Processes and Apparatus in Chemical-Pharmaceutical Technology

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The Synthesis of Medicinal Products

By

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Cambridge Scholars Publishing

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I dedicate this book to my wife who was my sincere friend throughout my life – Snejinka Manolova Samurova-Ilieva

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PREFACE

The textbook is intended for students of chemistry and pharmacy in medical universities.

The development of the material is tailored to the production and the need for medicinal products in the pharmaceutical market. Since the drug synthesis programs of the various universities do not differ substantially from each other in practice, the book can be used by a wider range of students as well as by professionals interested in synthetic organic chemistry and the specific features of industrial drug production.

Synthetic schemes for the production of some medicinal products are presented without a detailed description of the technological process. This approach would motivate the students to apply the acquired knowledge from process schemes of analogous products; to present not only the equipment and necessary apparatus for production, but also to propose conditions for disposal of any toxic products released.

The logical and sequential mastering of the material, as well as the creation of the ability to apply knowledge in a complex way when solving technological problems, will help to form future specialists more completely, regardless of the specific field of their implementation.

I. Manolov

RAW MATERIALS FOR THE CHEMICAL-PHARMACEUTICAL INDUSTRY

Many European countries do not have the necessary raw materials for the chemical-pharmaceutical industry. Acetone, benzene, mineral acids and bases, some alcohols, esters are available, but the main reagents are imported. In each technology the technical requirements for the quality of raw materials are high, with pharmacopoeial purity. Raw materials with technical qualification are the cheapest, but this makes the drug substance significantly more expensive due to the need for additional purification.

Raw materials are stored in warehouses, some of them multi-storeyed, served by a lift. Loading and unloading is difficult in these premises. Single-storey buildings with shelving between which the operators move with the appropriate machinery or robotic systems are best.

Each raw material requires certain storage conditions. It is necessary to know that acids and bases are stored in different rooms. Low boiling point solvents and reagents are stored at low temperatures. Very often solvents are stored in tanks and connected to the apparatus in the production room by special lines.

WASTE IN CHEMICAL-PHARMACEUTICAL PRODUCTION

The chemical and pharmaceutical industry is a serious polluter of the environment. Waste is divided by aggregate state into gaseous, liquid and solid.

Gaseous waste is captured in absorbers. Toxic gases enter these columns on the counter- current principle and are converted into non-toxic, odourless substances and from there transferred to treatment plants for processing. Hydrogen chloride, sulphur dioxide or hydrogen sulphide is often emitted during the manufacture of pharmaceuticals. It is detrimental to people and the environment if these gases enter the atmosphere.

Solid waste is the most difficult to process. Typically, an elemental analysis is performed on the solid residue - determining carbon, hydrogen, nitrogen, sulfur, phosphorus, etc. content. Solid organic residues are disposed of by incineration and the gases are captured and disposed of as described above. Inorganic solid waste is stored in the vicinity of the plant.

Disposal of **liquid organic waste** starts in the production plant. Their purification is realized by distillation and rectification.

Water is +a universal solvent and reaction medium. Aqueous solutions contain sometimes salts, and there is no effective method to purify them. Aqueous solutions must first be free of organic solvents. The water undergoes a microbiological purification step. The safest way to purify water is through water treatment plants. The way to build a water treatment plant is essential.

The water enters an intermediate basin. After a certain time, any sediment is separated. The solids-removed water enters a subsequent vessel, the pH is measured and, if necessary, adjusted with acid or base. It is then introduced into an averaging stage - the biological stage - the liquid from the settling tank is sprayed into a tower filled with plastic pieces, air flora.

At low velocity and in the presence of a lot of oxygen, water flows through the entire column. It has been found that about 60% of the organic waste decomposes. The second biological stage is a large fermenter - the liquid is heavily aerated, intensively agitated and the remaining organic matter is eliminated. Sedimentation and filtration follow and the water can be discharged into a nearby flowing river or into the city sewage treatment plant.

DEVELOPMENT OF DRUG SYNTHESIS TECHNOLOGY

The research work is divided into several stages:

1. The need of diagnostic and therapeutic practice for a given drug preparation defines the task of researchers working in this field. In order to design the project, a comprehensive literature study (literature review) is necessary.

