# IMPROVEMENTS IN THE TECHNOLOGY OF PRODUCTION OF ASPIRIN. CATALYTIC ACETYLATION OF SALICYLIC ACID

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Acetylsalicylic acid (aspirin) (I) is obtained under industrial conditions in 76.3% yield by acetylation of technical salicylic acid (II) with acetic anhydride (III) in chlorobenzene solution, followed by recrystallization of the technical product from 35-40% isopropyl alcohol.

This method is an industrial variant of known methods for the preparation of I [1, 2]. In order to attain the most economical conditions for carrying out the process, a 7-10% excess of the acetylating agent is employed.

The main drawback to this process is the duration, which is 9 h for a residual content of II in the technical I of 1-1.25%.

The known methods for acetylation using catalytic amounts of sulfuric acid and the ion exchange resin Vionite CS-2 result in very considerable shortening of the duration of the reaction, but under these conditions the consumption of II is increased nearly twofold [3]. In addition to acidic catalysts, the hydrates of certain divalent metal oxides and their nitrates have been employed in this reaction [4]. This group of catalysts enables the reaction time to be shortened to 2 h, and the excess of III to 43%.

Increasing the excess of III accelerates the reaction, but the increased raw material costs involved are not compensated for by the increased productivity.

The duration of the acetylation of II is probably due to hydrogen bonding arising from the mobility of the hydrogen of the phenolic hydroxyl group, which hinders the formation of ethers and esters, in particular I [5].

Compound I is known to form compounds with a number of metals differing in composition and structure with respect to the pH of the solutions and the total concentration of the acid [6]. The formation of sodium and silver salicylates and the salicylates of calcium, magnesium, barium, zinc and cadmium in the proportions Me:II = 1:2 (in acid solution) takes place without participation of the hydrogen of the phenolic group, with consequent disruption of the intramolecular hydrogen bond. When the ratio Me:II = 1:1, the salicylates of divalent metals (barium, calcium, zinc) and also iron, copper, and aluminum have a chelate structure [7].

With the aim of improving the technology of production of I we have examined the acetylation of II in the presence of salts of various metals as catalysts to increase the rate of reaction, to reduce the residual amount of II in the reaction product, and to increase the yield and quality of the technical I.

In order to determine the optimum conditions for the acetylation of I, the dynamics of the conversion of II to I were examined with respect to the solvent and the composition of the catalyst.

An investigation of the acetylation in the most suitable solvents for the reaction (acetic acid and chlorobenzene) showed that the rate of formation of I was greater in the

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nonpolar solvent chlorobenzene. These results are in agreement with the literature information on the existence of intermolecular hydrogen bonding between II and acetic acid, which slows down the acetylation.

In order to determine the catalytic effects of various metal salts on the acetylation of II, we added strictly equivalent amounts of the latter (0.01 mole per mole of I) to the reaction mixture. Twelve cations were tested: $Na^+$, $Ag^+$, $Mg^{2+}$, $Ca^{2+}$, $Cd^{2+}$, $Zn^{2+}$, $Ba^{2+}$, $Cu^{2+}$, $Co^{2+}$, $Ni^{2+}$, $Fe^{2+}$, and $Al^{3+}$. The experimental results showed that $Ca^{2+}$, $Mg^{2+}$, $Zn^{2+}$, and $Na^+$ were active and led to significant increases in the reaction rate, although their catalytic effects were dependent on the nature of the anion, since $Na^+$ in $Na_2SO_4$ and NaCl was less active catalytically than in $CH_3COONa$, and in general it was less active than the divalent cations $Ca^{2+}$ and $Mg^{2+}$. The cations $Fe^{2+}$, $Cu^{2+}$, and $Al^{3+}$, which are capable of complexing with II, had virtually no effect on the reaction rate.

The acetylation of II in the presence of $CaCl_2$ and zinc powder, which showed the greatest catalytic activity, was investigated in greater detail. Acetylation in chlorobenzene and acetic acid takes place over 8-9 h, the residual amount of II being 0.4 and 1.20%, respectively. ly. A catalytic amount of $CaCl_2$ shortened the reduction time to 30 min and reduced contamination by II to 0.2-0.9%. This reduction in the content of II in technical I resulted in an increase in its quality, and hence in a reduction in the consumption of isopropyl alcohol for washing, and losses resulting from the solubility of I in the solvent.

