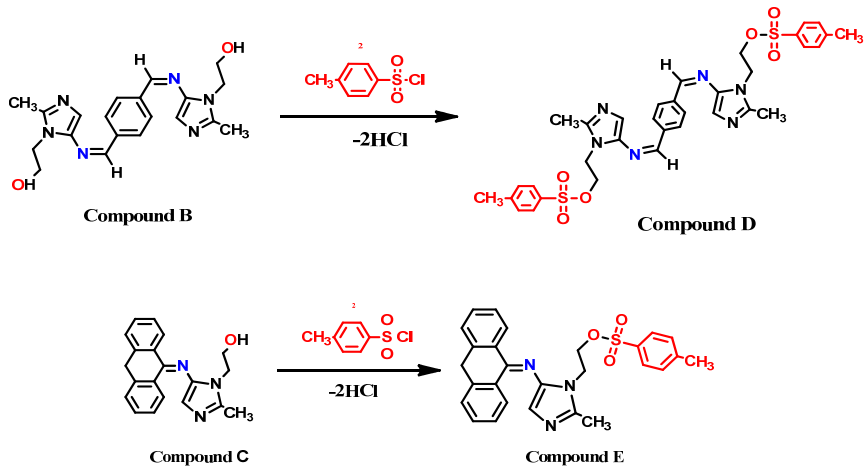

Figure 3. Synthesis scheme of compounds **D** and **E**.

2.2.1. Synthesis of Compound **A**

Method of Reducing the Nitro Group in Metronidazole to Prepare Compound **A**

First, 0.510 g (3.0 mmol) of metronidazole was dissolved in 70.0 mL of ethanol, and 1.500 g (9.0 mmol) of sodium dithionite ($Na_2S_2O_4$) was added to the solution. The resulting mixture was heated to 55 °C for a duration of 2 h. Subsequently, 4.5 mL of a 25% hydrochloric acid (HCl) solution was introduced, and the mixture was stirred for an additional 3 h. After cooling the mixture to room temperature, it was neutralized by adding a 50% sodium hydroxide (NaOH) solution. The overall yield of the product obtained through this procedure was 72%.

2.2.2. Continuous Process 1 (**A**→**B**→**D**)

Method of Preparing Schiff Base Compound **B**

Compound **A** (1.0 mmol, 0.142 g) was dissolved in 25.0 mL of ethanol to form the first solution. In a separate vessel, terephthalic aldehyde (2.0 mmol, 0.262 g) was dissolved in 10 mL of ethanol, with the addition of a few drops of glacial acetic acid. Subsequently, the terephthalic aldehyde solution was introduced into the solution containing compound **A**. The resulting mixture was then subjected to reflux conditions for a duration of 8 h. Thin-layer chromatography techniques were utilized to track the progression of the reaction. Upon the completion of the reaction, the mixture was allowed to cool, after which it was filtered to recover the precipitated product. The isolated solid was subsequently dried and subjected to recrystallization from ethanol, yielding a yellow crystalline solid with a melting point of 179 °C. The overall yield of the purified product was 63%.

Method of Preparing Compound **D**

Compound **B** (2.054 g, 5.4 mmol) was combined with pyridine (1.0 mL, 12.4 mmol) and 4-methylbenzenesulfonyl chloride (2.000 g, 11.3 mmol). The resulting mixture was heated to 45 °C and maintained under reflux conditions for 1 h. Subsequently, the reaction mixture was introduced into 25 mL of a cold 2% sodium bicarbonate solution and subjected to vigorous stirring until an oil solidified. The crude solid product, designated as compound **D**, was purified via recrystallization from methanol, yielding the pure product with a 77% yield.

2.2.3. Continuous Process 2 (**A**→**C**→**E**)

Method of Preparing Schiff Base Compound **C**

Compound **A** (1.0 mmol, 0.144 g) was dissolved in 25.0 mL of ethanol to form the first solution. In a separate vessel, anthracene-9(10H)-one (1.0 mmol, 0.194 g) was dissolved in 10 mL of ethanol, with the addition of a few drops of glacial acetic acid. Subsequently, the anthracene-9(10H)-one solution was introduced into the solution containing compound **A**. The resulting mixture was then subjected to reflux conditions for a duration of 8 h. The progress of the reaction was monitored using thin-layer chromatography techniques. After the completion and cooling of the reaction mixture, it was filtered to isolate the precipitated product, which was then dried. The dried solid was recrystallized from ethanol, yielding a yellow crystalline solid with a melting point of 123 °C. The overall yield of the purified product was 68%.

