

Optimizing synthesis and applications of sodium valproate: Towards efficiency, affordability, and sustainability

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Abstract. This study reviews the synthesis, optimization, and potential applications of sodium valproate, a key pharmaceutical agent in the treatment of neurological disorders such as epilepsy, bipolar disorder, and depression. The primary focus is on refining the synthesis process of sodium valproate to enhance production efficiency, reduce costs, and increase the accessibility of this crucial medication. By exploring various synthetic routes and optimizing reaction conditions—such as temperature, pressure, and solvent selection. The study aims to develop a more efficient and cost-effective manufacturing process. Special attention is given to the environmental impacts of the synthesis methods, seeking to establish greener and more sustainable practices. The study also discusses advancements in drug formulations, including the development of new therapeutic indications and combination therapies that could potentially improve patient outcomes. Future research directions include optimizing sodium valproate's molecular structure, investigating its use in personalized medicine, and minimizing its side effects. Through meticulous analysis and innovative approaches, this research contributes to the ongoing development of sodium valproate, ensuring its efficacy, safety, and environmental sustainability in pharmaceutical production.

1 Introduction

Sodium valproate stands as a key medication in the arsenal against neurological disorders, playing a pivotal role in the management of conditions such as epilepsy, bipolar disorder, and depression. Its pharmacological efficacy is chiefly derived from its ability to modulate neurotransmitter levels within the brain, particularly through the enhancement of gamma-aminobutyric acid (GABA) activity. This action is essential not only for its anticonvulsant properties but also for its effectiveness in alleviating depressive symptoms.

The production and clinical utilization of Sodium valproate are closely interconnected, emphasizing the importance of advanced research in its synthesis and manufacturing processes. Continuous improvements in these areas are critical to maximize the drug's efficacy and safety while maintaining cost-efficiency. This ongoing research is vital, as it supports the development of superior synthesis methods and production techniques that meet stringent quality control standards, thereby ensuring the drug's reliability and accessibility for those in need [1].

The synthesis of sodium valproate is a sophisticated chemical process that begins with a three-carbon atom saturated monocarboxylic acid, typically propionic acid, or its derivatives. These initial compounds serve as the foundational precursors in the creation of valproic acid derivatives, which are essential for constructing the final product. The transformation process extends these

molecules to include five carbon atoms, a critical modification that sets the stage for subsequent chemical reactions.

Following this alteration, the elongated compounds react with sodium salts to form sodium valproate. This multistep synthesis not only involves intricate chemical maneuvers such as substitution, elimination, and addition reactions but also requires precise control over various reaction conditions. These conditions include temperature, pH, and reaction time, which must be meticulously managed to ensure the reactions proceed efficiently and safely. Achieving optimal purity and yield of sodium valproate is paramount, as any deviations can impact the efficacy and safety of the drug. The complexity of this synthesis underscores the importance of rigorous quality control and advanced chemical engineering techniques to maintain the integrity and therapeutic value of the final product [2, 3]. The exploration of sodium valproate's medical utility encompasses a multifaceted approach that reflects its significant role in contemporary pharmacotherapy. Renowned for its efficacy in managing conditions such as epilepsy, migraines, and various mood disorders, sodium valproate is categorized as an indispensable therapeutic agent for these ailments. Its broad application underscores the importance of ongoing pharmacological research aimed at delving deeper into its mechanisms of action, pharmacokinetic properties, and potential drug interactions. This research is crucial not only for enhancing the clinical efficacy and safety profile of

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sodium valproate but also for refining treatment protocols and patient outcomes.

Advancements in the synthesis process of sodium valproate are equally vital. By optimizing these methods, scientists aim to increase the yield and reduce production costs, thereby enhancing the drug's accessibility and affordability for clinical use. Such improvements could dramatically impact global health, particularly in underserved areas where treatment options are limited. However, the use of sodium valproate is not without risks. Notable among its potential side effects is hepatotoxicity, a concern that necessitates ongoing rigorous safety evaluations. These studies are critical to ensuring that sodium valproate remains a safe treatment option, particularly for vulnerable populations such as children, pregnant women, and the elderly. By continuously monitoring and assessing these risks, healthcare providers can make informed decisions that prioritize patient safety. Furthermore, a deeper understanding of sodium valproate's therapeutic mechanisms might open new avenues for pharmaceutical innovation. By exploring modifications to its molecular structure or leveraging insights into its pharmacological actions, researchers could potentially develop novel therapeutics. These new drugs could not only enhance treatment options for epilepsy and other neurological disorders but also offer improved efficacy and safety profiles, benefiting a broader patient demographic.