2. The project includes general provisions, motives for future development, qualities of raw materials, materials and product, extraction, prospect of development. E.g. if it is necessary to synthesise cinnamyl chloride:

It is known from the literature that it is obtained

in several ways:

(a) cinnamyl alcohol is treated with hydrochloric

(b) acid (boiling hydrochloric acid);

(c) cinnamyl alcohol is treated with thionyl chloride in the presence of pyridine. The interaction of alcohols with thionyl chloride is accompanied by the evolution of significant amounts of sulphur dioxide and hydrogen chloride and therefore the basic properties of pyridine are used to bind the acid gases evolved;

(d) styrene reacts with methanal (formaldehyde) and hydrochloric acid. According to literature data, the product of this interaction is phenyl dioxane, but it has been shown that under certain experimental conditions, cinnamyl chloride is produced.

On the basis of the studies, a list of reagents and chemicals required is made. The reported yields are noted.

A material-cost norm is made for the production of 1 kg of product.

Data analysis has shown the advantage of the third scheme, but the preparation of phenyl dioxane seriously hinders the purification of cinnamyl chloride. For this reason, the preparation of cinnamyl chloride by the interaction of styrene, formaldehyde and hydrochloric acid fails.

The second method, based on the interaction of cinnamyl alcohol with thionyl chloride, has been implemented in production, but severe environmental pollution has served as a serious prerequisite for refusal.

The conversion of cinnamyl alcohol to cinnamyl chloride is best when treated with boiling hydrochloric acid.

The experiments carried out in laboratory conditions and the results obtained are used to develop laboratory technology. This technology is experimented in factory conditions but in pilot apparatus.

On the basis of the semi-plant trials, a process regulation is again prepared, covering a complete description of apparatus, process, reaction conditions.

Documentation for the manufacture of the medicinal product

Industry Standard (IS) - contains the analytical methods and quality indicators to characterize the product.

On the basis of the documentation, a plant is being designed and constructed to produce the required drug produce.

When implementing a technology, the process is labour intensive. It is worked with extreme care and alongside this, the staff working in the workshop must be trained

WHAT DOES A TECHNOLOGY CONTAIN?

1. Characteristics of the finished end product - name, generic name, brand name, chemical name, structural and gross formula, properties, melting point, boiling point, odour, appearance (a kind of compound reference).
2. Characteristics of raw materials and starting materials.
3. Chemical scheme of the process - a brief description of the individual phases.
4. Technological part - exact description of each phase in turn - the materials, the apparatus. Description of the technological process. This section also notes incidents in emergency situations - e.g. power cuts, water cuts etc.
5. Waste from the production process - to be presented in tabular form. Treatment facilities must be provided.
6. Description of waste treatment methods - describe the in-plant treatment.
7. Description of the processes in time - too important to calculate the economic effect - what labour is needed to produce a certain amount of product.
8. Methods of analysis - the State Standard of the respective country, pharmacopoeia articles. For the final product, the description should be as complete and detailed as possible.
9. Safety technique - all substances in the production cycle have a certain degree of harmfulness and toxicity. For each of them, safety measures are described, even the most well-known things.
10. List of instructions.

11. Material-cost norm - the quantities of raw materials and materials required for the production of 1 kg of product.

12. A list of the apparatus and equipment required during the production process.

13. Number of people needed to serve a given production.

14. Currency chart of accounts based on the bill of materials. Alphabetical order of imported and national materials.

15. Calculation – it presents the product price:

- Materials;
- wages of workers;
- 30% taxes;
- production costs.

PATHWAYS TO ORIGINAL MEDICINES

There are three main approaches to creating original drug substances:

1. Random - all newly synthesized substances are examined. Primary screening of substances is started;

2. By way of imitation - analogues of known preparations are synthesized;

3. Current knowledge of the disease, the mechanism of action of drugs is used and on this basis a compound with a particular pharmacology is sought.

What is needed is not just an active substance, but a product with high pharmacological activity, a large therapeutic range without reaching LD_{50}, with a specific action on a given disease. The chemical structure - biological action relationship is being studied.

- The newly synthesized and characterized compound is submitted to a pharmacologist for screening study. Initially, a series of tests are conducted to determine LD_{50}.