Method of Preparing Compound **E**

A mixture comprising compound **C** (1.714 g, 5.4 mmol), pyridine (1.0 mL, 12.4 mmol), and 4-methylbenzenesulfonyl chloride (2.000 g, 11.3 mmol) was subjected to reflux conditions at 45 °C for 1 h. Subsequently, the reaction mixture was introduced into 25 mL of a cold 2% sodium bicarbonate solution and subjected to vigorous stirring until the formation of a solid product occurred. The crude solid product, designated as compound **E**, was purified via recrystallization from methanol, affording an 88% yield of the pure compound.

3. Design and Additive Manufacturing Process and Integration of Reactor System

3.1. Design of the Reactor System

AM is actively used to create prototypes of reactors in the chemical industry for rapid prototyping [27]. Figure 4 shows that the reactor system comprises three series-connected reactors. Each reactor has several key components, including a housing, a lid, a stand, inputs for ingredients. There are holes in the reactor cover to accommodate the temperature sensor and the stirrer motor. The shaft and blade of the agitator connect to the agitator motor, mounted on the reactor cover. The reactor design includes a system of heat exchangers. This system has a housing with built-in tubes for liquid circulation. Additionally, each reactor features inlet valves for loading ingredients, a drain outlet, and a drain valve. This configuration makes it possible to effectively regulate the temperature and process materials during the reaction process. The reactors are interconnected by tubes to connect the reactors. The coolant in the heat exchanger tubes, the ingredients in the reactor, and the draining liquid from the reactors are pumped using peristaltic pumps.

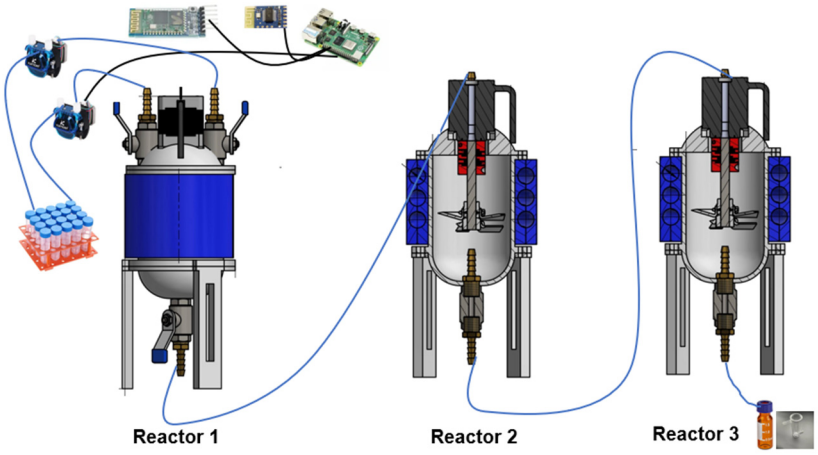

Figure 4. Design of the continuous reactor system for the synthesis of pharmaceutical ingredients.

The reactor system is equipped with a microcontroller system that manages the operation of the various components. It controls the peristaltic pumps and agitator motors. The system has a display panel, a control interface, a power supply, drivers for the agitator's stepper motor, a temperature sensor, and Bluetooth/Wi-Fi modules enabling remote monitoring and control via a mobile app. The reactor control program incorporates features to temporarily start/stop the peristaltic pumps as well as increase or decrease the pumping rates of the liquid streams.

3.2. Manufacturing of the Reactor Components

Reactor housings, covers, stands, and stirrers were additively manufactured on an industrial AM machine with the brand VSHAPER 270 PRO (VSHAPER, Jasionka, Poland) via fused deposition manufacturing technology using a PET-G filament (Figure 5).

