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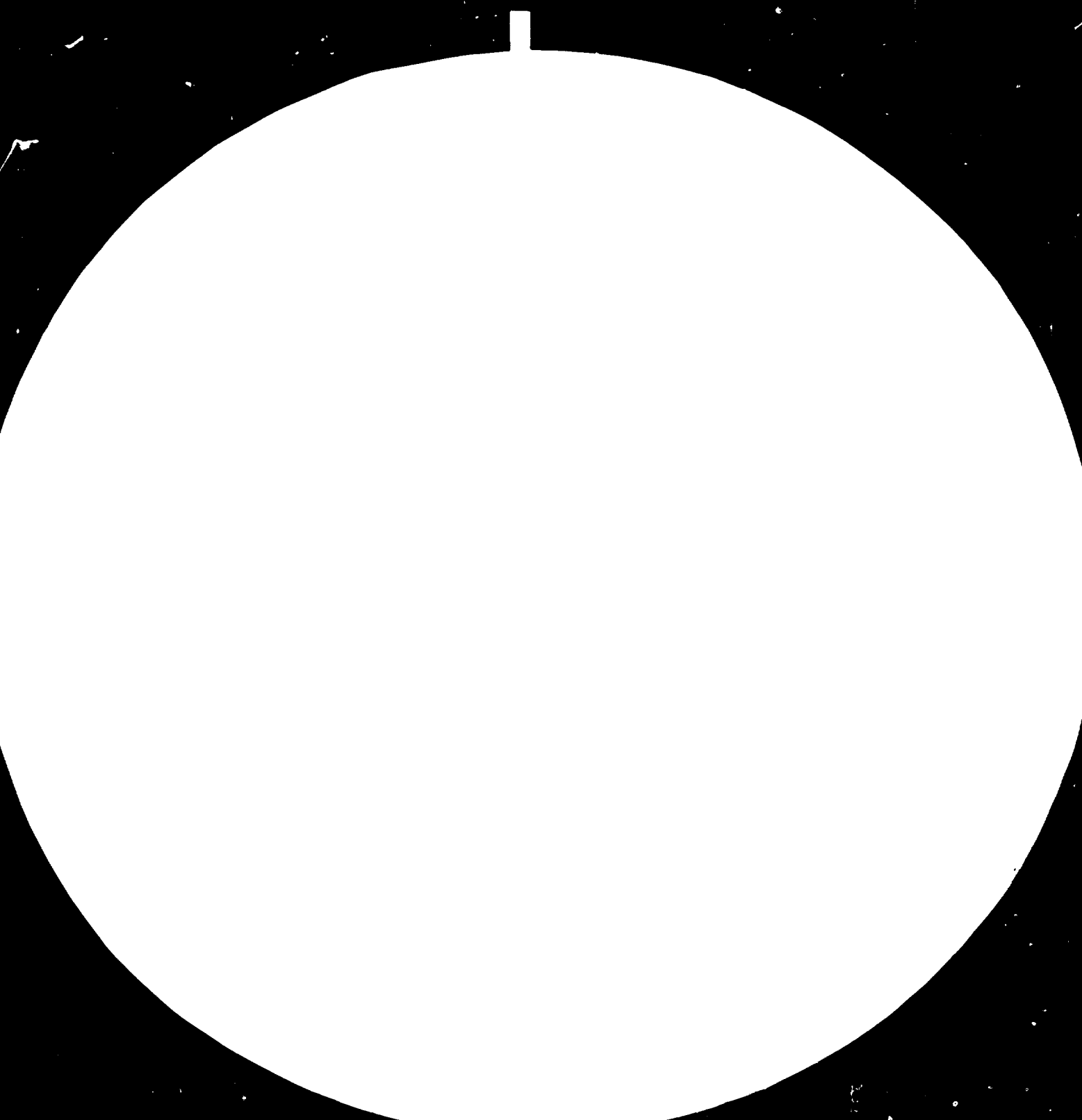

