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# Crystallization and morphological characteristics of acetyl-salicylic acid (aspirin) synthesized from substrates of different source

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**Abstract:** Salicylates, like many other drugs, originating from the plant world, are present in the leaves and bark of plants Salix, Spiraea and Gaultheria, making them very useful in the prevention and treatment of many diseases. One of the most famous salicylate drug today is acetylsalicylic acid, a pharmaceutically active compound known as aspirin. Considering the great importance of aspirin in the medicine, synthesis was performed in order to explore differences in purity of laboratory synthesized acetyl-salicylic acid using salicylic acid obtained from commercial and from natural sources. In the Paper is compared the properties of the crude product with the properties of aspirin recrystallized in a variety of solvent systems. The results of analysis show that "natural aspirin", obtained by the hydrolysis of oil of wintergreen as a renewable source of salicylic acid, has a higher purity compared to aspirin obtained from commercial salicylic acid. As a recrystallization solvents it is used the polar (methanol, ethanol, isopropanol, n-butanol and isobutanol), the partially polar (acetone) and non-polar (toluene), wherein is monitoring effect of polarity, concentration, and long chain branching on the solvent properties of the obtained products.

**Keywords:** salicylates, oil of wintergreen, recrystallization, FTIR spectroscopy

## INTRODUCTION

Acetylsalicylic acid (aspirin), is an acetyl derivative of salicylic acid. According to structural characteristics, aspirin belongs to the class of esters. It has a chemical structure consisting of three chemical groups: an aromatic ring, an ester and a carboxyl group. The structural formula of acetylsalicylic acid is shown in **Figure 1**.

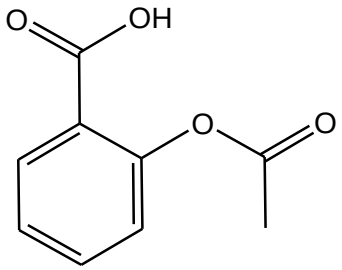



**Figure 1:** The structural formula of acetylsalicylic acid

IUPAC name of acetyl-salicylic acid is 2-(acetyloxy) benzene carboxylic acid. The molecular formula is $C_9H_8O_4$ and a molecular weight of aspirin is 180.2 g /mole. The CAS number is 50-78-2. Aspirin occurs in the form of colorless crystals, white crystalline powder or granules, without or almost odorless. Acetylsalicylic acid is weakly acidic substance with a melting point 136°C. It is poorly soluble in water, alcohol and good in ether[1]. Acetylsalicylic acid as pharmaceutically active compound is one of the most accessible and most used medicines. Aspirin has multiple actions in the treatment and prevention of various diseases. It acts as an analgesic, antipyretic, anti-inflammatory, anti-rheumatic. It also inhibits platelet aggregation because it affects the biosynthesis of thromboxane and is therefore antithrombotic. Because of its commercial importance, great attention was paid to get adequate purity of aspirine. Aspirin is prepared in the laboratory by classical esterification reaction of salicylic acid with acetic anhydride. Ester bond obtained by reaction of OH-group of salicylic acid and COOH- group of acetic anhydride. As a catalyzer was used a sulfuric acid or phosphoric acid [2]. The reaction is shown in **Figure 2**.

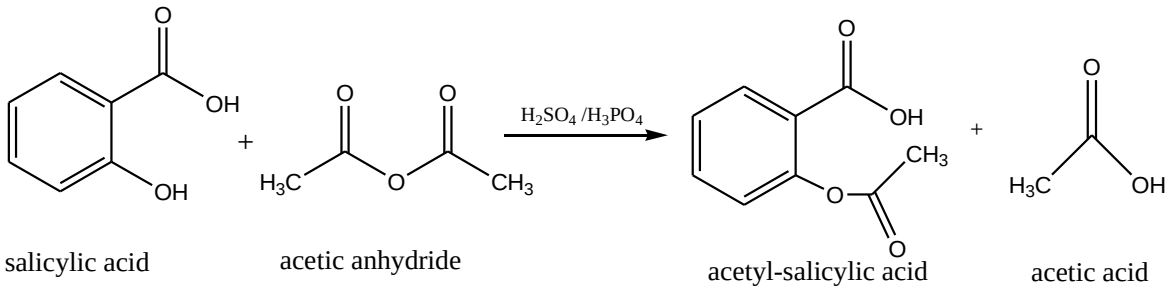



**Figure 2:** Synthesis of acetyl-salicylic acid from salicylic acid and acetic anhydride

In the presence of acid, the carbonyl oxygen of acetic anhydride are protonated, wherein increasing the electrophilic character of the carbonyl carbon. Nucleophilic hydroxyl group of salicylic acid then attacks the carbonyl carbon of anhydride, forming a tetrahedral intermediate. This is followed by proton transfer,

wherein the electrons return to the oxygen of the hydroxyl group, restoring the carbonyl group, which also induces departure formation of acetic acid and aspirin. The mechanism is shown in **Figure 3**.