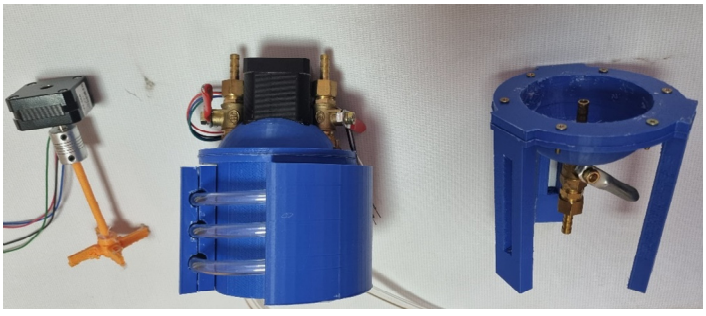

Figure 5. AM-based reactor components (main body with heat exchanger and mixer).

PET-G (polyethylene terephthalate glycol) was chosen to manufacture the body of the reactor system presented in this study because of its exceptional chemical resistance, high thermal stability, and mechanical strength. This material maintains dimensional stability and structural integrity over a wide range of operating conditions. For printing with a PET-G thread on the SHAPER 270 PRO (SHAPER Tools, San Francisco, CA, USA), a nozzle temperature of 240 °C and a working plate of 80 °C were selected. The optimal resolution was achieved by employing a printing speed of 30 mm/s.

After the additive manufacturing of the reactor components, which included the main body and the mixer system, the reactors were assembled and equipped with parts according to Section 3.1 (Figure 6). These parts were the valves, heat exchanger, electrical motors, and microcontroller system.

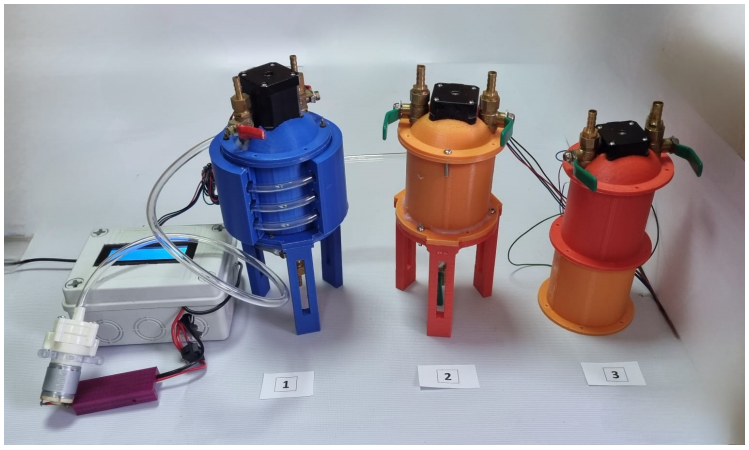

Figure 6. AM-based continuous processing reactor system for the synthesis of metronidazole derivatives.

4. Chemical Processes in the AM-Based Reactor System

AM enables the execution of diverse chemical processes within printed reactors, facilitating the development of reactor systems for the synthesis of active pharmaceutical ingredients, including metronidazole derivatives. To evaluate the efficacy and operational capability of these reactor systems, a series of experiments involving the synthesis of three distinct types of antibiotics derived from metronidazole were proposed (see Figure 7).

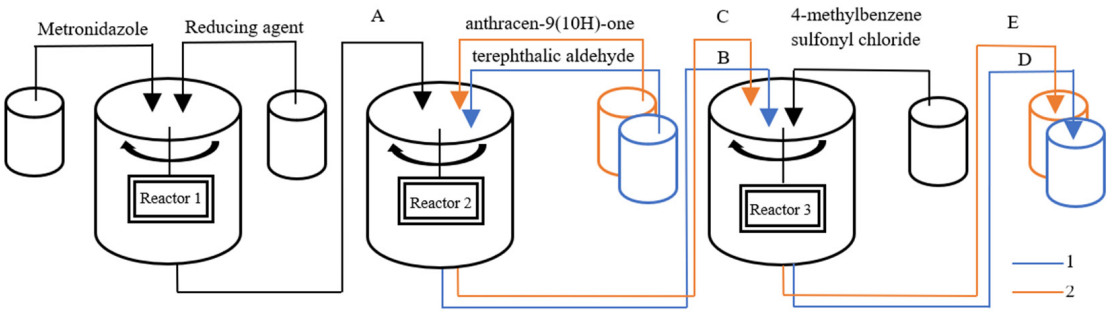

Figure 7. Scheme of synthesis of five metronidazole derivatives via two continuous processes (1 and 2—continuous processes 1 and 2), involving metronidazole reduction and its subsequent reactions with terephthalic aldehyde and anthracen-9(10H)-one to form Schiff bases.