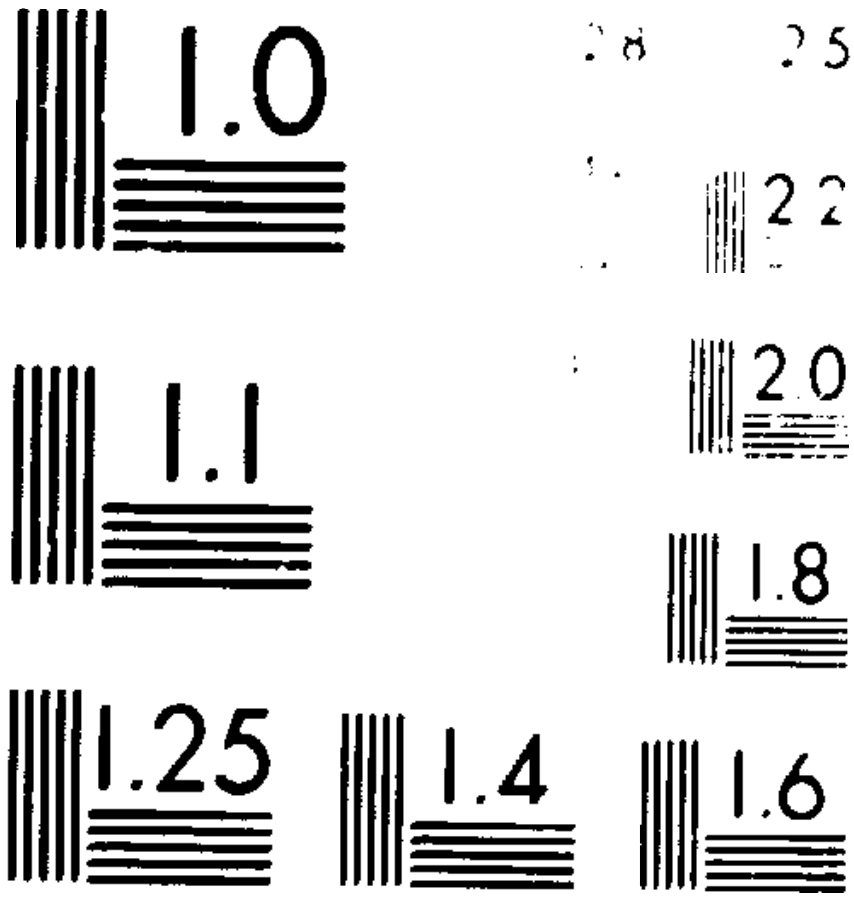
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Technical Consultation on the Production of Drugs in a Multipurpose Plant

Visegrad, Hungary, 1 - 12 March 1982

DRAFT REPORT*

(Production of Drugs in a multipurpose plant).

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PREFACE

The Lima Declaration and Plan of Action on Industrial Development and Co-operation calls for the share of developing countries in total world industrial production to be increased to at least 25 percent by year 2000. The world production of pharmaceuticals in 1977 amounted to US$ 64.52 billion out of which the share of the developing countries was only 11.43 percent. This reveals the wide gap that exists between the current level of production in developing countries and the target in the Lima Declaration. As national health programmes gain momentum, the demand for pharmaceutical products in the developing countries is bound to increase and the main objective of the pharmaceutical industry in these countries is to make available the essential medicines required for such social health programmes.

However, in most of the developing countries the pharmaceutical industry is confined to formulation and packaging of drugs. The major problems encountered by the developing countries in the matter of development of an integrated pharmaceutical industry and in moving to the backward integration to the manufacture of active ingrediants are the non-availability of the required technology as well as economies of scale. In view of this the exchange of information on technological capabilities and experience amongst developing countries assumes considerable importance.

In many of the developing countries a number of drugs in relatively small quantities are required. In such situations a multipurpose plant would be more appropriate wherein a number of drugs can be manufactured either sequentially or to some extent simultaneously using single/double series of equipment. The product mix and capacity are optimally balanced to minimize initial investment and yet to cover a broad spectrum of pharmaceutical chemicals. Flexibility is also built

in the design to take care of the varying and ever changing demands of the pharmaceutical market. In this design provision is made to increase the capacity substantially by marginal additional investment. In view of this UNIDO is promoting the concept of multipurpose plant and one such plant is being established in Cuba under the auspices of UNIDO.

In the light of above and as a follow up action to the Regional Seminar on the Industrial Application of Microbiology in the Pharmaceutical Industry which was held in Havana, Cuba in July 1979 and the Pharmaceutical Meeting on the Production of Essential Drugs in Developing Countries which was held at Balatonfured, Hungary in September 1979, UNIDO in co-operation with the Hungarian pharmaceutical industry together with the Hungarian Chemical Industries Engineering Centre (VEGETERV) organized the Technical Consultation on the Production of Drugs in a Multipurpose Plant.

The purpose of the consultation was to provide information on the different processes involved in the production of essential drugs and the projection of multipurpose plants to manufacture such drugs with a view to promoting their production in developing countries at national and regional level in order to attain self-sufficiency in essential drugs.

CONTENTS

INTRODUCTION

Consultants from Hungary presented papers on the following topics:

- Application of Unit Processes in Organic Chemistry.
- Projecting of Multipurpose Plants.
- The technology of Ascorbic Acid.
- The technology of Chloramphenicol.
- The technology of Sulphamethoxazole.
- The technology of Trimethoprim.
- The technology of Indomethacin.
- The technology of Phenobarbital.
- The technology of Phenylbutazone.
- The technology of Methyldopa.
- The use of fermentation processes in the pharmaceutical industry - technologies of Cyanocobalamine and Prednisolone.
- The technology of Penicillins.
- The technology of Gentamycin.
- The technology of Insulin and Heparin.
- Energy supplies and plant maintenance in the pharmaceutical industry.
- The conditions of air and liquid sterilization in fermentation processes.
- Formulation and packaging of drugs.
- From the laboratory to the plant.
- Open systems approach of pharmaceutical assets.