In sum, while sodium valproate continues to be a cornerstone in the treatment of several neurological conditions, its full potential is yet to be unlocked. Ongoing research and development efforts are crucial for maximizing its benefits and mitigating risks, ultimately leading to broader therapeutic applications and the development of new medicinal compounds based on its proven mechanisms.

2 Literature review on synthesis and processing methods

The synthesis of sodium valproate, a compound commonly used in the pharmaceutical industry for its therapeutic properties, involves a meticulously defined series of steps that are crucial for obtaining a final product of high purity and optimal yield. At the foundation of this laboratory synthesis is the preparation of absolute ethanol, which serves as a critical component in the chemical reaction process.

To begin, absolute ethanol must be prepared to ensure that no water is present, as any residual moisture can initiate undesirable side reactions that could compromise the purity and efficiency of the synthesis. This preparation starts with anhydrous ethanol, which is ethanol that has been stripped of any water content. The anhydrous ethanol is reacted with metallic sodium, a process that effectively absorbs and removes any traces of water from the ethanol. Following the reaction with sodium, the ethanol undergoes a reflux process with diethyl phthalate. Refluxing is a technique used in chemistry where a mixture is heated to its boiling point and then cooled via a condenser, allowing the vapor to

return to liquid form and flow back into the reaction vessel. This method is particularly effective in this context because it ensures any remaining traces of water are thoroughly eliminated. The diethyl phthalate acts as a drying agent in the reflux system, enhancing the dehydration process and thus securing the production of high-quality, anhydrous ethanol.

This highly pure ethanol is indispensable for the subsequent steps in the synthesis of sodium valproate, as it helps in maintaining the integrity and efficiency of the reaction, ultimately leading to a final product that meets stringent pharmaceutical standards. By ensuring the ethanol used is entirely devoid of water, the synthesis process promotes a smoother reaction pathway, minimizing byproducts and maximizing yield.

2.1 Methodological approaches 1

The synthesis of diethyl dipropyl malonate is a detailed chemical procedure that begins with an alkylation reaction, as depicted in Fig. 1. This initial phase is crucial and requires the precise preparation of sodium ethoxide, a key intermediate in the process. Sodium ethoxide is produced through the reaction of sodium with ethanol, a step highly sensitive to any water contamination. The presence of water in this reaction can result in the formation of sodium hydroxide, which can adversely affect the progression of the reaction by altering the chemical environment. Once the sodium ethoxide is successfully synthesized, it reacts with diethyl malonate to generate a carbanion, an active nucleophile that is central to the next phase of the synthesis. This carbanion then engages in a nucleophilic substitution reaction with 1-bromopropane, a critical step that leads to the formation of the desired product, diethyl dipropyl malonate. The order in which reactants are added plays a pivotal role in the efficiency and success of this synthesis. Previous research underscores the importance of this sequence; specifically, diethyl malonate should be introduced before 1-bromopropane. If the order is reversed, or if the reactants are added simultaneously, there is a substantial risk of initiating unwanted side reactions, such as ether formation. These side reactions not only complicate the reaction mixture but also detract from the overall yield and purity of the final product.

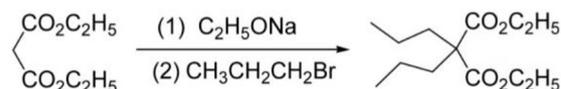


Fig. 1. Alkylation reaction.

The synthesis of dipropyl malonic acid progresses to a crucial stage following the formation of diethyl dipropyl malonate, involving its hydrolysis to convert the ester into the corresponding acid. This transformation is accomplished through the careful addition of a sodium hydroxide solution, which initiates the hydrolysis of diethyl dipropyl malonate. The process is delineated in Fig.2, highlighting its importance in the overall synthesis pathway. In this step, the sodium hydroxide solution

serves to break the ester bonds in diethyl dipropyl malonate, gradually transforming it into dipropyl malonic acid. This reaction must be meticulously controlled to ensure complete hydrolysis; any residues of the ester can significantly impede the purity of the final product, affecting its usability in further applications. To address this, the reaction mixture is maintained in a homogeneous phase, which is critical for promoting effective and complete hydrolysis. Maintaining homogeneity in the reaction mixture ensures that the sodium hydroxide interacts efficiently with all molecules of the ester, thus avoiding partial hydrolysis and the resultant impurities.