The catalytic effect of $CaCl_2$ is apparently due to its ability to increase the reactivity of the acylating agent under conditions of acid catalysis. Salicylic acid, being a comparatively strong acid ($pK_1$ 3.00, $pK_2$ 13.82), is able to form mixed salicylate-hydrochloride salts, thereby liberating a proton which activates a molecule of III: $HOC_6H_4COOCaCl + H^+ \rightleftarrows HOC_6H_4COOH + Ca^{2+} + Cl^-$.

It has been shown that zinc powder, in addition to its catalytic effect on the process of acetylation, also reduces colored impurities present in the technical II used as starting material, converting them into colorless compounds which are readily soluble in the acetic acid solvent.

As a result of these investigations, a technological process has been developed and tested under plant conditions for the catalytic acetylation of II in the presence of $CaCl_2$, which shortens the time required for the reaction to 30 min and increases the yield of pharmacopeia quality I to 81.6%, at the same time reducing the consumption of chlorobenzene by half by reuse of the mother liquors used as solvent.

## EXPERIMENTAL

To a mixture of 138.2 g (1 mole) of technical II and 120 ml of chlorobenzene at 55-60° were added 107 g (1.07 mole)* and 1 g (0.009 mole) of anhydrous calcium chloride. In subsequent runs, instead of chlorobenzene, the mother liquors from an earlier acetylation (120 ml) were used. These contained 0.6-0.7 g of calcium chloride, and a further 0.4-0.3 g of calcium chloride was added to bring the total amount in the reaction mixture to 1 g. After the catalyst had been added, the reaction mixture was kept at 78-80° for 30 min. The endpoint of the reaction was determined by the content of residual II (0.25-0.5%) in the reaction mixture [8].

The mixture was then cooled to 20° during 2 h, and the technical I which separated was filtered off and washed with 35-40% isopropyl alcohol (100 ml) and water (100 ml) to give 144-147 g of technical I, calculated on the dry basis, when chlorobenzene was used as solvent. When the mother liquors from an earlier acetylation were used for this purpose (13 times), the yield of I was higher, averaging 175.75 g (96%). The content of residual II in the technical I was not greater than 0.1%. Recrystallization from 35% isopropanol (320 ml) with the addition of activated charcoal (1.5 g) gave 146.1 g of pharmacopeia grade I. From the mother liquors there was obtained a further 1.2 g of technical material which when similarly recrystallized gave 0.9 g of pharmacopeia grade I. In all, 147 g (81.6%) of pharmacopeia grade I was obtained.

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# SELECTIVITY OF INTENSIVE MEMBRANE PROCESSES OF SEPARATING DISSOLVED SUBSTANCES.

# I. CLASSIFICATION AND CHARACTERISTICS OF PRESSURE-DRIVEN MEMBRANE PROCESSES (REVIEW)

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## I. GENERAL CHARACTERISTICS OF MEMBRANE SEPARATING PROCESSES

In the pharmaceutical chemicals industry, various processes for separating substances are widely used: filtration, extraction, adsorption, fractional distillation, crystallization, etc. Separating mass-exchange processes also include ultrafiltration and reverse osmosis, in which synthetic semipermeable membranes are used.

The active interest in membrane processes that has long been known has been connected in recent years with the actualization of problems of isolating the products of microbiological synthesis, the purification of solutions of biologically active compounds, and the production of pure drinking water, and also with the elucidation of the role of biological membranes in the regulation of various functions of the human organism [1], etc.

The necessary basis for the development of modern economically justified membrane processes was the production [2] and subsequent improvement [3-7] of highly selective and strong synthetic membranes (mainly from polymers), and also apparatuses for their utilization which are convenient in the operation of industrial plants.

Among liquid-phase membrane processes a distinction is made between: a) electrodialysis (mainly using ion-exchange membranes); b) electrophoresis (also using semipermeable membranes); c) dialysis; d) ultrafiltration (UF); and e) hyperfiltration, or reverse osmosis (RO).

The first two processes take place in an electrostatic field and are characterized by a directed flow of charged particles through ion-exchange membranes (a review by N. E. Kozhevnikova et al. [8] has been devoted to the investigation of such processes, the properties of the membranes, and the fields of their application). The last three processes do not require the presence of an external difference in electric potentials but are based on the use of nonionogenic semipermeable membranes and are characterized by an oriented flow both of ions and of undissociated molecules. The objects of the present discussion are dialysis, UF, and RO, in the mechanisms of which there is much in common (Fig. 1).

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