A process design exercise was distributed to the participants to be solved by different groups. The spokesmen from different groups presented the designs worked out by them.

During the presentation of the papers, the lecturers answered questions put by the participants giving clarifications where necessary. The summaries of the papers are as follows:

I. Organization of the Meeting

The Technical Consultation on the Production of Drugs in a Multipurpose Plant which was held in Visegrad, Hungary, from 1 - 12 March 1982 was opened by Mr. Ödön Kallos, President of the Hungarian Chamber of Commerce. Dr. György Csákvari, Director of the Hungarian Pharmaceutical Union and the representative of the Pharmaceutical Industries Unit, UNIDO, also spoke at the opening.

Adoption of the agenda

The agenda was adopted with the addition of information on the production of semisynthetic penicillins to be provided by the Hungarian experts.

II. Summaries of Papers

Application of unit processes in organic chemistry

The paper was presented by Mr. Jozsef Hay, Director of Vegyterv. He discussed with the participants the important basic chemical processes and unit operations which are frequently used in the manufacture of synthetic drugs such as:

- Nitration
- Reduction
- Halogenation
- Sulfonation
- Oxidation
- Alkylation
- Esterification
- Hydrolysis etc.

and gave examples of the application of these processes in the manufacture of Chloramphenicol, Ascorbic Acid, Indomethacin, Sulphamethoxazol etc.

During the discussion there were some general questions arising from the participants concerning the kinetics of the reaction, orientation of substituted groups, heat exchange. Mr. Hay answered them briefly.

A process design exercise to determine the size of the production capacity for different drugs to be solved by different groups was distributed.

Projecting of Multipurpose Plants

The paper was presented by Dr. Istvan Szentpeteri, Head of the Organic Division of Vegyterv and was followed by a presentation of Mr. László Brankowics , Head of Dept. at Vegyterv, on the architectural and structural features of plant building.

Slides were projected which showed a typical multipurpose plant designed and constructed in Hungary at various stages of construction. The special features of such a plant are that it consists of a main central area, 12 m wide, flanked on both sides by a 3 m pass way which also serves as emergency escape corridor and as housing for electrical switch-gears, piping and effluent waste water collection. The building design consists of a ground floor, first floor at 4.8 m level and a mezzanine structure at 7.5 m level. The reactors are mounted on steel structures at 4.8 m level and centrifuges, filters, dryers etc. are installed on the ground level. Service tanks, coolers, condensors etc. can be installed on the mezzanine. The outside structure of the building can be of R.C.C. whereas inside structures of the building are of steel. Flooring may be of steel or R.C.C. or special spark proof cement concrete mix.

A typical size of the building could be of 18 m width and 48 m length. If more area is required, similar modules in 18 m W x 6 m L may be added. At the end of the building, service area for recreation, canteen, washing place, laboratory and small work-shop is provided.

Tank batteries for bulk storage and transport pumps are located on one side of the building, whereas effluent waste water collection

and preliminary treatment systems are located on the other side of the building. It is advisable to have preliminary effluent treatment facility for each unit process individually. Adequate ventillation through side windows and forced exhaust duct system separately for each module of 18 m x 12 m section of the plant is provided so as to achieve an air recirculation rate of 18 - 20 times per hour.

Mr. László Brankowics narrated the history of architectural and structural development of pharmaceutical plants in Hungary since the early fifties to the present state with appropriate slide projections. It was emphasized that subsoil water level, convenience of raw material transportation etc. are important for proper location and design of plant layout. Various aspects of plant design in consideration of support of structures, regulations of Hungarian authorities regarding the construction material for hazardous chemicals, ventillation and standardisation of structural members such as prefabricated columns, claddings, doors, windows etc. were discussed.

Both sessions generated excellent response from all participants and invoked keen interest.

Manufacture of Vitamin C

The paper was presented by Dr. Károly Horváth, Director of EGYT.

The manufacturing process which was explained was divided into four separate steps:

First step: Transformation of sorbitol to sorbose by fermentation using acetobacter suboxidans.

Second step: Transformation of sorbose to diacetone sorbose synthetically with acetone and sulfuric acid.

Third step: Production of diaceto-ketogulonic acid by oxidation with sodium hypochlorite, alkali and nickel sulfate as catalyst.

Forth step: The production of vitamin C starting from ketogulonic acid by acting with dichloroethane-ethanol mixture.

