CHEMISTRY AND TECHNOLOGY OF MEDICINAL COMPOUNDS AND BIOLOGICALLY ACTIVE SUBSTANCES

ХИМИЯ И ТЕХНОЛОГИЯ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ И БИОЛОГИЧЕСКИ АКТИВНЫХ СОЕДИНЕНИЙ

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REVIEW ARTICLE

Microfluidic method as a promising technique for synthesizing antimicrobial compounds

Anh C. Ha[1,2,@]

[1]*Faculty of Chemistry, Ho Chi Minh City University of Technology (HCMUT), 268 Ly Thuong Kiet Street, Ho Chi Minh City, Vietnam*
[2]*Vietnam National University Ho Chi Minh City (VNU-HCM), Linh Trung ward, Thu Duc District, Ho Chi Minh City, Vietnam*
[@]*Corresponding author, e-mail: hcanh@hcmut.edu.vn*

Abstract

Objectives. *The study aimed to analyze the current antiseptics and disinfectants, explore the possibility of synthesizing various antiseptics including oligohexamethylene guanidine hydrochloride (OHMG-HC) using microfluidic technology, and investigate the main synthesis parameters affecting the properties of the resulting product.*

Methods. *This article presented a review of literature sources associated with investigations of antimicrobial resistance, the uses of agents based on polyhexamethylene guanidine hydrochloride, oligohexamethylene guanidine hydrochloride, and other salts, obtained using modern synthesis technologies with microreactors.*

Results. *The relevance of developing production technologies for the "OHMG-HC branched" substance was determined. The microfluidic method for the synthesis of polymers, and its application prospects for obtaining the target substance were compared with the existing methods. Advantages of the microfluidic method were indicated.*

Conclusions. *Microreactor technologies allow for more accurate control of the conditions of the polycondensation reaction of the starting monomers and increase the yield and selectivity of the oligomers obtained, leading to an increase in the product purity and process efficiency, in contrast with other known methods. The use of microreactor technologies for the synthesis of branched oligohexamethylene guanidine hydrochloride products is a promising strategy.*

Keywords: *antiseptic, disinfectant, alkylene guanidines, oligohexamethylene guanidine hydrochloride, microfluidic technologies, microreactor*

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ОБЗОРНАЯ СТАТЬЯ

Микрофлюидный метод как перспективная технология для синтеза антимикробных соединений

А.К. Ха[1,2,@]

[1]*Химико-технологический факультет, Технологический университет Хошимина, 268 Ли Тхыонг Кьет ул., г. Хошимин, Вьетнам*
[2]*Вьетнамский национальный университет, Район Тхёк, г. Хошимин, Вьетнам*
[@]*Автор для переписки, e-mail: hcanh@hcmut.edu.vn*

Аннотация

Цели. *Цель исследования – проанализировать применяющиеся антисептики и дезинфектанты, рассмотреть возможность синтеза различных антисептиков и отдельно синтеза олигогексаметиленгуанидина гидрохлорида (ОГМГ-ГХ) с применением микрофлюидной технологии, а также изучить основные параметры синтеза, влияющие на характеристики получаемого продукта.*
Методы. *Представлен обзор литературных источников, связанных с иследованиями антимикробной резистентности, применением средств на основе полигексаметиленгуанидина гидрохлорида, олигогексаметиленгуанидина гидрохлорида, а также других солей, полученных современными технологиями синтеза с использованием микрореакторов.*
Результаты. *Определена актуальность разработки технологии получения субстанции «ОГМГ–ГХ разветвленный». Рассмотрены существующие способы получения субстанции и их недостатки. Также рассмотрен микрофлюидный способ синтеза полимеров, его достоинства и перспективы его использования для получения целевой субстанции.*
Выводы. *Микрореакторные технологии позволяют более точно контролировать условия реакции поликонденсации исходных мономеров и повышать выход и селективность полученных олигомеров, что приводит к повышению чистоты продукта и эффективности процесса, в отличие от других известных способов. Использование микрореакторных технологий для синтеза разветвленных продуктов гидрохлорида олигогексаметиленгуанидина является перспективной стратегией.*

Ключевые слова: *антисептик, дезинфектант, алкиленгуанидины, олигогексаметиленгуанидина гидрохлорид, микрофлюидные технологии, микрореактор*

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INTRODUCTION

Currently, one of the most important global problems is the progressive resistance of pathogenic microorganisms to applied biocidal drugs, and special measures are being developed to combat this problem [1]. Approximately 50000 people die annually from infectious diseases caused by antimicrobial-resistant microbes in Europe and the United States, with this number reaching hundreds of thousands in developing countries.