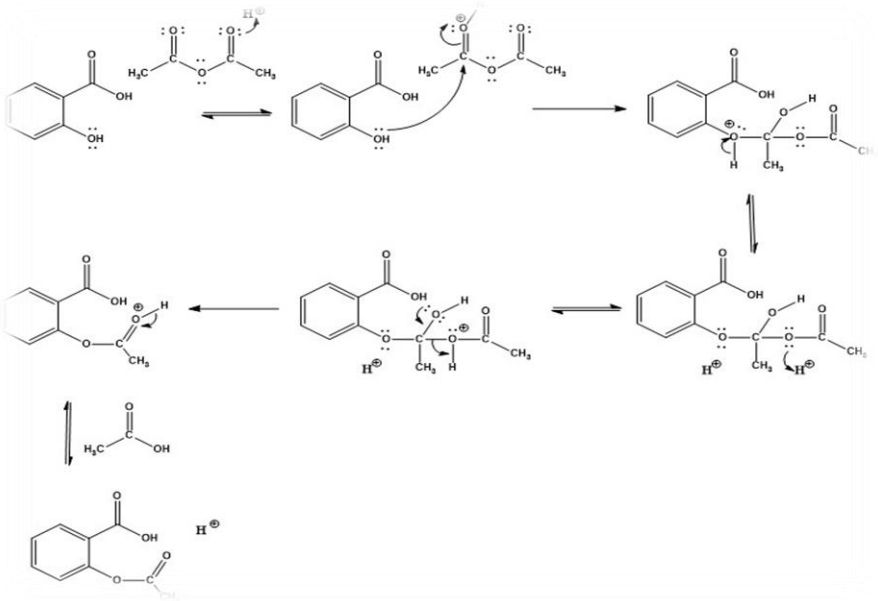


**Figure 3:** The mechanism of the synthesis of acetyl-salicylic acid

Salicylic acid as a precursor in the synthesis of aspirin is obtained industrial by Kolbe-Schmitt synthesis[3]. Salicylic acid can also be obtained from natural sources, ie. from substances that occur naturally in plants. Methyl salicylate as a derivative of salicylic acid is an organic ester of naturally produced by many plant species, but the most common species is the Gaultheria procumbens L. of the family Ericaceae, this type of Betula lenta L., family Betulaceae. It was first isolated by steam distillation from the leaves of evergreen (wintergreen) in Year of 1843.

**Figure 4:** Wintergreen- *Gaultheria procumbens*

Wintergreen is a small evergreen plant native to North America. It is a low growing plant height of 10-15 cm, dark green, leathery leaves and white bell flowers after which produces the fruit red. The berries are healing and have, as well as sheets, specific odor. The plant is rich in essential oils that are obtained by distillation from the leaves and one of the main ingredients is methyl salicylate (99% and more) [4, 5].

Hydrolysis of methyl salicylate from oil of wintergreen give a salicylic acid. Therefore, periwinkle is a renewable source of salicylic acid. The hydrolysis is carried out from oil of wintergreen with sodium hydroxide to form an intermediate of disodium salicylate as shown in **Figure 5**.