The basic process, giving details of raw materials, material balance, flow sheets and broad equipment details were presented. The process is essentially a batch process. The participants were informed that the plant was in operation until 1978 and since then, the production has been discontinued on account of uneconomic size and updating the technology.

The technology of Chloramphenicol

The paper was presented by Mr. Istvan Läm of EGYT.

The process description which included material quantities, chemistry of the process and flow sheets was divided into the following steps:

1. Preparation of oxymethyl compound from p-nitroacetophenone, bromine, acetic anhydride, sodium bicarbonate, formic acid, hexamethylene tetra amine, hydrochloric acid etc.

2. Preparation of racemic aminodiol from oximethyl compound, aluminium powder, carbon tetrachloride and hydrochloric acid.

3. Preparation of active aminodiol from racemic compound by resolution with dimethylamide derivatives of dibenzoic-D-tartaric acid.

4. Preparation of chloramphenicol from condensation of dichloroacetic acid methyl ester and resolved aminodiol.

5. Purification, crystallization and drying procedures were also described.

The production processes of sulphamethoxazole and trimethoprim

The papers were presented by Dr. Ivan Beck of EGYT.

The process details included manufacturing chemistry, raw material requirements, process flowsheet, broad equipment, sizing of reactors and was divided into various stages as given below:

SULPHAMETHOXAZOLE

1. Preparation of crotonic nitrile from allylchloride and sodium cyanide in presence of copper as catalyst.
2. Preparation of isooxazole from crotonic nitrile by bromination and reaction with sodium salt of hydroxy urea. Hydroxyl urea is prepared from hydroxylamine sulfonic acid and ethylureathane.
3. Coupling of isooxazole with p-acetaminobenzene sulfochloride in pyridine medium. The sulfochloride compound is prepared from acetanilide and chlorosulfonic acid.
4. The acetyl sulfa compound is deacetylated using alkali hydrolysis, the crude product obtained by acidification.
5. Purification and crystallization steps are also described.

TRIMETHOPRIM

After a brief review of other process possibilities, the process under production in Hungary was described as given below:

1. Trimethoxy benzyl alcohol is chlorinated with thionylchloride to give the chlorinated compound.

2. Cyanoacetic ethyl ester is reacted with trimethoxy benzyl chloride, followed by condensation with guanidine base in presence of sodium methoxide to give 6 hydroxy trimethoprim.

3. 6 Hydroxy trimethoprim is converted to 6 chloro compound by using phosporus trichloride followed by dehalogenation using zinc and acetic acid.

4. Purification of crude product and drying process was described.

The technology of Indomethacin

The paper was presented by Mr. Janos Tompe based on the production process used in Hungary until a few years ago. The production however, has since been discontinued on account of a very low production capacity. A brief account of present and future trends in the non-steroidal anti-inflammatory drug consumption in the world market was discussed and it was mentioned that although other new drugs such as Ibuprofen, Naproxen etc. are gaining popularity, Indomethacin still retains a good share in the market.

The process including chemistry and material consumption is divided into the following steps:

1. Preparation of p-chlorobenzolchloride from o-chlorobenzoic acid and thionyl chloride in pyridine medium.
2. Preparation of p-methoxyphenylhydrazo-sulfonic acid-sodium salt monohydrate by diazolization of o-anisidine with sodium nitrite and acid. It follows reaction with sodium sulfite and reduction with zinc and acetic acid using copper sulfate as catalyst.
3. Preparation of crude Indomethacin by coupling o-chloro benzol chloride with o-methoxy phenyl hydrazo-sulfonic acid sodium salt monohydrate using tertiary butyl alcohol and sodium hydroxide followed by reaction of the formed intermediate with levulinic acid in presence of phosphoric acid as catalyst in toluene medium.
4. The crude Indomethacin product formed above is crystallized from tertiary butanol after clarification with activated carbon under nitrogen atmosphere, centrifuged and dried.

The technology of Phenobarbital

The paper was presented by Dr. Peter Lonyai, based on the process under production in Hungary.

A short description of different barbiturate compounds was made with emphasis on the relation beween the structure of the compound and its pharmacological effects.

The process description includes the chemistry, material balance and time scale for different stages of the manufacturing process and is divided into the following steps:

1. Preparation of phenyl cyanoacetic ester, sodium salt - by reaction of diethyl carbonate with benzyl cyanide in presence of metallic sodium using benzene as solvent.
2. Preparation of sevenal ester (mixed ester of phenyl cyanoacetic methyl/ester) from sodium salt of phenyl cyanoacetic ester and ethyl bromide/methanol.
   Ethyl bromide itself can be prepared from by-product sodium bromide and alcohol in presence of sulfuric acid.
   Sevenal ester so prepared is vacuum distilled at 12 - 14 torr, 155 - 156°C temperature.
3. Preparation of phenobarbital from sevinal ester by condensation with guanidine base followed by reaction with sulfuric acid.
4. Purification and crystallization of crude sevenal from active carbon and ethanol. The final product is centrifuged dried and packed. Alcoholic mother liquors are worked up to give further yield of Sevenal.