Compound **A** was generated by combining a metronidazole solution, sodium dithionite, and hydrochloric acid in reactor **A**, as described in Section 2.2.1. Subsequently, the resulting compound **A** from reactor 1 was transferred to reactor 2, where it was mixed with a solution containing terephthalic aldehyde and glacial acetic acid per Section 2.2.2 to yield compound **B**. In parallel, compound **A** was transferred from reactor 1 to reactor 3, where it reacted with a solution of anthracen-9(10H)-one and glacial acetic acid in accordance with Section 2.2.3 to produce compound **C**. Compounds **D** and **E** were synthesized following

procedures outlined in Sections 2.2.2 and 2.2.3, respectively, which involved continuous processes 1 and 2 using 4-methylbenzenesulfonyl chloride.

The synthesis of metronidazole derivatives proceeded through distinct stages: initial reduction of metronidazole using a reducing agent in reactor 1 to convert the nitro group to an amino group, followed by the synthesis of a Schiff base in reactor 2 by reacting component **A** with anthracen-9(10H)-one (continuous process 1) and terephthalic aldehyde (continuous process 2). Compounds **B** and **C** obtained from reactor 2 were further utilized to synthesize compounds **D** and **E**.

The optimal synthesis parameters in the reactor system were determined by investigating the dependency of reaction product yields on time and temperature. Analytical methods were employed during each reaction to assess reaction yields, followed by purification of the synthesized substances.

Dependence of Product Yields on the Reaction Time and Temperature

Figures 8–13 show that the yield of **A**–**D** products depends on reaction duration and temperature.

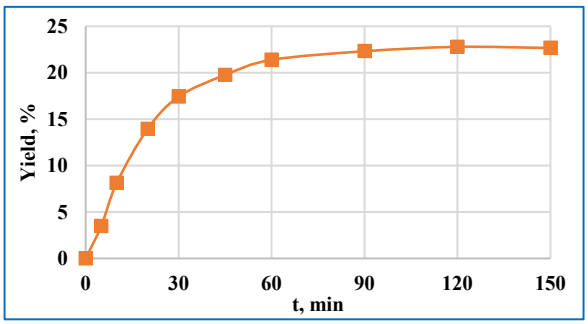

Figure 8. Time-dependent product yields in the synthesis of component **A**.

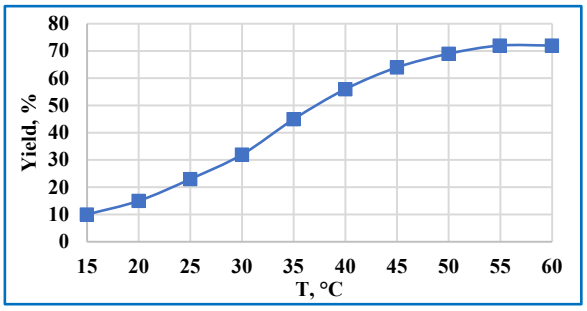

Figure 9. Temperature dependence of the yield of compound **A** during the hydrogenation of metronidazole with a process duration of 2 h.

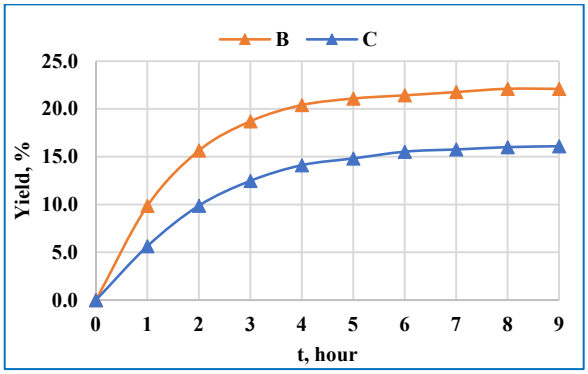

Figure 10. Time-dependent product yields in the synthesis of components **B** and **C**.