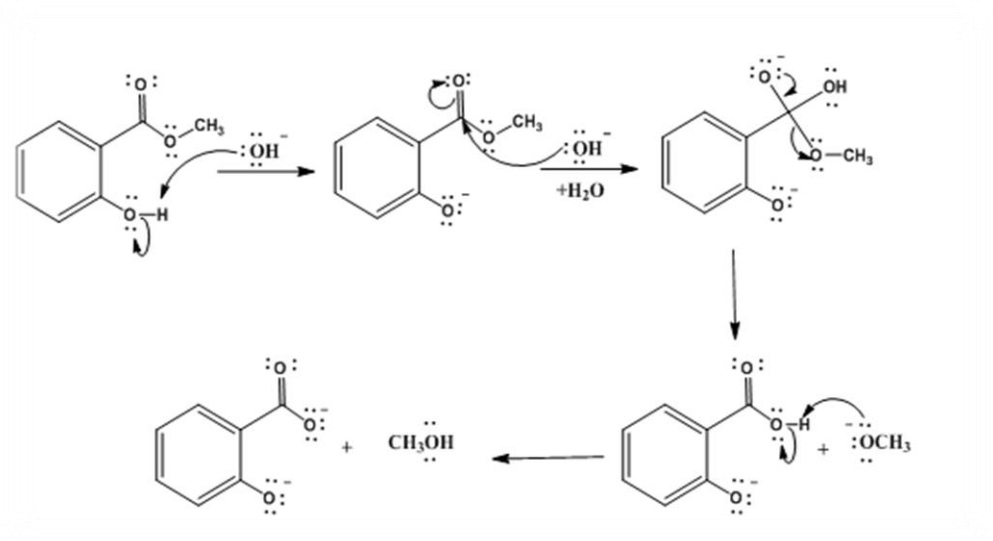


**Figure 5:** The mechanism of the reaction of methyl salicylate with NaOH

By adding acid, disodium salicylate was converted to salicylic acid. Salicylic acid is soluble in water and precipitates from the reaction mixture. **(Figure 6.)**

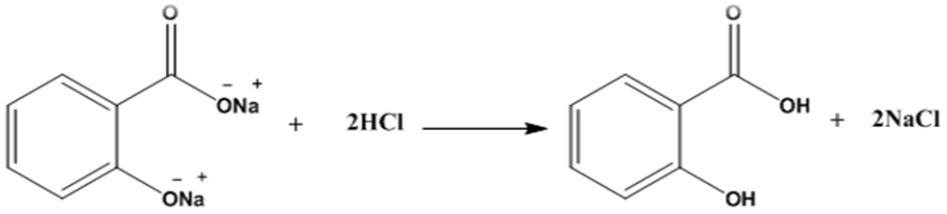



**Figure 6:** Translation disodium salicylate to salicylic acid

Most organic compounds isolated from natural materials or reaction mixture, containing ingredients or impurities which must be removed. Recrystallization is a process of purification solids by removing impurities and it is based on differences in solubility[6]. Recrystallization is a simple and inexpensive method for the treatment of solid organic matter, wherein a crystalline form of a compound may be obtained from other solid forms of the same substance. The most active pharmaceutical ingredients have been produced in crystalline form because of their chemical stability during shipping, packaging and storage[7]. The recrystallisation process comprising making a hot saturated solution of the drug with a suitable solvent using a boiling point from which, after cooling allocates a new crystalline form of the drug. The crystalline state of the drug is an important feature in pharmaceutical production. Depending on the crystallization conditions, the substance is crystallized in the form of what are known as polymorphs. The existence of different crystalline forms of a pharmaceutically active compound affecting to key properties such as solubility, bioavailability, crystal morphology and density. Polymorphs are agents of the same chemical composition

but a different crystal structure. Different crystalline forms of a pharmaceutically active compound having different physical characteristics (solubility properties, biological activity) but are chemically identical. Polymorphism (Gr. Of poly-Morph-form) means the ability of a substance to crystallize in more than one crystal structure, usually under different crystallization conditions. First, there is a reaction solids with solvent, during which disrupts the crystal lattice solids (amorphous). On that occasion, creates a cavity in the solvent (phase change), where the solid is dissolved. After dissolution, molecule is recrystallized to another crystalline form. For a long time it was known only one crystal structure of aspirin. Using X-ray, Year of 1964, for the first time discovered monoclinic crystal form of aspirin. Although there were indications of the existence of other crystalline forms of aspirin, the first alternative crystal form of this important pharmaceuticals was discovered in Year of 2005. Both forms of aspirin (I and II) **(Figure 7**.) show a great similarity in the packaging of the crystal lattice and they are distinguished primarily by intermolecular hydrogen bonds[8].

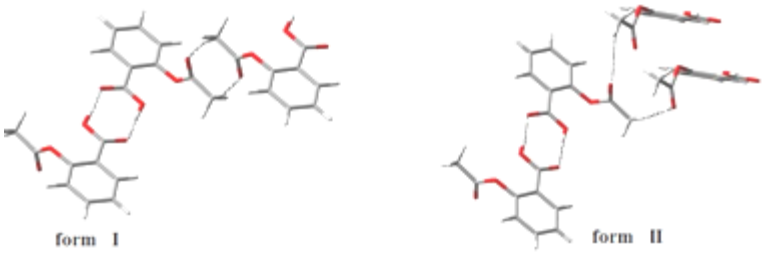



**Figure 7:** Polymorphic forms of aspirin

Both forms are Centro symmetric dimer molecules that are interconnected by O-H ••• O hydrogen bonds, between their carboxyl groups[9] as is seen on **Figure 8.**