The technology of Phenylbutozone

The paper was presented by Dr. Joszef Pelmeri of Gedeon Richter Pharmaceutical Works, Hungary.

The process is in production in Hungary. A brief review of the production of this drug in various countries was given. However, it was commented that the statistical information was not reliable. Some descriptions about other possible chemical processes for preparing this drug were made. However, the most popular process in use in most countries as in Hungary, was described, including the chemistry, material balance and equipment specification. The process steps were divided as follows:

1. Preparation of n-butyl ester of dimethyl malonate from dimethyl malonate and n-butyl bromide through sodium methoxide.
2. Rectification of n-butyl malonic ester - methyl - by vacuum distillation at 40 - 50 torr, 200°C.
3. Preparation of hydrazo benzene from nitrobenzene by reduction with Pd/C catalyst and fusion of two molecules in presence of sodium methoxide.
4. Condensation of n-butyl dimethyl malonate with hydrazo benzene in presence of sodium methoxide and sulfuric acid to give crude product.
5. Crude phenylbutazone is clarified with carbon, crystalized from ethanol, centrifuged and packed after drying.
6. Sodium bromide formed in the first step is used to prepare butyl bromide using n-butyl alcohol.
7. It was emphasized that because of the competitive nature of the market, it is necessary to recover all solvents and sodium bromide, as ethyl/butyl bromide to be recycled in the process.

The technology of L-Alpha-Methyldopa

The paper was presented by Mr. Janos Tomoe of EGYT. The technology described is based on the process patented by M/S Boehringer, Ingelheim, Germany. A brief review of some possible chemical reactions for synthesis was given. However, the process in production in Hungary is different and is based on their own patent, the details of which were not furnished for obvious reasons. The basic chemistry of the process, estimated material consumption, material balance and flow sheet are given. The process is basically divided into following steps:

1. Preparation of racemic D-propionitrile using stricker synthesis starting from dimethoxy phenyl acetone - DMPA - through reaction with Ammonia, ammonium chloride and sodium cyanide.

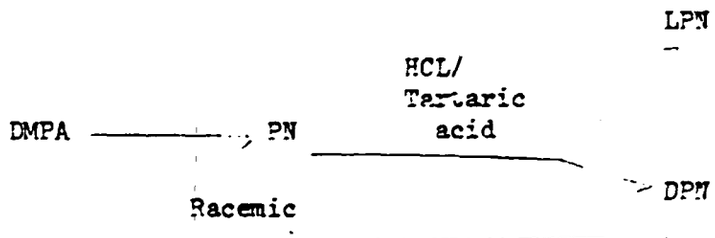
2. Resolution of D-propionitrile to L-form using D-tartaric acid and hydrochloric acid.

3. D and L mixture of propionitrate tartarate HCL salt is cooled to 0°C, after adding some more tartaric acid. The D-salt precipitates out and is centrifuged. After washing with ice-cold water the same could be used for the preparation of the D-propionitrile tartarate by mixing with equal part of DMPA for racemization.

4. The L-salt in the solution is obtained after removing the D-salt. The pH is adjusted with Ammonia to 6/7 and L-salt extracted with dichloroethane. Aqueous layer is separated and solvent phase acidified by hydrochloric acid to separate out L-salt of propionitrile hydrochloride. This is centrifuged at 0°C and washed out with cold water and dichloroethane. It is expected that the purity of D and L salts would be approximately 80% respectively.

5. Crude L-Alpha-Methyldopa is prepared from the L-salt by carrying out hydrolysis with hydrobromic acid. Excess HBr is removed, residue diluted with water/NaHSO3 and pH adjusted with Ammonia to pH 4.5 to crystalize out crude methyl dopa.

6. Crude crystals after cooling and centrifuging are redissolved in water, decolorized by active carbon and crystalized by cooling to 5°C. The pure crystals are centrifuged and washed with cold water, dried and packed.



The use of fermentation processes in the pharmaceutical industry

The session commenced with the presentation by Dr. (Mrs.) Eva Udvardy Nagy, Head of the Biotechnological Department, Hungarian Biochemical Society, on the technology of making Prednisolone, an anti-inflammatory/anti-allergic drug of steroid family which also finds application in treatment of hypersensitivity and dermatopathies by a fermentation process starting from cortisolone.

The fermentation technique involves production of chemical compounds by moulds, fungi or bacteria of specific varieties with the help of ingredients and salts which are essential for the development of suitable moulds, which in turn, biosynthesize the desired chemicals.

The technology involves the following steps:

1. Laboratory stage
   a) Preparation of suitable culture.
   b) Purification and isolation of the culture, storage under proper conditions.
   c) Preparation of the seed or inoculum.