The resistance of microorganisms is manifested by the presence of structural polymers in their cell membrane, e.g., peptidoglycan. Peptidoglycan provides mechanical strength and structure to the cell, as well as thickness and shape, which depend on the type of peptidoglycan.[1] To protect their cytoplasmic membrane, gram-positive bacteria possess a thick layer of peptidoglycan, while gram-negative bacteria possess inner and outer membranes surrounding a relatively thin peptidoglycan matrix and periplasmic space. There are components associated with both types of cell walls that limit the ability of antibiotics and antiseptics to penetrate these structures (efflux pumps that remove toxins, protective enzymes (e.g., β-lactamases), and complex carbohydrate networks). In general, the resistance of microorganisms can be divided into two types. The first is antibiotic tolerance, i.e., where a cell under the influence of chemical action reduces its growth and metabolism or inactivates the targets of the antibacterial drug. Antibiotic tolerance is not inherited, but is developed under certain external conditions, where part of the population evolve into persistent forms with multiple tolerance. The second type is antibiotic resistance, in which the targets are modified, destroyed, released from the cell, or rendered inaccessible because of the decrease in the cell membrane permeability. This decrease in cell permeability is the nonspecific resistance mechanism that leads to the development of multidrug resistance. This resistance information is transmitted at the genetic level and is an invariable trait in particular species [2]. Furthermore, this resistance problem is aggravated by the enclosure of most pathogenic bacteria in biofilms, which create an additional barrier for antimicrobial agents [3]. The biofilm contains a cellular component—one or several cultures of bacteria—and an extracellular matrix containing polysaccharides, glycopeptides, nucleic acids, and lipids in its structure [4].

In addition to antibiotic resistance, the resistance of pathogenic microflora to disinfectants is attracting significant concern. According to a study [5], several microorganisms exhibit resistance to the ubiquitous chlorhexidine, as evidenced by the increased value of the minimum inhibitory concentration. Healthcare-associated infections (HCAIs) pose a threat to patients in hospitals. The inappropriate use of antibacterial agents by medical institutions has led to the rapid development of multidrug resistance. According to expert forecasts, the mortality rate associated with HCAI will increase annually, if effective measures to combat resistance are not developed. There are various/different routes for solving this problem, from reducing the use frequency of antibiotics and replacing them with antiseptics [6–9] to, of course, exploring and implementing new antimicrobial agents that meet modern requirements.

The development of new antibacterial agents is a long and complex process, which is why large companies are wary of investing in this area. The results of screening new compounds against a group of ESKAPE pathogens characterized by significantly high resistance have been reported, and not a single compound was found to be active against gram-negative organisms. Many compounds that exhibit good whole cell activity have been found to be cytotoxic to mammals. In this regard, the development of new and effective antibiotics requires an in-depth study of the mechanisms of cell permeability, point mutations using molecular modeling, and other innovative methods; unfortunately, these require high material costs that may be unjustified [10].

Regarding the above information, it is necessary to review the antiseptics currently in use, considering the advantages and disadvantages of each of the presented classes.

TYPES OF ANTISEPTICS

The current classes of antiseptics can be categorized as follows.

Oxygen-active compounds (hydrogen peroxide, sodium percarbonate, peracetic and performic acids, and others). The biocidal effect is manifested by the released active oxygen. The representatives of this class have several disadvantages, namely toxicity, the ability to cause burns, and high cost[2].

Chloractive compounds (bleach, chloramines, sodium and lithium hypochlorites, and others). The antimicrobial action is effected by the released

[1] The Review on Antimicrobial Resistance, 2014. Available from URL: https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf (accessed March 27, 2021).