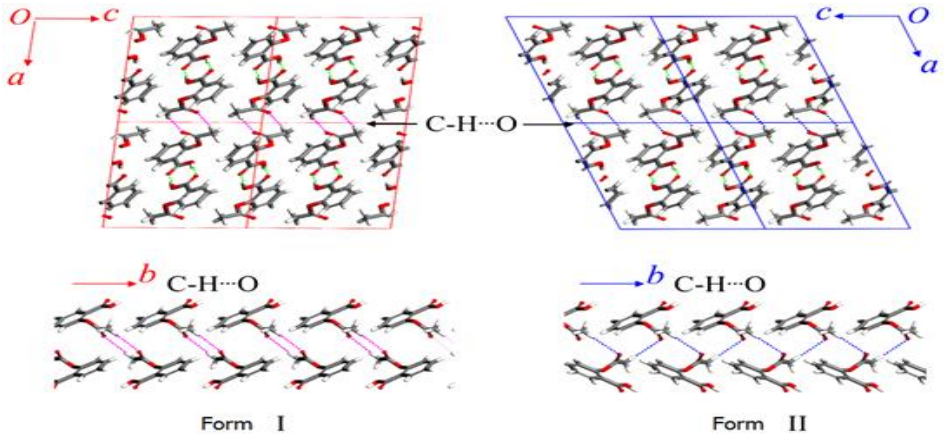



**Figure 8:** The differences in polymorphic forms of acetyl-salicylic acid

The objectives of this study are as follows:

- Synthesis of acetyl-salicylic acid from natural materials (oil of wintergreen-methyl salicylate)
- Synthesis of acetyl-salicylic acid from commercially available substrates
- The recrystallization of laboratory synthesized aspirin from organic solvents of different polarity

- Morphological characterization of synthesized crystals acetylsalicylic acid
- Qualitative and quantitative characterization of recrystallized samples of aspirin

## MATERIAL AND METHODS

As a material for laboratory synthesis of acetylsalicylic acid were used the following reagents:
• oil of wintergreen (Gaultheria procumbes) - 99% methyl salicylate, Melasan, Eugendorf, Austria
• sodium hydroxide-Semikem, Sarajevo
• Hydrochloric acid-Semikem, Sarajevo
• salicylic acid- Semikem, Sarajevo
• acetic acid-Zorka, Sabac
• sulfuric acid, conc.- Semikem, Sarajevo

For the analysis and characterization of acetylsalicylic acid obtained by crystallization from different solvents, were used the following methods:

- Colorimetric method
- Determination of melting point
- Fourier transform infrared spectroscopy(FTIR)
- Optical microscopy

## RESULTS AND DISCUSSION

In order to obtain higher purity of acetylsalicylic acid, the synthesized samples were purified using the solvent of different polarity, chain length and in different concentrations. In the Paper it is compare the properties of the crude product with the properties of aspirin which is recrystallized in a variety of solvent systems[9,10]. To investigate the properties of purified acetyl-salicylic acid for recrystallization were used solvents from among polar, partially polar and non-polar whose characteristics [11] are shown in **Table 1.**

**Table 1:** List of used solvents with accompanying physical characteristics

| Solvent | Formula | Mr | Boiling point (°C) | Melting point (°C) | Permittivity (20°C) | Density (g/ml) |
|---|---|---|---|---|---|---|
| water | $H_2O$ | 18 | 100 | 0 | 79.7 | 0.998 |
| methanol | $CH_4O$ | 32 | 64 | -98 | 32.6 | 0.792 |
| ethanol | $C_2H_6O$ | 46 | 78 | -114 | 22.4 | 0.789 |
| 2-propanol | $C_3H_8O$ | 60 | 82 | -88 | 18.3 | 0.786 |
| n-butanol | $C_4H_{10}O$ | 74 | 118 | -80 | 18.2 | 0.810 |
| 2-butanol | $C_4H_{10}O$ | 74 | 108 | -108 | 17.7 | 0.802 |
| acetone | $C_3H_6O$ | 58 | 56 | -95 | 20.6 | 0.790 |
| toluene | $C_7H_8$ | 92 | 110.6 | -95 | 2.38 | 0.867 |