2. Plant stage
   a) Preparation of fermentation media and sterilization at 121°C.
   b) Inoculation of the fermentor.
   c) Fermentation under controlled conditions.
   d) Isolation of active drug by various processes such as filtration, extraction, ion-exchange etc.
   e) Purification, crystallization, drying etc.

The world consumption of Predisolone is estimated at about 90T/year and the price fluctuates between US Dollar 800 to US Dollar 1.000 per kg.

The parent compound of cortisolone, starting chemical for prednisolone, could be a compound from natural origin, such as diosgonine, stigmasterol or sitosterol. Cortisol is prepared by chemical synthesis and is activated upon by strain Arthrobacter simplex to produce prednisolone.

The process in production in Hungary is described as follows:

The freeze-dried culture from vial is taken in 100 L of medium and after about 2 days, a part of the culture is transferred to seed fermenter containing 300 L of medium. When 70% of the growth is reached, 0.02 mg/ml of cortisol is added. After 6 hours a culture of high activity is obtained. This is then transferred to a fermenter after diluting 1:16 and Methanol, cortisol and calcium chloride are added. A conversion of 97 - 98% is achieved after 4 hours.

After this, the reaction is stopped by adding ethyl acetate and the active component is subjected to counter current extraction with ethyl acetate in a series of extractors. The final product is crystallized from the solvent after clarification, conforming to approved standards. The yield obtained is 90% on cortisol.

The process flow sheet, material balance and time schedule for production of 4.7 ton of prednisolone is presented with the paper.

Vitamin B-12

It is a corrinoid with a characteristic nucleotide part. It plays a very important role in maematopoiesis, for that reason it is used as a medicament in the cases of anaemia.

The technological process for the production of vitamin B-12 feed grade was discussed, starting from the sludge and applying an obligatory selection force by increasing amounts of methanol, culture and process is developed by anaerobic, septic fermentation in Vitamin B-12.

The fermentation process carried out uses pseudomonas of protaminobacter which are able to utilize simple methanol for their growth and for the biosyntheses.

The production steps are the following:

- Two stage fermentation starting from sludge water with constant addition of methanol and nutrients using cobalt chloride as processor.
- Recovery of feed additive vitamin B-12 using spray-dryer process.

The flow sheet and material consumption for one-day production were given.

The technology of Penicillin G

The paper was presented by Mr. Kalman Polya of BIOGAL Pharmaceutical Works, Hungary, based on the process in production in the country.

The prospective consumtion of penicillin in developed countries is 132.000 - 165.000 billion units for a population of 10 million and 70.000 - 80.000 billion/year in the developing countries.

The strain for the production of penicillin G is Penicillium Chrysogenum.

The inoculum is prepared from micro-elements, 50% corn steep liquor, saccharose at pH 6.0. The fermentation is either done batch-wise where the activity of mould controls the conversion rate, or continous operation in controlled manner where nutrients are added at controlled rate. Controlled metabolism results in higher yields and requires less power consumption, but higher capital investment is required for storage, metering pumps, regulations and controls, The fermentation is conducted under following conditions:

Temperature:	25°C
Air consumption:	200 NM^3/h
Pressure:	0.4 bar
Power consumption:	2.75 KW/M^3 of broth
Incubation time:	48 hours

The fermentation broth is prepared from 50% corn steep liquor, calcium carbonate, sodium thio-sulfate, arachis meal and soya bean oil. During fermentation, the volume of the broth increases by 50%. Therefore, the agitator has to be designed accordingly. A typical fermenter design used in Hungary was discussed. Total material consumption of fermentation in a typical 115 M^3 fermenter was given.

The broth is filtered in rotary filters. The filtrate is treated with formaldehyde, pH adjusted to 6.0 - 6.2 by sulfuric acid (dilute) and extracted with a mixture of butyl alcohol/butyl acetate in countercurrent manner. The solvent extract is cooled to -13°C,

to remove water as ice which is filtered in nutsche filter and again dehydrated with anhydrous sodium sulfate. The dehydrated solvent phase is clarified with carbon, warmed to 18 - 20°C and calculated quantity of potassium acetate is added. The penicillin G potassium salt is filtered and solvent recycled for recovery. The Potassium salt of penicillin G is taken in dry ethanol, centrifuged and dried at 60°C.

The material balance, flow sheet, time diagramme, broad equipment list and utility consumption for 115 M^3 fermenter were presented. The yield of penicillin salt is 600 kg, with penicillin content of about 1515 IU/mg/95 percent.

The sterilization procedure, safety regulations and quality requirements of G-penicillin-K intermediate product were also briefly discussed.

The technology of Gentamycin

The paper was presented by Mr. László Kegl.