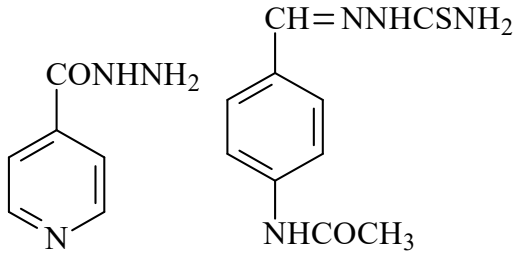
- Extended screening follows

- Prior to the clinical trial, it is necessary in some countries to submit to a special committee - the Committee for Medicinal Products with documents proving the purity and individuality of the product, as well as the effects obtained in a study on experimental animals.

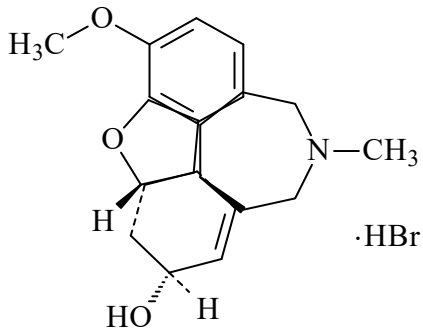
- With positive clinical trial results, technology development and manufacturing follow.

From a global point of view, a new drug appears on the pharmaceutical market only after the synthesis and investigation of about 10,000 new compounds.

There are at least two approaches for creating new medicines. The first one comprises obtaining new drugs by analogy of existing known medicines. The second one is connected with establishing new action of known biologically active substances. E.g. the drugs hydrazide of isonicotinic acid and thiosemicarbazone of p-acetylaminobenzaldehyde (Tubigal) have been used in the fight against tuberculosis/



isonicotinic acid hydrazide; thiosemicarbazone to p-acetylamino-benzaldehyde (Tubigal).



Nivaline (Galanthamine) – (Product of Dimitar Pascov)

After creating an original preparation in a market economy, protection is necessary: 1. Creation of an original trademark and 2. Patenting - the main way to maintain priority.

What is patented?

1. New technical solution - e.g. substance;
2. Composition Patent;
3. Method Patent;
4. New application of substance, composition, method.

Territorial patenting - valid only for the country in which it is granted; *temporal* - 15 to 20 years depending on national law.

Copyright - owned by the state, although the authors' names are noted. Patent - issued to the author and owned by the author.

What does a patent contain?

1. Description of existing methods or similar compounds that led to the invention.
2. Brief description of the method or new substance.
3. Examples - something that is done experimentally.
4. Patent claims - after the phrase "characterizing" comes the new thing the author has done, it is the most essential for future protection.

Patenting is done in almost all countries as the new drug product can find a niche market. It is usually patented in Western Europe, USA, Japan, and Latin America. In Eastern Europe, such protection was hardly practiced until recently. It does not significantly affect the quantity and quality of the product. The European patent retains priority in all Western countries. The filed application is subjected to meticulous examination and exhaustive literature search.

Another way of protection is the trademark. A trademark can be considered similar to a patent, but it does not have its legal force, but is mainly an indication for the manufacturer:

1. Socio-economic functions;

2. Identifying feature;
3. Stimulating function;
4. Activating function.
5. Advertising function.
6. Legal functions: protective and warranty functions. *Brands* indicate the origin of the goods, their quality.

GOOD MANUFACTURING PRACTICE (GMP)

The production of medicinal products is a complex of various processes and the end result is a means of treatment, prophylaxis and diagnosis of humans and animals. The requirements in this respect are very strict - it is related to the health of people and their nutrition. In all countries, the process is regulated to be strictly, thoroughly, professionally and responsibly controlled. Nevertheless, mistakes are made. Therefore, the World Health Organization (WHO) has developed rules, desirable for all, which ensure the possibility of obtaining high-quality preparations. The rules are improved annually.

The more the conditions of production comply with the rules, the more the quality of the product is guaranteed.

1. **A medicine** is any substance or composition manufactured, sold or presented for use in the treatment, prophylaxis or diagnosis of man or animals.

2. **Manufacturing** - includes all operations for the production of a drug - raw material processing, compounding, packaging, labelling, etc.

3. **Raw materials** - all substances used in the manufacture of the medicinal product - active and inactive.