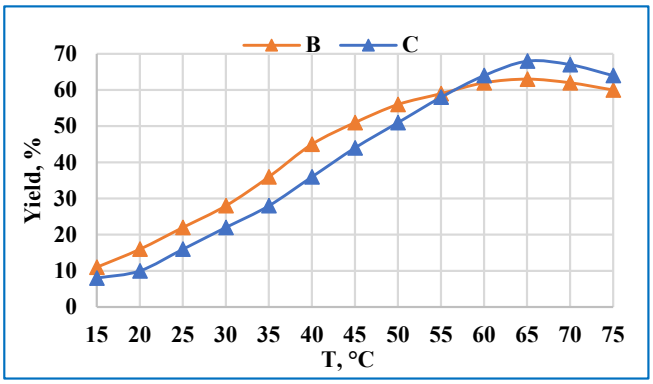

Figure 11. Temperature dependence of the yield of Schiff base products **B** and **C** with a process duration of 8 h.

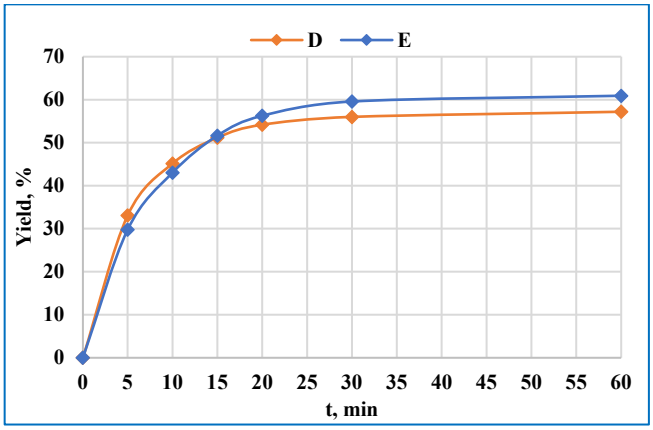

Figure 12. Time-dependent product yields in the synthesis of components **D** and **E**.

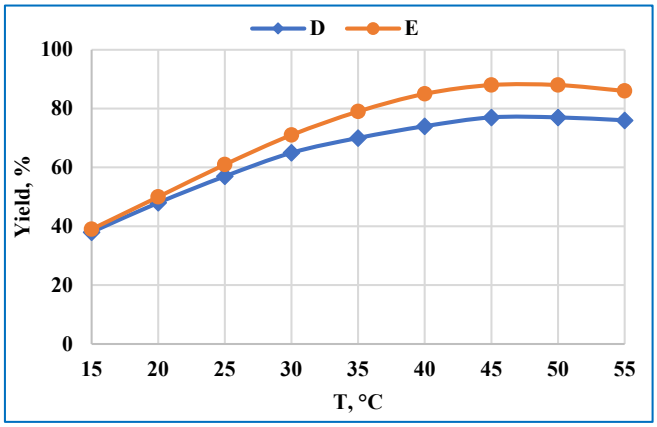

Figure 13. Temperature dependence of the yield of compounds **D** and **E** during the tosylation of the OH-group with a process duration of 8 h.

The examination of the plot depicted in Figure 8 reveals that the most favorable reaction duration is 120 min, achieving a product yield of 23%. To explore the influence of temperature on the yield of product **A** during the hydrogenation of metronidazole, this optimal reaction time was chosen for further investigation.

The temperature dependence of the compound **A** yield was examined during the hydrogenation process of metronidazole (see Figure 9).

At lower temperatures (15–20 °C), the yield of compound **A** remains relatively modest, ranging from 10% to 15%. As the temperature rises, there is a notable enhancement in product yield. The most significant increase occurs within the temperature range of 25 °C

to 45 °C, where the yield escalates from 23% to 64%. A temperature of 55 °C yields a maximum product yield of 72%.

The plot depicted in Figure 10 illustrates the evolution of reaction yields (in percentage) for components **B** and **C** over a 9 h synthesis period.