[2] Policy for the Control of Multi-Resistant gram Negative Bacteria. NHS, The document for the development and management of UHSM-wide policy or procedural documents. Available from URL: http://mft.nhs.uk (accessed March 30, 2021).

chlorine. These compounds are economical and effective against many groups of microorganisms; however, they exhibit high toxicity [11, 12].

Aldehydes (glutaraldehyde, succinic aldehyde, formaldehyde, glyoxal, and others). Most representatives of this group are toxic and exert allergenic, carcinogenic, mutagenic effects; further, they cause diseases of the skin, mucous membranes, internal organs [13, 14].

Alcohols (ethanol, 2-propanol, and others). For the manifestation of antiseptic properties, the concentrations of ethanol and isopropanol must be above 70% and 60%, respectively. Alcohols are fire hazardous substances and can have a narcotic effect [15].

Phenol and its derivatives have a film-forming effect, which accounts for their prolonged action. However, the representatives of this group are overly toxic [16].

Iodine compounds. They consist of iodine–carrier complexes, which allow the release of iodine. The main disadvantages of these compounds are their weak sporicidal effect and the ability to cause burns [17].

Alkylamines. Here, the biocides are primary, secondary, and tertiary amines. Although they influence most microorganisms, they do not exert any sporicidal effect. Thus, as a rule, they are used in combined composition [18].

Quaternary ammonium compounds (QACs) are widely used in practice and meet safety requirements. However, they have a narrow spectrum of action, which manifests in the absence of proper action against spores, simple viruses, gram-negative bacteria, and mycobacteria. Additionally, QACs are inactivated by negatively charged surfactants. Therefore, this group can be used in a combined composition with guanidines, amines, and aldehydes. In this combination, they are effective against both non-enveloped and enveloped viruses [19, 20].

Guanidines. An important advantage of guanidine derivatives is their propensity for prolonged action. These compounds have a wide spectrum of activity, including against bacteria from the ESKAPE group [21] and viruses [22], as well as low toxicity to humans and animals [23]. Compared to other compounds, guanidine derivatives are promising and have practically no drawbacks; therefore, their use as alternatives to antibiotics and antiseptics that have lost their relevance due to resistance is recommended.

GUANIDINE DERIVATIVES

Guanidine derivatives are referred to as cationic surfactants. For most guanidines, the main targets are important biogenic compounds and cell biopolymers, which have a high affinity for nitrogenous bases, such as pyridines and xanthines. There are two interaction mechanisms for binding with the targets: 1) by metabolite substitution and 2) competitive antagonism with normal metabolites [24]. In general, the action mechanism of guanidine derivatives is initiated by the protonation of guanidine, followed by the formation of a cation (Fig. 1), in which the positive charge is evenly distributed among all nitrogen atoms [25].

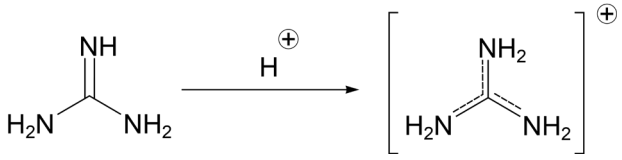
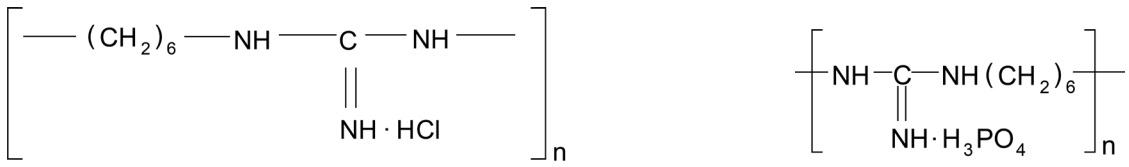


Fig. 1. Guanidinium cation formation.