4. **Definition of batch** - an inscription - numerical, alphabetical, or numerical-alphabetical, which identifies the batch to which the raw material, packaging, etc., belongs and enables one to know every detail (for the purpose of an inquiry) and the whole series of operations in production and control.

5. **Personnel** - specialists responsible for the manufacture of the relevant medicinal product. It is mandatory that they hold the relevant qualification.

6. **Premises** - all drug manufacturing operations to be carried out in

suitable premises - to allow compatibility with other manufacturing operations but not interfere with each other; sufficient space, walls to be smooth, cleaned regularly. Provide heating, ventilation, adequate lighting and hygiene.

7. **Warehouses** - sufficiently spacious, well lit, well ventilated, tidy, dry and clean. Separate flammable and non-flammable, poisonous from non-poisonous chemicals, authorized for use from unauthorized.

8. **Household conditions** - ways to clean. Prohibition of smoking, eating, drinking alcohol. Number of toilets and their cleanliness, number of bathrooms.

GOOD LABORATORY PRACTICE (GLP)

This is a system of rules related to the quality of finished products, developed by WHO. The rules are followed and ensure the accurate assessment of the quality of medicinal products. It is based on the following indicators:

1. **Representativeness of** the sample submitted for analysis;
2. **Documentation;**
3. **Accurate adherence to** analytics methodology;
4. **Competent** assessment of the result of the analysis.

Analyses are performed in the Central Plant Laboratories. Highly qualified specialists are also needed there.

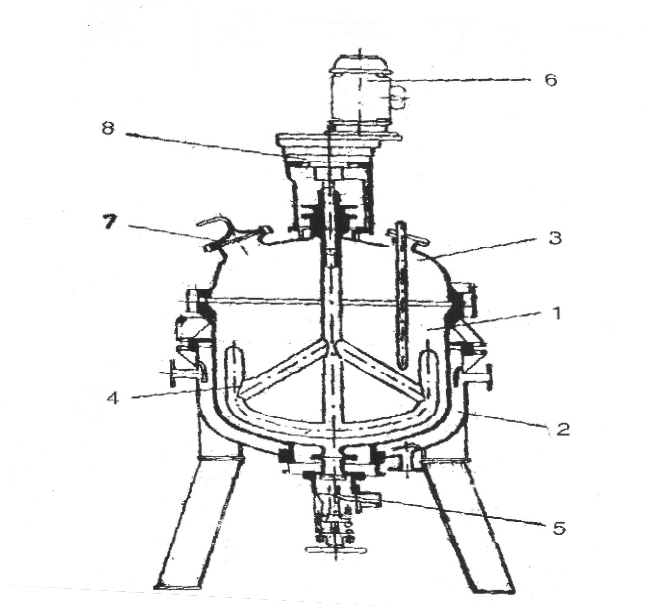
It is essential that the sample is registered with a number, place of collection, date, name of analyst.

The final protocol records all the data, the results of the analysis, the final assessment. The tested samples are stored so that a control analysis can be performed if necessary.

APPARATUS IN THE CHEMICAL-PHARMACEUTICAL INDUSTRY

Reactor

The main apparatus in the production of drug substances is the reactor. It is where the chemical reactions take place. Reactors are of several types and differ in shape and construction. The relatively small volume of production in the chemical-pharmaceutical industry makes it necessary to use periodically working reactors. The most widespread reactors are of the kettle type, which are open and closed. Open-air reactors can be used only in cases where none of the components of the reaction mixture is volatile at the process temperature, no harmful and toxic gases are emitted, polluting the environment. Enclosed reactors are more complex and are designed to operate in a closed system. When elevated pressure is used, the apparatus are called autoclaves.



Reactor
1.Cauldron; 2. Shell; 3. Lid;
4. Stirrer; 5. Bottom drain hole; 6. Electric motor;
7. Hatch; 8. Transmission box

Depending on the nature of the reactants, reactors are metallic and non-metallic. There is a correlation between the material used to construct the reactor and its shape, and the method of connection to the required fittings. A durable enamel coating can only be applied to rounded smooth steel or cast iron surfaces.

In chemical-pharmaceutical production, mainly metal closed reactors with cylindrical shape and rounded or conical bottom and rounded lid are used. The lids are made separately and are mounted using bolts which fasten the two parts.