Both components exhibit a similar trend of increasing reaction yield over time, albeit with discernible differences in rate and final values. Throughout the entire observation period, component **B** consistently demonstrates a higher reaction yield and faster growth compared to component **C**. As the synthesis progresses, the rate of yield increase for both components gradually diminishes. By the 8th hour mark, component **B** reaches a yield of 22.1%, whereas component **C** stabilizes at 16.1%.

Based on these observations, an optimal reaction time of 8 h was selected to further investigate the temperature dependence of reaction yields.

Figure 11 presents the relationship between the temperature and the yield of Schiff base products **B** and **C** over an 8 h period.

Overall, product **B** demonstrates a higher reaction yield relative to product **C**. The maximum yield for product **B** is achieved at 65 °C, reaching 63%, while product **C** also attains its highest yield at 65 °C, with a yield of 68%.

Figure 12 illustrates the time-dependent progression of reaction yields in the synthesis of components **D** and **E**.

The graph shows similar trends for both substances, marked by a rapid initial increase followed by a deceleration. Throughout the synthesis process, component **E** consistently demonstrates a slightly higher yield compared to component **D**. The yields peak at 57% and 61%, respectively, towards the conclusion of the hourly period.

Figure 13 demonstrates the temperature dependence of the yields of compounds **D** and **E** during the tosylation of the OH group over an 8 h reaction period.

Both compounds exhibit an overall trend of increasing yield with rising temperatures, reaching a peak before a slight decline occurs. Compound **E** generally shows a higher reaction yield than compound **D**. The yield difference between the compounds becomes more pronounced at higher temperatures, with the maximum yields observed at 45 °C: 74% for compound **D** and 85% for compound **E**.

5. Conclusions

This study showcases the successful synthesis of metronidazole derivatives using an additive manufacturing (AM)-based reactor system. Five compounds (**A**, **B**, **C**, **D**, and **E**) were synthesized through continuous processes, beginning with metronidazole reduction and culminating in Schiff base formation. The optimal reaction conditions were determined for each compound: for compound **A**, a reaction time of 120 min at 55 °C yielded 72%; for compounds **B** and **C**, 8 h at 65 °C yielded 63% and 68%, respectively; and for compounds **D** and **E**, 8 h at 45 °C yielded 74% and 85%, respectively. The temperature and reaction time significantly influenced the product yields, with each compound having distinct optimal conditions.

The AM reactor system exhibited several advantages, including the ability to perform multi-step chemical processes—such as reduction, Schiff base formation, and tosylation—in a continuous flow. This method offers flexibility in pharmaceutical synthesis, facilitating the efficient production of active pharmaceutical compounds and their derivatives. Additionally, the system allows precise control over reaction conditions, enabling the optimization of the yields for various compounds.

However, some limitations were noted. The reaction times for compounds **B**, **C**, **D**, and **E** were relatively long, at 8 h, potentially impacting the overall process efficiency. Furthermore, while promising, the yields for compounds **A**, **B**, and **C** could still be improved.

These findings highlight both the potential and challenges of additive manufacturing in chemical synthesis, particularly in developing reactor systems for pharmaceutical compound production. The flexibility and control provided by AM systems offer significant advantages, but further optimization of reaction conditions and yields is necessary.

Future research could focus on refining reactor designs to reduce reaction times and enhance yields, investigating a broader range of pharmaceutical compounds to assess the system's versatility, and scaling up the process for potential industrial applications. Additionally, future studies will aim to synthesize vinyl acetate and modify the final molecule using a continuously operating reactor system developed through additive manufacturing.

Author Contributions: Conceptualization, S.D.; methodology, A.K.; validation, A.M.; formal analysis, D.K.; investigation, M.K.; data curation, A.M.; writing—original draft preparation, A.K. and S.D.; writing—review and editing, A.M.; visualization, M.K. and D.K.; supervision, S.D. and A.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Science Committee of the Ministry of Science and Higher Education of Kazakhstan, grant number AP15473571.

Data Availability Statement: The data presented in this study are available from the corresponding author upon request. The data are not publicly available due to the complexity of the analysis which needs guidance for reproduction.

Conflicts of Interest: The authors declare no conflicts of interest.

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