The subsequent processes are as follows. Upon adsorption on the negatively charged surface of the cell membrane of bacterial cells, guanidine polycations block important vital processes, such as respiration, nutrition, and the transport of metabolites through the bacterial cell wall. Further diffusion of antiseptic macromolecules through the cell wall causes irreversible damage to the cytoplasmic membrane, nucleotide, and cytoplasm. This process depends on many factors, including the magnitude of the surface activity, lipophilicity, water solubility, and the molecular volume of the guanidine derivative molecule. The binding of guanidine derivatives with acid phospholipids, proteins of the cytoplasmic membrane, leads to its rupture. Subsequently, the blockage of the respiratory system, loss of pathogenicity, and collapse of the microbial cell occur [26].

Among the derivatives of guanidine are compounds with polymeric and oligomeric structures, containing fragments of various guanidine derivatives. The advantages of polyguanidines, which are applied in the form of salts of various acids, enable their application as biocidal agents in various fields.

Polyguanidines and their derivatives. The prominent representatives of this class of compounds are polyhexamethylene guanidine hydrochloride (PHMG-HC) and PHMG phosphate (Figs. 2a and 2b). The spectrum of antimicrobial activity of PHMG-HC covers gram-positive and gram-negative bacteria, aerobic and anaerobic bacteria, spore-forming bacteria, mycobacteria, and viruses. Despite its wide spectrum, PHMG-HC is hypoallergenic and has low toxicity [27, 28]; it can also be used in conjunction with other biocidal components, e.g., as a skin antiseptic [29, 30] or in solid dosage form [31]. The antifungal activity of PHMG-HC enables its application for conservation [32] and as an effective sporicidal tool for combating bacterial spores and nosocomial infections [33]. This compound can be applied as a component of composite nanofibers based on chitosan and polyethylene oxide [34].



a b

where n = 30–90

Fig. 2. Structural formulas of polyguanidine derivatives: (a) PHMG-HC and (b) PHMG phosphate.

Phosphate PHMG, similar to PHMG-HC, is synthesized by incorporating an acid anion into the structure of PHMG. In preclinical studies, this salt has exhibited increased antimicrobial activity against gram-positive and gram-negative bacteria, as well as fungi [35]. Fungicides based on PHMG phosphate can be formulated for use in dental practice [36, 37].

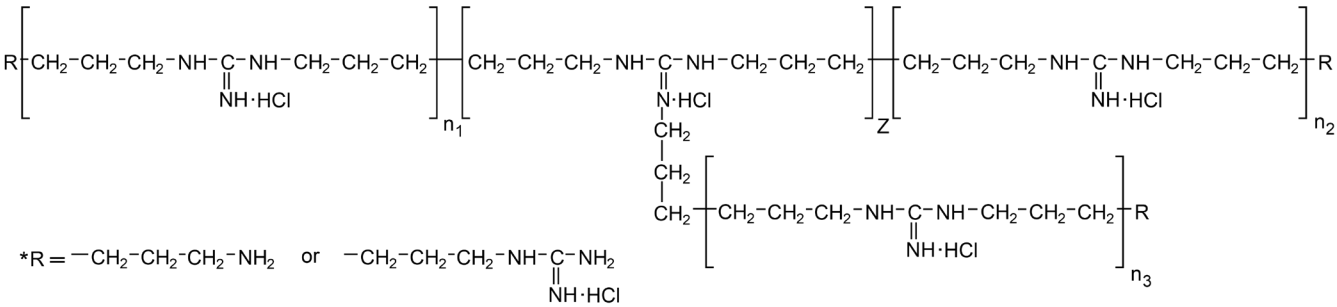
In addition to PHMG-HC and PHMG phosphate, other salts of this guanidine derivative can be used in practice. Gluconate and sulfate PHMG are employed for the treatment of infectious diseases of the gastrointestinal tract; hydrosuccinate PHMG, for ophthalmic diseases, particularly conjunctivitis [38]; and stearate and myristate PHMG, for use as biocidal additives [39, 40]. In addition, PHMG can be used in combination with chitosan [41], since this combination has good biocidal activity against gram-positive bacteria.

According to the literature [42, 43], the salts of PHMG can be widely used in medicine and pharmacy. In particular, the oligomeric analogs of PHMG, namely oligoguanidines, are known for their biocidal activity and low toxicity.