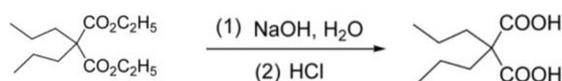


Fig. 2. Hydrolysis reaction.

The decarboxylation of dipropyl malonic acid at elevated temperatures results in the formation of valproic acid. This reaction is typically carried out under reflux conditions with zeolite to absorb evolved gases, primarily CO₂, ensuring the reaction proceeds to completion (Fig. 3).

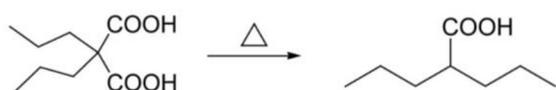


Fig. 3. Decarboxylation reaction.

Finally, the synthesized valproic acid is neutralized with sodium hydroxide to form sodium valproate (Fig. 4). The purity of sodium valproate is critical, especially for pharmaceutical applications, necessitating meticulous process control and purification steps, including vacuum distillation and recrystallization to ensure high purity and yield.

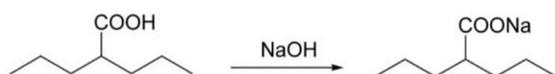


Fig. 4. Salt reaction.

Overall, the synthesis of sodium valproate requires precise control over each step, from the dehydration of ethanol to the final neutralization reaction. The literature supports the methodology adopted in this study, emphasizing the need for anhydrous conditions and careful sequence of reactant addition to minimize side reactions and maximize yield. This process is deemed suitable for industrial production due to its simplicity and effectiveness, as evidenced by the substantial yield of 45.1% [4-6].

2.2 Methodological Approaches 2

The synthesis of sodium valproate using 2-cyano-2-valproate derivatives is a meticulously designed process, aimed at maximizing both the purity and yield of the

final pharmaceutical product. This method involves several critical steps, each integral to the successful production of high-quality sodium valproate (Fig. 5).

The process begins with an initial reaction stage that is crucial for setting the foundation for the synthesis. In this stage, a reaction mixture containing water, sulfuric acid, and 2-cyano-2-valproate is prepared in a specialized reactor. This mixture is then heated to a precise temperature of 120°C. This specific temperature is carefully chosen to facilitate the hydrolysis of the ester group in the 2-cyano-2-valproate and to initiate its deacidification, as depicted in Figure 5 of the accompanying documentation. The application of heat helps break down the ester into a more reactive form, which is essential for the subsequent steps in the synthesis pathway.

To ensure thorough conversion of the ester into the desired product, the reaction mixture is maintained at temperatures ranging from 120 to 150°C. This temperature range is critical as it provides the necessary energy to drive the reaction forward while preventing the degradation of the sensitive compounds involved. The duration of this heated phase is equally important, typically spanning 20 to 40 hours. This extended period allows for the complete reaction of all components, ensuring that the conversion is both comprehensive and consistent.

The careful control of these reaction conditions—temperature, time, and the chemical environment—is vital for the success of the synthesis. It ensures that the hydrolysis and deacidification processes are completed effectively, without any degradation of the product. These controlled conditions lead to the successful transformation of 2-cyano-2-valproate into a more reactive intermediate, setting the stage for the final steps needed to produce high-purity sodium valproate.

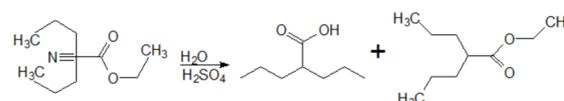


Fig. 5. Return water separation, hydrolysis and deacidification reaction.

Following hydrolysis, the system is diluted with water to assist in the separation of the oil and aqueous phases, where the oil phase contains a mixture of propionic acid and valproate. This phase is subsequently washed to yield a yellow oily mixture of valproic acid and propionate. An alkaline solution, typically comprising sodium carbonate, potassium hydroxide, or other alkalis, is added to the oily mixture. This step is maintained at 60 to 80°C for 4 to 6 hours, facilitating the transformation of valproic acid into its salt forms (Fig. 6). The alkali treatment is critical as it influences the esterification reaction's efficiency and the final product's purity.