Gentamycin is a broad spectrum antibiotic. It acts against infection caused by gram positive and gram negative bacteria including pseudomonas, proteus, staphylococcus etc. It can be used also in septicaemia, pyelonephritis, perilonitis etc.

It is produced according to the Hungarian technology by using micromonospera purpurea microorganism. The industrial process starts with the inoculation of the specified microorganism to the sterile media in the seeding tank and fermentation is continued at 38°C. The

optimal development time of the culture is 45 - 50 hours. Then it is transferred to a stainless steel fermenter where fermentation is continued at 35°C for 110 to 115 hours.

After that, crude processing is started by adding sulphuric acid to the broth and the sludge obtained is filtered on drum filter. At the end of the crude processing neutral filtrate is obtained. Gentamycin content should be between 1000 to 1100 meg/ml.

The Gentamycin is obtained by adsorption on carboxylic ionexchange resin amberlite IRC-50 and after that it is eluted either by using sulphuric acid or ammonium hydroxide. Then the gentamycin C complex is separated from minor antibiotics, biosynthesized in the fermentation and being present in the gentamycin sulphate by using amerlite CG-50 resin.

At the end, the material balance and the flow sheets were given.

The technology of drug formulation and packaging

The paper was presented by Mr. László Döbróntey and Mr. János Lázár, Hungarian Chemical Industries, Engineering Centre/Vegyterv.

They discussed the most typical technological processes and equipment used for drug formulation plants. They concentrated especially on production of tablets, syrups, ointments, ampoules and capsules. Also they discussed some viewpoints about establishing pharmaceutical formulation plants with regard to GMP recommendations.

Regarding the lay-out of technological equipment they projected slides to show the lay-out, flow-diagrams, material handling, storing, ventilation and air-conditioning systems and personnel traffic.

The production of sterile air and water and the sterilization of appliances

The paper was presented by Mr. Gabor Berencsy (Vegyterv).

He discussed the machinery engineering problems which might effect the sterilization of the equipment like the manner being used for welding the manhole of a fermentor, thermometer connections, hollow parts present on the surface of equipment and packing materials.

The discussion continued on how to produce sterile air and the lecturer presented a flow diagram showing the system they use in Hungary with its different stages. Also the participants discussed with the lecturer how they could produce sterile water and different methods of heat sterilization of nutrient media.

Plant visit

The participants visited the plants of Gedeon Richter.

The first plant specialized in organic synthesis and the whole group saw a multipurpose plant for pesticides. It was a practical demonstration to see how a multipurpose plant could be designed based on the papers presented.

The participants visited also a second plant which was dealing with the production of pharmaceutical specialities for different dosage forms.

Extraction of animal organs: Technology of Insulin and Heparin

The paper was presented by Dr. János Fári of B.C.R. Balbone, Hungary.

Insulin is a polypeptide hormone and is used in treatment of diabetes. Heparin is a polysaccharide, which is used for the control of blood coagulation and in treatment of thrombosis. Insulin is extracted from pancreas of cattle and heparin from lungs and livers of sheep and pigs. Both these drugs are produced in Hungary.

There are two processes for the manufacture of insulin:

(a) Salt-out-procedure
(b) Evaporation procedure

The important thing in the process is the conservation of glands which can be achieved by instant freezing or by treatment with acidified alcohol.

The description included process details, material consumption, flow sheet and equipment list.

Heparin is produced by the following process:

- Autolysis of lung with sodium hydroxide
- Extraction, filtration and purification of the product.

The production of Insulin and Heparin can be taken up in the same plant.

Energy supplies and plant maintenance in the pharmaceutical industry

The paper was presented by Mr. György Bartha of Vegyterv.

The paper included description of utilities such as steam generation, fuels and their combustion equipment, boiler systems, water treatment, water cooling systems, refrigeration, vacuum and compressed air supply, power generation, energy economy and lastly the planned preventive maintenance requirements of pharmaceutical industry. The paper was generalized as introduction to the energy supplies system.

From the laboratory to the plant

The paper was presented by Mr. György D. Honti, of Vegyterv, on scale-up aspects of chemical processes from laboratory scale to commercial plant production scale, with special reference to various difficulties and bottlenecks faced by engineers when the laboratory data is used for full scale designs. It was emphasized that pilot plant investigations were essential for any such work, as M/S Baekeland had said in 1976:

> "Commit your blunders on a small scale and make your profits on a large scale".

Open systems approach on pharmaceutical assets

The paper was presentet by Prof. Dr. György Somló, General Director, VEGYTERV.

A manufacturing plant was compared to a living being in that it might flourish, survive or perish depending on its inherited and acquired

adaptibility to coming events which could not be foreseen accurately. Particular emphasis has to be laid on the following aspects of the plant:

- natural surroundings including such artificial items as the neighbouring cities
- the plant location and site
- the general layout
- the system of internal services
- the structures
- the plant items and
- their interconnections including material flow, transport, stores, piping, instrumentation.