Branched oligoguanidines have significantly lower toxicity and pronounced bactericidal and antiviral activities compared with polymer analogs with linear structures [44, 45]. This confirms their application potential as active ingredients in the development of antibacterial drugs. A well-known representative of oligoguanidines is oligohexamethylene guanidine hydrochloride (OHMG-HC), the structural formula of which is shown in Fig. 3.

PREPARATION OF POLYGUANIDINES AND THEIR DERIVATIVES

Polyguanidines and their derivatives are obtained mainly in bulk reactors under different conditions, e.g., by the interaction of melts of guanidine hydrochloride (GHC), formed, in turn, from dicyandiamine and ammonium chloride, and hexamethylenediamine (HMDA) at 180°C, followed by heating to 240°C [46]. The disadvantages of this method are the impurities introduced by the initial highly toxic substances and the sublimation of HMDA at high temperatures. Later, a method was proposed for obtaining these compounds at relatively low temperatures by the fusion of GHC and HMDA in the presence of polyethylene glycol (PEG) [47]. However, with this method, it was impossible to achieve the required degree of purity and activity of the product. Preparation methods involving the stepwise heating of a suspension obtained by adding crystalline GHC to molten HMDA, followed by stirring and heating, have been reported. Although these methods allow one to obtain the final product with a sufficient degree of purity, the compound obtained has a wide molecular weight distribution, which negatively affects its antibacterial properties [48]. A preparation method has been reported, in which pre-crushed dicyanamide and ammonium chloride are fused at 200°C in the first stage, after which the melt is transferred to the second reactor, where the HMDA melt is gradually introduced at temperatures of 170–200°C. The disadvantage of this method is the presence of melamine in the product, which is formed by the thermal transformation



where n = 3–10, and z = 0.15–1.10

Fig. 3. Structural formula of branched OHMG-HC.

of dicyandiamide [49]. A synthesis method using equimolar amounts of HMDA and GHC has also been reported. Using this method, various derivatives with trilinear and cyclic or branched structures can be obtained (Fig. 4).

The main disadvantage of this method is the large number of products, which complicates the isolation of any particular compound.

Branched oligomers are obtained by the interaction of HMDA and GHC in the melt, in molar ratios of 1.0:1.0 to 1.0:1.2, at temperatures of 180–230°C, with a residence time in the range of 3–12 h [45].

In general, the existing methods for the synthesis of polyguanidines and their derivatives in bulk reactors have several disadvantages. In such methods, the heat- and mass-transfer rates are inadequate. This induces temperature and concentration anisotropies, which subsequently affect the molecular weight characteristics of the compound. Furthermore, large-volume reactors require a more sophisticated design to ensure explosion and fire safety, which leads to an increase in the process cost and the cost of the final product. Alternatively, one can consider the production of polyguanidines and their derivatives using microfluidic hardware.

MICROREACTOR TECHNOLOGIES

Historical development of microreactor technology

The first solid publications on the possibilities of using microfluidic technologies appeared in the second half of the 20th century. Among others, it is possible to highlight the manufacture and testing of a gas chromatograph based on a microcircuit [50] and research carried out in the field of miniature analytical systems, which aroused the greatest interest in this area of technology [51]. The development became possible thanks to advances in the field of microelectronics, which became the prototypes of future microreactors.

A great contribution to the study of microfluidic technologies was made by the staff of the Massachusetts Institute of Technology (USA), as well as by scientists from the Mainz Institute of Microtechnology (Fraunhofer Institute for Microtechnology and Microsystems) (Germany) [52, 53].

Currently, microfluidic technologies are actively developing, the possibility of their implementation in the production of various substances and compounds is under discussion.