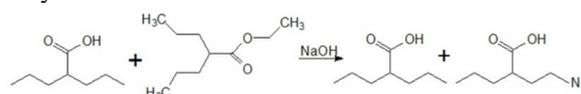


Fig. 6. Separation of oil and water, extraction of water phase.

The aqueous phase extraction using organic solvents such as chloroform or ethyl acetate follows, which is essential for removing impurities and isolating the valproate brine solution (Fig. 7). The crude valproic acid is then extracted from this solution, neutralized with sulfuric acid, and distilled under pressure to purify it further. Each of these steps must be meticulously controlled to prevent any degradation of the valproic acid and to ensure its purity before proceeding to the final stage of synthesis.

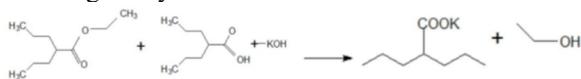


Fig. 7. Oil and water separation, extraction, and distillation.

The purified valproic acid is then neutralized with a sodium hydroxide solution to form sodium valproate (Fig. 8). Adjusting the pH to between 8 and 10 is crucial for the stability of sodium valproate, which is then spray-dried to obtain the final product. The drying process must be carefully managed to preserve the chemical integrity of sodium valproate.

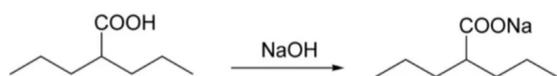


Fig. 8. Add sodium hydroxide.

The literature emphasizes that the control of reaction conditions such as temperature, pH, and catalyst presence significantly impact the purity and yield of sodium valproate. For instance, the catalyst's selection and concentration are paramount in driving the esterification process efficiently while minimizing side reactions. Additionally, the synthesis equipment must be designed to withstand the harsh reaction conditions and maintain high cleanliness standards to prevent cross-contamination. Analytical techniques, particularly high-performance liquid chromatography (HPLC), play an essential role in monitoring the synthesis process, ensuring that each step achieves the desired purity and yield levels.

This methodological review thoroughly examines the intricate process of synthesizing sodium valproate, underscoring the complexity and the rigorous precision required in controlling numerous variables at each stage of the synthesis. Sodium valproate, widely used in the pharmaceutical industry for its anticonvulsant properties, demands a synthesis process that is both exacting and finely tuned to achieve the desired standards of purity and efficacy. The synthesis of sodium valproate involves a series of chemical reactions, each influenced by specific conditions such as temperature, pH, reactant concentrations, and reaction times. The review highlights that even slight deviations in these conditions can lead to significant variations in the yield and quality of the final product. Therefore, meticulous optimization of these variables is critical. It is not merely about adhering to a formula; it is about fine-tuning each parameter to enhance the reaction outcomes and efficiency.

3 Discussion

This study focuses on improving the efficiency of the sodium valproate synthesis process through several innovative strategies. The primary goal is to refine the synthesis pathway by exploring alternative raw materials, catalysts, and reaction conditions. This exploration aims to streamline the production process by minimizing the number of reaction steps, thereby significantly reducing overall production costs, and improving the sustainability of the process. Moreover, a critical aspect of this research involves optimizing key reaction conditions such as temperature, pressure, and solvent selection. By fine-tuning these parameters, the study aims to lessen the demands on production equipment and reduce energy consumption, which can have a significant impact on the operational costs. Such optimizations are expected to not only make the synthesis process more energy-efficient and cost-effective but also increase the overall yield of sodium valproate, thus enhancing its accessibility for clinical use. These efforts reflect a comprehensive approach to drug synthesis, balancing the technical aspects of chemical engineering with the practical considerations of large-scale production. By reimagining the synthesis process through the lens of efficiency and cost-effectiveness, this research paves the way for more sustainable and scalable production methods for sodium valproate, ensuring that this essential medication remains both accessible and affordable to those who need it most [7, 8].

Refinements in the synthesis process of sodium valproate aim to significantly improve the conversion rate and selectivity of each reaction step, which is projected to boost the overall yield of the drug. These enhancements are especially crucial given the heavy reliance of patients on sodium valproate, particularly those who require consistent and uninterrupted medication. Cost reduction remains a central goal, achievable by sourcing more cost-effective raw materials and catalysts, and by simplifying the production process to minimize resource consumption [9].

