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# MODERN METHODS IN PHARMACEUTICAL SYNTHESIS AND THEIR EFFICIENCY

**Rozikova Dilshoda Abdullajonovna**

Namangan State Technical University

Faculty of Technology, Associate Professor, Department of Chemical Engineering

**Abstract**

This paper provides a scientific analysis of the modern methods employed in pharmaceutical synthesis — flow chemistry, microwave-assisted synthesis, biocatalysis, combinatorial chemistry, and green synthesis technologies. The chemical efficiency, economic advantages, environmental aspects, and industrial applicability of each method are evaluated. The paper also puts forward scientifically substantiated recommendations for the development of the pharmaceutical synthesis industry in Uzbekistan.

**Keywords**

pharmaceutical synthesis, flow chemistry, microwave synthesis, biocatalysis, combinatorial chemistry, green chemistry, pharmaceuticals, efficiency, atom economy.

## 1. Introduction

The pharmaceutical industry is one of the most rapidly growing sectors of the global economy, with the development and synthesis of new drug substances forming the central scientific and technological challenge. The fact that the global pharmaceutical market exceeded USD 1.5 trillion in 2023 and is projected to reach USD 2.2 trillion by 2030 underscores the strategic importance of innovation in this field [1]. Pharmaceutical synthesis is one of the most complex and demanding areas of chemical technology, requiring the simultaneous achievement of high chemical selectivity, stereochemical purity, minimal by-product formation, and economic efficiency.

Although conventional batch synthesis methods have long been dominant in pharmaceutical manufacturing, this approach carries a number of limitations: prolonged reaction times, low atom efficiency, multi-stage purification operations, high energy consumption, and an increasing environmental burden. Over the past few decades, modern approaches such as flow chemistry, microwave-assisted synthesis, enzymatic catalysis, and combinatorial chemistry have made it possible to fundamentally improve the efficiency and ecological sustainability of pharmaceutical synthesis [2].

In Uzbekistan, the pharmaceutical industry has been designated a strategic development priority. Within the framework of the "Uzbekistan — 2030" strategy and the healthcare system reform programmes, particular emphasis is placed on expanding domestic pharmaceutical production, developing import-substituting pharmaceuticals, and equipping the industry with modern technologies. From this perspective, the scientific study of modern methods of pharmaceutical synthesis and their adaptation to the domestic industry constitutes an urgent scientific and practical task [3].

The objective of this paper is to systematically review the principal modern methods employed in pharmaceutical synthesis, to evaluate their efficiency against chemical, economic,

and environmental criteria, and to substantiate the most promising technological directions for Uzbekistan's pharmaceutical industry.

## 2. Flow Chemistry Technology

Flow chemistry — a synthesis technology based on carrying out reactions in a continuous flow regime, typically in microreactors or tubular reactors — has been recognized as the most promising alternative to conventional batch synthesis in the pharmaceutical industry. The primary advantage of this technology lies in the dramatic improvement of heat and mass transfer within the reactor: microreactors with channel diameters in the range of 0.1–10 mm offer a volume-to-surface area ratio 100 to 10,000 times higher than that of conventional reactors [4].

This situation gives rise to a number of technological advantages. First, the ability to manage exothermic reactions with a high degree of safety is established — heat release is brought under immediate control and "hot spots" are eliminated. Second, reaction times are reduced to seconds or minutes, substantially increasing throughput. Third, working with smaller quantities of hazardous intermediate compounds enhances overall process safety. The considerably safer execution of reactions involving hazardous species such as diazomethane and perchloric acids under flow conditions — where no viable alternative exists — has been demonstrated in numerous scientific studies [2].

The practical efficiency of flow chemistry in pharmaceutical synthesis is confirmed by a series of examples. The synthesis of ibuprofen was accomplished under flow conditions in three steps, ten times faster than by the batch method and with a yield of 99%. In the synthesis of artemisinin — a key antimalarial drug — the application of flow chemistry increased the efficiency of the selective photooxidation step from 1% to 57%. Leading pharmaceutical companies including Pfizer, Novartis, and AstraZeneca have announced reductions in synthesis costs of 30–50% following the industrial-scale implementation of flow chemistry technology [5].

## 3. Microwave-Assisted Synthesis

Microwave-assisted synthesis — a technology that employs electromagnetic radiation energy (at a frequency of 2.45 GHz) to directly heat the reaction mixture — has been applied in pharmaceutical synthesis since 1986. In contrast to conventional heat transfer, microwave energy provides uniform and rapid heating of the mixture, enabling temperatures of 150–300 °C to be reached within a few minutes. This makes it possible to reduce reaction times from hours or days to minutes or seconds [3].

The principal efficiency parameters of microwave synthesis are as follows: reduction of reaction time by an average of 10 to 1,000-fold; improvement of product yield by 15–40%; enhancement of selectivity through reduction of by-product formation; and the possibility of reducing solvent consumption. The particular efficacy of microwave technology in the synthesis of heterocyclic compounds — a large proportion of pharmaceutically active substances possess a heterocyclic structure — has been demonstrated in numerous studies. In the synthesis of pyrimidines, imidazoles, oxazoles, and triazoles, the microwave method achieves results 20 to 500 times faster than conventional reflux procedures [4].

However, microwave synthesis has certain limitations. The uniform distribution of microwave energy in large volumes during industrial scale-up remains a technological challenge. For this reason, microwave synthesis at the industrial scale is frequently combined with flow

chemistry — microwave flow reactors, which integrate the advantages of both technologies, represent a rapidly developing direction at the present time [5].