Technological principles of microreactor hardware operation

Microfluidics includes devices, systems, and methods for controlling fluid flows with characteristic length scales that are in the range of micrometers, and reaction volumes are in the range from nanoliter to microliter [54]. Microfluidic systems exhibit properties that are fundamentally different from generally known concepts of the behavior of liquids. Fluid flow will be driven by viscous forces and pressure gradients with low moment of inertia and thus inertial effects. The result is a laminar flow without turbulence. One of the parameters is the Reynolds number (Re), which is the ratio of inertial forces to viscous forces. At large Re, inertial forces prevail, and at small Re, viscosity

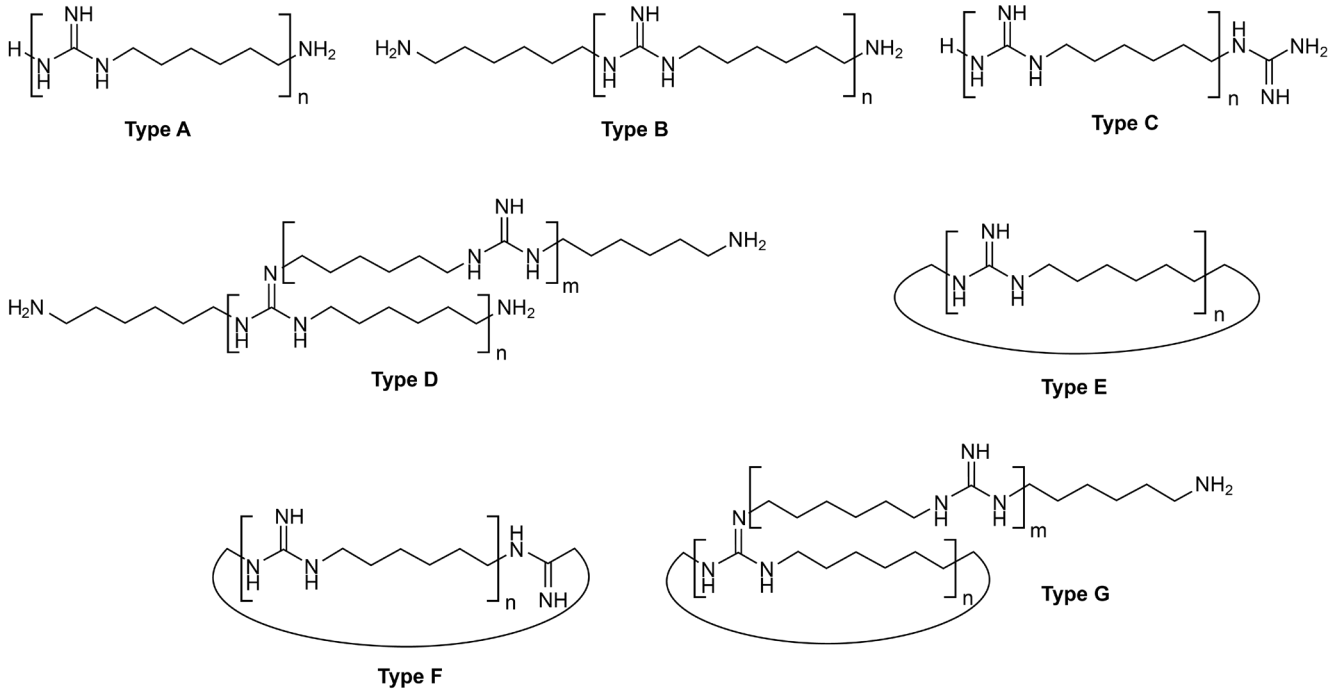


Fig. 4. Polyguanidine derivatives formed during synthesis:
A, B, C (linear); D (branching); E, F (cyclic); G (cyclic branching).

forces prevail. Consequently, a decrease in the channel size has the same effect on the behavior of the liquid in terms of Re as an increase in the viscosity of the solution. In most microfluidic systems, the Re value for fluxes is much less than ten, and often less than one. With such a laminar fluid flow, the velocity at the center of the capillary is greater than at its walls due to the parabolic velocity profile [55], which leads to a nonuniform velocity distribution over the fluid flow. This adjusts, for example, the dwell time is distributed, which can reduce the yield and selectivity. However, the undeniable advantage is the absence of gradients of both concentration and temperature relative to volume and time.

It is also worth noting the high surface-to-volume ratio and small diffusion distances, which leads to a reduction in the diffusion time of particles, an increase in conversion, and the overall efficiency of the process [56]. One of the consequences of laminar flow is the fact that the mixing of molecules in a liquid is solely due to molecular diffusion. This can be a significant advantage when mixing in a particular process is undesirable. Diffusion plays an important role in the processes of mass transfer; in microreactor technologies, the diffusion distance is small.