Moreover, ensuring the quality of sodium valproate is of utmost importance. The study involves a detailed investigation of the drug's crystal form and purification methods, aiming to enhance its purity and stability. Such improvements are pivotal, as they have a direct bearing on the drug's therapeutic efficacy in clinical settings. By ensuring a high level of purity and stability, healthcare providers can rely on the consistent quality of the medication, which is vital for managing epilepsy, migraines, and mood disorders. Environmental factors are crucial in this research endeavor. The focus is on developing a synthesis method for sodium valproate that is green and eco-friendly, aiming to reduce the ecological footprint linked with its production. This strategy not only matches worldwide sustainability objectives but also addresses the growing calls from both regulators and consumers for manufacturing practices that are environmentally sound [10, 11].

Overall, the aim of this research is to create a method for producing sodium valproate that is more economical, efficient, and environmentally sustainable. This would enhance its availability and effectiveness in clinical

settings while promoting responsible environmental management.

4 Conclusion and prospects

The exploration of diverse synthetic routes in this study was aimed at comparing their production efficiency, cost, environmental impact, and the purity and yield of the final product. The optimization of the synthetic route was shown to significantly enhance production efficiency, reduce costs, and ensure the quality of the product. Key factors in the synthesis process such as temperature, pressure, reaction time, and solvent selection were critically analyzed due to their pronounced effect on the yield and purity of the product [12]. Future experiments will focus on identifying the optimal reaction conditions that maximize yield and purity.

The use of catalysts in certain synthetic steps was another area of focus, as these can expedite reaction rates and improve both yield and purity. Ongoing research will involve screening various catalysts to determine the most effective ones. Moreover, product quality will be rigorously tested using analytical methods such as high-performance liquid chromatography and mass spectrometry to ensure compliance with clinical standards. The environmental safety of by-products and waste generated during the synthesis process will also be evaluated to promote a sustainable and safe production environment.

In the realm of drug development, efforts to optimize the molecular structure of sodium valproate are ongoing, aiming to enhance its efficacy and develop new therapeutic indications. The potential for combination therapy is particularly promising, especially considering the efficacy of sodium valproate in certain types of epilepsy. Research will investigate its use in conjunction with other anti-epileptic drugs to enhance therapeutic outcomes.

Advancements in drug delivery systems, such as the development of nanoparticles and liposomes, are anticipated to improve the bioavailability of sodium valproate while mitigating side effects. This aligns with the growing interest in personalized medicine, which seeks to tailor medication regimens based on individual genetic profiles, physiological characteristics, and other personal factors. Furthermore, addressing the challenge of reducing side effects associated with sodium valproate, such as liver toxicity and weight gain, is crucial. Future studies will focus on developing strategies to decrease these adverse effects and improve patient tolerance.

The development of new drug formulations, such as controlled release systems, could revolutionize the way sodium valproate is administered, enhancing therapeutic efficacy while reducing dosing frequency. This could significantly improve patients' quality of life. Lastly, exploring non-traditional uses of sodium valproate could uncover additional therapeutic benefits, expanding its applicability beyond its established role as an antiepileptic drug [13].

Authors Contribution

All the authors contributed equally, and their names were listed in alphabetical order.

References

1. Y. Yang, Q. Yang, Y. Sun, *West. Chi. Med. J.* **36**, 05 (2021)
2. W. Sun, R. Xeng, L. Jing, *West. Chi. Med. J.* **18**, 4 (2003)
3. W. Liu, Z. Huang, H. Yang, The invention relates to a preparation method of sodium valproate (2024)
4. F. Lin, C. Nie, Y. Wei, Preparation technology of sodium valproate tablet (2024)
5. Chang. Wu, G. Li, L. Niu, *Chem. Engin.* **29**, 08 (2015)
6. Z. Zhao, C. Nie, Y. Zhang, The invention relates to sodium valproate and preparation process (2012)
7. H. Sheng, C. Liu, S. Wu, *Shandong Chem. Indus.* **50**, 08 (2021)
8. L.Liu. The invention relates to a preparation method of sustained-release sodium valproate preparation (2024)
9. M. Li, D. Zhang, J. Dong, *West. Chi. Med. J.* **32**, 06 (2017)
10. X. Hu, Y. Hu, L. Wei, *Chi. J. Hosp.* **37**,13(2017)
11. Q. Zhou, H.Sang, C. J. *Pharmaceu. Indus.* **24**, 8 (1993)
12. X. Hu, Shihezi University. *J.* (2017)
13. Y. Jin, F. Zhang, A. Shi, *J. Lanzhou.Univercity (Medical Edition)* **43**,03 (2017)