While dealing with the above aspects in some detail, a brief reference was made to the experience of the Hungarian Pharmaceutical Industry in these areas.

Special reference was made to major reconstructions which should be carried out in such a way that the production section should be in a state to take over during the period of reconstruction, all the productive functions of the older plant so that the obsolete parts of the plant could be demolished during this period and some of its structures down-graded to lesser tasks.

General design is aimed at the formulation of the specific technological solution and its implementation. Its basic disciplines are chemical and mechanical engineering, economics, management, sociology and politics.

III. PLAN OF ACTION

The pharmaceutical industry has achieved enormous growth during the past 30 years as a result of which significant achievements in social welfare have been registered in developed countries and some of the developing countries. The value of the production of pharmaceuticals was estimated at US Dollars 64.52 billion in 1977, out of which the share of the developing countries was only 11.43 percent. The developing countries had a trade deficit in pharmaceutical of about US Dollars 2 billion in 1977. The importation of bulk drugs in these countries is increasing by 15 - 17 percent each year and the deficit is, therefore, expected to reach a figure of US Dollars 9 billion by 1985.

In view of above, it is obvious that there is an urgent need for the effective development of the pharmaceutical industry in the developing countries. Such a development should take place not only in the area of the formulation and packaging of pharmaceuticals but in the backward integration to the manufacture of bulk drugs or active ingredients to sustain the formulation industry.

In many of the developing countries smaller quantities of a variety of drugs are required. In such cases, a multipurpose plant is suitable for the production of a number of products either sequentially or to some extent simultaneously. Such a plant is also versatile enough to take care of new products for which the technology might be under development. Flexibility is thus built into the design of the multipurpose plant to cope with the varying and ever changing demands of the pharmaceutical market.

In order to accelerate the development of the pharmaceutical industry in the developing countries, UNIDO, in association with the Hungarian Pharmaceutical Industry has organized the seminar on the production of drugs in a multipurpose plant.

The main topics discussed during the seminar are:

- Application of Unit Processes in Organic Chemistry.
- Projecting of Multipurpose Plants.
- The technology of ascorbic acid.
- The technology of chloramphenicol.
- The technology of Sulphamethoxazol.
- The technology of Trimethoprim.
- The technology of Indomethacin.
- The technology of Phenobarbital.
- The technology of Phenylbutazone.
- The technology of Methyldopa.
- The technology of Insulin and Heparin.
- The use of fermentation processes in the pharmaceutical industry. Technologies of Cyanocobalamine and Prednisolone.
- The technology of Gentamycin.
- Energy supplies and plant maintenance in the pharmaceutical industry.
- The conditions of air and liquid sterilization in fermentation processes.
- Formulation and packaging of drugs.
- From the laboratory to the plant.
- Open systems approach of pharmaceutical assets.

The consultants and participants, after the presentation of papers on various subjects, most of which related to the manufacture of synthetic drugs in a multipurpose plant, had a detailed discussion and the concensus was that every effort should be made to develop the pharmaceutical industry through the establishment of multipurpose plants in the developing countries.

In order to facilitate the development of the pharmaceutical industry in the developing countries, Recommendations and a Plan of Action were worked out. The following Plan of Action was recommended:

The establishment of such multipurpose plants in the developing countries having well established formulation and packaging industry in order to produce bulk drugs or active ingredients will have on the development of chemical industries and the economy as such a great impact. In this connection the following measures are recommended:

i) UNIDO in association with the Hungarian Pharmaceutical Industry should make an assessment of the possibilities of establishing such multipurpose plants in Asia, Africa and Latin America. This assessment should include technology, product mix, investment, training, supply of raw materials, intermediates etc.

ii) In order that the assessment reflects the actual needs of the Governments and their interest, UNIDO and Hungary should include in their programme such countries from which requests for such an assessment have been received.

iii) With a view to anticipate/facilitate such requests, UNIDO should prepare a briefing note and programme in this sector and forward it to the Governments. In this exercice, the participants of this seminar will be the focal point for the first phase of the project for the assessment.

iv) UNIDO is requested to organize such technical meetings for multipurpose plants for fermentation, biologicals and medicinal plants.

v) UNIDO is also requested to organize training programmes at the plant level on production, control and management.

vi) It is recommended that UNIDO should prepare an official publication on the technical discussions and papers with the recommendations for the benefit of the developing countries.

vii) On the completion of the assessment as mentioned above UNIDO shall assist the developing countries, where the markets and means justify, in the establishment of multipurpose plants.

viii) UNIDO should repeat this Seminar in English/French for the benefit of Francophone developing countries.

ix) UNIDO should conduct a seminar on multipurpose plants at an advanced level with a bias on practical aspects for the benefit of the developing countries in the process of establishing such multipurpose plants.

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