The difference in the physical behavior of microscopic and macroscopic systems makes it possible to create functions that are difficult or even impossible to obtain on a macroscopic scale; therefore, it is necessary to strive for the development of microfluidic systems, proceeding from the design rules, considering the peculiarities of fluid physics, mechanics and diffusion in a confined space [57].

The advantage of using microreactor devices is associated with thermal processes and mass transfer. The large surface area to volume ratio ensures thermal uniformity in the reactor and fast heat transfer between the device and the liquid contained in it, which determines the high energy efficiency of the process [58]. Microreactor technologies make it possible to adjust the process temperature in a shorter time compared to bulk reactors. It should be noted that the use of microreactor technologies has a special economic advantage, since small volumes of expensive reagents are used, since the work is carried out with a minimum amount of substance [59].

Microfluidic reactors have intrinsic properties that enhance the safety of potentially hazardous reactions. Small instantaneous volumes mean that reactions involving toxic or explosive intermediates can be carried out safely [60]. In addition, the high surface area to volume ratio inside the channel allows rapid heat transfer during exothermic reactions [59].

In microreactors, the degree of control over the conditions allows the product to be selectively produced with high accuracy [61]. This has several advantages: cleaning can be less stringent, more technologically simpler. During the synthesis, the reagents are continuously fed into the microreactor, and at the end of the process they are immediately separated from the initial mixture, which makes it possible to simplify the process itself, less time is required for the reaction to proceed, and more accurate process control can be provided.

As mentioned earlier, heat transfer in microfluidic reactors becomes more efficient as the reaction volumes decrease, that is, the amount of energy consumed to raise the temperature by one degree can be made very small, which is beneficial from an environmental point of view [59].

It is often claimed that microfluidic reactors allow "faster reactions" than bulk reactor reactions. It is noted that the product yield in microfluidic reactors is higher than in similar processes using bulk reactors [62].

An important advantage is that when glass or polymer parts are used, the uncontrolled decomposition of reaction mixtures at the reaction temperature is leveled [63].

Application of microreactor technologies in the chemical industry

Currently, microreactor technologies find their application in fine chemical technology, the synthesis of organic, inorganic and polymer particles, pigments, emulsions, in steam reforming. Since microfluidic reactors can be used in organic chemistry, they must be resistant to the action of various solvents, acids, bases, oxidants and reducing agents. It is important to maintain performance between −78 and 300°C. It should also be possible to carry out the initial purification of the reaction, for example, by extraction [59]. Thus, microreactors are actively used in carrying out a wide variety of reactions in compliance with all the above requirements, for example, in high-temperature processes, reactions with unstable intermediates that are difficult to scale with traditional synthesis methods, and reactions involving hazardous or toxic reagents, which in turn can be converted into a safer product [64]. In [59] it was indicated that microreactors are used in glycosylation reactions, Paal–Knorr synthesis, and for fluorination and perfluorination of organic compounds. The use of microfluidic reactors for multiphase processes [65] gives clear advantages over traditional methods (higher surface area to volume ratio).

Microfluidic technologies are also actively used to carry out various types of polymerization. In all examples of using microreactor technologies for carrying out polymerization reactions, a decrease in the polydispersity coefficient and an increase in yield are noted due to efficient heat transfer and a larger specific surface area. These advantages make it possible to

achieve a homogeneous chemical process and, as a result, to increase the homogeneity of the product. In [65], the product obtained in a microreactor had a lower viscosity compared to the product obtained in an ordinary batch reactor, while their other characteristics are comparable. In [67, 68], the polymers obtained in a microreactor tended to be branching, which was explained by the short diffusion path and the accelerated mass transfer during this. Another example illustrates how microfluidic devices can be used with aqueous solutions and with melts. As a result, a high selectivity of the process was achieved along with a low content of impurities [69].

Industrial research has led to the development of methods aimed at creating reliable microfluidic reactors with production facilities on an industrial scale. One of the important advantages of microfluidic reactors over traditional manufacturing methods is the ease of scaling up. Any microreactor can be used both for laboratory research and for industrial production [70]. The use of microfluidic reactors could also open new synthetic pathways for industry.