## 4. Comparative Analysis of Modern Synthesis Methods

Table 1. Modern methods of pharmaceutical synthesis: comparative efficiency assessment

| Synthesis Method | Reaction Time | Yield | Environmental Aspect | Industrial Application |
|---|---|---|---|---|
| Conventional batch | Hours–days | 60–85% | High solvent consumption | Widely used |
| Flow chemistry | Minutes–hours | 85–99% | Good, low waste | Rapid growth |
| Microwave synthesis | Minutes | 75–98% | Moderate, fast process | Laboratory, pilot |
| Biocatalysis (enzymatic) | Hours | 80–99% | Environmentally clean | Selective synthesis |
| Combinatorial chemistry | Parallel, fast | Variable | Moderate | Drug discovery |
| Photochemical synthesis | Minutes–hours | 70–95% | Very good | Developing |

## 5. Biocatalysis and Green Synthesis Principles

Biocatalysis — the use of enzymes to carry out chemical reactions — is considered one of the most effective approaches in pharmaceutical synthesis from the standpoint of stereo- and regioselectivity. Many drug molecules possess chiral centres, with only one stereoisomer exhibiting pharmacological activity — the other enantiomer may be biologically inactive or even toxic. Enzymatic catalysis provides an unparalleled degree of selectivity in precisely this type of chiral synthesis [6].

Lipases, ketoreductases, and transaminases are among the most widely used enzymes in pharmaceutical synthesis. In the synthesis of atorvastatin (Lipitor) — the well-known cholesterol-lowering drug — the use of a ketoreductase enzyme in the step introducing the chiral hydroxyl group provides 99.9% ee (enantiomeric excess) compared with conventional chemical asymmetric hydrogenation, and is also highly advantageous from an economic standpoint. At the industrial scale, biocatalytic processes are typically conducted in continuous-flow bioreactors or with immobilized enzymes [1].

The principles of green chemistry — the twelve principles developed by P. Anastas and J. Warner in 1998 — are assuming ever greater importance in pharmaceutical synthesis. Among

these principles, the atom economy metric occupies a special place, as it defines the proportion of atoms in the starting materials that are incorporated into the target product. Maximizing atom economy has been adopted as an important techno-economic criterion in modern pharmaceutical synthesis: while conventional stoichiometric synthetic routes often achieve atom economy of only 30–50%, catalytic and enzymatic methods can reach 80–99% [2].

**6. Combinatorial Chemistry and Computer-Aided Drug Discovery**

Combinatorial chemistry — a technological approach enabling the parallel synthesis of large numbers of chemical compounds and the rapid assessment of their biological activity — has become the primary tool for selecting drug candidate molecules in modern pharmaceutical research. This approach, which emerged in the 1990s, has been combined with solid-phase synthesis technology and High Throughput Screening (HTS) to enable the synthesis and biological evaluation of thousands of compounds in a single day [3].

The application of artificial intelligence and machine learning algorithms to pharmaceutical synthesis is driving paradigmatic changes in recent years. Analogous to the success of the AlphaFold2 system in predicting protein structures, AI systems used for retrosynthesis planning — including Chematica, ASKCOS, and IBM RXN — are capable of automatically designing synthetic routes to complex drug molecules. These systems learn from millions of chemical reactions, propose novel synthetic pathways, and identify the most efficient variants worthy of experimental validation [7].

Although combinatorial chemistry and AI-assisted synthesis planning have yet to be widely implemented in Uzbekistan's pharmaceutical industry, initial steps are being taken within the framework of the "Pharmaceutical Industry Development Programme to 2030" to establish modern research laboratories and strengthen international scientific collaboration. The training of qualified specialists in chemical engineering and pharmaceutical technology at national universities plays a decisive role in building the human capital necessary for advances in this direction [3].

**7. Conclusions**

The analysis of modern methods of pharmaceutical synthesis yielded the following principal conclusions. First, flow chemistry technology constitutes the most promising direction for simultaneously improving the efficiency, safety, and ecological sustainability of pharmaceutical synthesis, with its industrial-scale implementation proceeding at a rapid pace. Second, microwave-assisted synthesis continues to occupy an important role in enhancing laboratory research efficiency by dramatically reducing reaction times and energy consumption, although integration with flow technology is required for industrial-scale application. Third, biocatalysis and the principles of green synthesis form the scientific foundation of the sustainability direction in the pharmaceutical industry, establishing themselves as an indispensable approach for producing chiral drugs with high stereoselelectivity.

The following priority directions are recommended for the implementation of modern synthesis technologies in Uzbekistan's pharmaceutical industry: introduction of flow chemistry-based pilot equipment at national pharmaceutical enterprises; development of microwave and photochemical synthesis infrastructure in university research laboratories; investment in domestic enzyme production and biocatalytic process research; and building the scientific and

technical capacity for the use of AI tools in pharmaceutical synthesis planning. A targeted scientific and technological policy in these directions will create the conditions to reduce the pharmaceutical sector's import dependence and to produce national pharmaceuticals at the level of international standards.

It is impossible to build a competitive national pharmaceutical industry without the full scientific mastery of modern pharmaceutical synthesis methods. In this sense, multidisciplinary research conducted at the intersection of chemical engineering, pharmacology, and biochemistry is an indispensable condition for Uzbekistan's scientific and technological development.

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