Microfluidic hardware in drug development and manufacturing

Microreactors have become more and more important over time in the pharmaceutical formulation industry due to their improved properties over batch reactors. It has been suggested [71] that chemicals, especially drugs, could be produced in miniature factories at points of use rather than in large factories.

Over the past few years, drip microfluidic systems have been widely used in drug discovery research. Microfluidic technologies enable very high throughput analyzes (up to thousands of samples per second). Drug screening, high-throughput analysis is one of the most exciting possibilities of microfluidic technology.

The use of microfluidic systems as a valuable tool for the discovery of new drugs is of great interest. Compared to equivalent bulk reactions, reactions carried out in a microreactor consistently give cleaner products in a much shorter time. Roberge *et al*. [72] believe that up to 50% of reactions in the fine chemical or pharmaceutical industries can benefit from a continuous process based mainly on microreactor technology, and for the majority (44%) a microreactor will be the preferred reaction device. After optimization of the microreactor, it can be easily introduced into industry [73].

Many large pharmaceutical companies, including *Roche* and *Pfizer* (USA), are investing in capillary microfluidic technologies for drug development. *RainDance Technologies* (Billerica, MA, USA) has developed commercial drip microfluidic systems that enable targeted DNA sequencing and digital PCR. They announced a collaboration with *Roche* for a simple and cost-effective study of drug absorption, distribution, metabolism and excretion [74].

Microreactors are used in the synthesis of various drugs, for example, ibuprofen [75, 76] or an HIV protease inhibitor [77]. Using microfluidic technology, an antitumor drug docetaxel with an increased content of a hydrophobic active substance with optimal physicochemical characteristics is obtained [78].

Directions for the development of microfluidic technologies

The field of microfluidics is evolving and, until recently, was largely technology-driven. The focus was on the development of new functional components (pumps, valves, and new economical production technologies), as well as their functional demonstration. A wide range of components and manufacturing technologies are currently available, and while new technologies are emerging at a rapid pace, the focus in the future is likely to shift toward implementation, i.e., existing technologies will be transformed for new applications. Undoubtedly, microfluidics will play a critical role in the drug discovery process to develop drugs with ever-improving quality [57].

CONCLUSIONS

The fight against the resistance of pathogenic microflora to antibiotics requires special measures. One strategy involves reducing the use frequency of antibiotics and replacing them with antiseptic drugs everywhere. Antiseptics, as a rule, are obtained using volumetric reactors, which have drawbacks that affect the quality of the target compound. Microreactor technologies, considering their many advantages, are considered suitable alternatives. This article describes the advantages of microreactor systems over volumetric reactors and testifies to the expediency of their application in polycondensation and polymerization reactions. Thus, it can be concluded that microreactor technologies are applicable in the synthesis of promising polyguanidines and their derivatives. The proposed method allows for more accurate control of the conditions of the polycondensation reaction of the starting monomers. In addition, microreactor technologies can increase the yield and selectivity of the oligomers obtained, leading to an increase in the product purity and process efficiency, in contrast with other known methods.

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About the author:

Anh C. Ha, PhD, Dr. Sci. in Chemical Engineering, Faculty of Chemical Engineering, Ho Chi Minh City University of Technology (268 Ly Thuong Kiet Street, District 10, Ho Chi Minh City, Vietnam); Vietnam National University Ho Chi Minh City (Linh Trung Ward, Thu Duc District, Ho Chi Minh City, Vietnam). E-mail: hcanh@hcmut.edu.vn. Scopus Author ID 56485522100, https://orcid.org/0000-0001-7919-4028

Об авторе:

Ань К. Ха, PhD, к.х.н., Химико-технологический факультет, Технологический университет Хошимина (268 Ли Тхыонг Кьет ул., Район 10, г. Хошимин, Вьетнам); Вьетнамский национальный университет Хошимина (Линь Чунг Уорд, Район Тхёк, г. Хошимин, Вьетнам). E-mail: hcanh@hcmut.edu.vn. Scopus Author ID 56485522100, https://orcid.org/0000-0001-7919-4028

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