**Characterization of acetylsalicylic acid obtained from commercial funds:** For recrystallization of synthesized acetyl-salicylic acid it is used lower alcohols (methanol, ethanol, isopropanol, butanol), where it is possible to monitor the influence of the length and branching of the hydrocarbon chain to the yield and

purity of recrystallized samples. Acetone, which is one of the partially polar solvents and toluene which is belong to aromatics and it is nonpolar solvent. Scale solvent polarity is its dielectric constant. Dielectric constant or permittivity is a measure of the ability of a substance to reduce the electrostatic force between two charged parts[12,13]. When is the value of the dielectric constant higher, electrostatic forces are less. If it is known that an order of magnitude matching IR spectra (analyzed and API standards) more than 70% qualify as positive and acceptable identification of pharmaceutical active substances, we can say that the crude acetyl-salicylic acid have acceptable degrees of purity of the synthesized pharmaceutically active substances and it is shown in **Figure 9**.

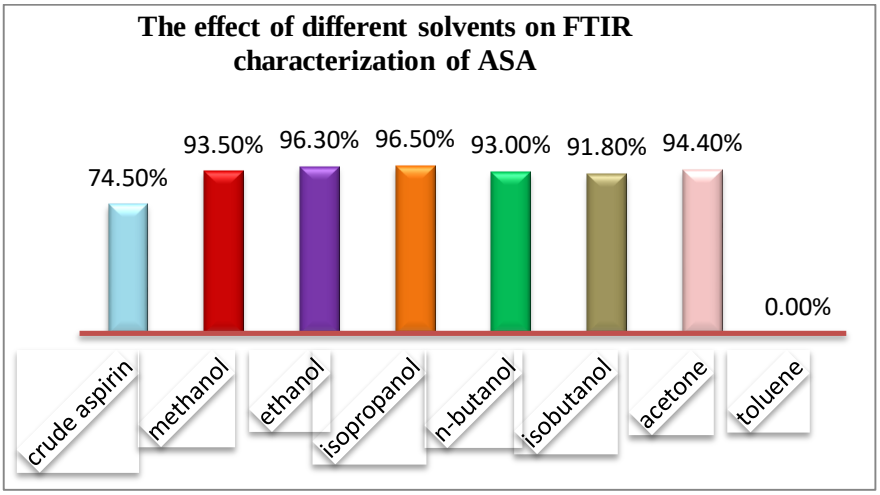



**Figure 9:** The effect of different solvents on FTIR characterization recrystallized aspirin

Obtained products have a satisfactory recrystallisation result in terms of purity, as can be seen from the values of their melting points (**Figure 10**.) corresponding to the melting point of the standard of acetylsalicylic acid. Increasing concentration of alcohol leads to a slight increase in melting point, which goes to136.9 °C. Using 10-50% mixtures of solvent, synthesized samples of acetylsalicylic acid have the melting point which is corresponding to the highest standard of pure aspirin (136°C).

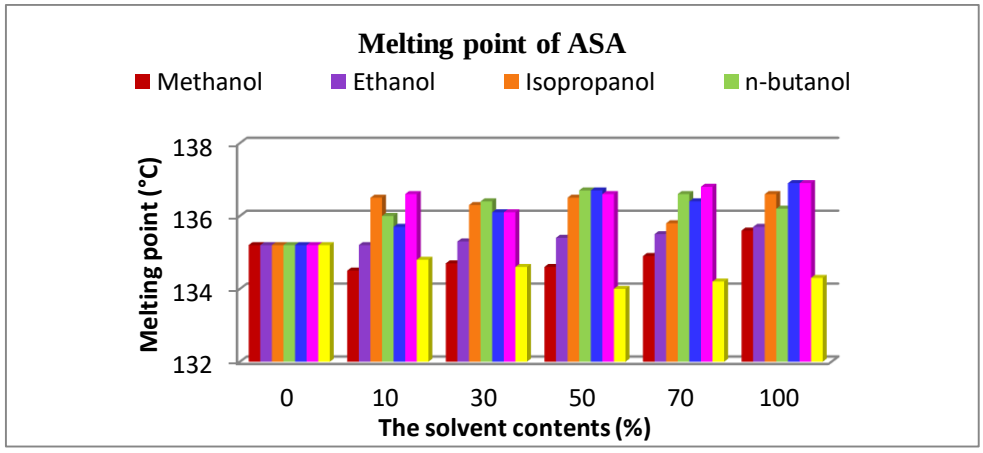



**Figure 10:** Melting points of recrystallized acetyl-salicylic acid (ASA)

The use of methanol and ethanol in the form of binary mixtures with water of various percentage ratios, results in recrystallization of acetyl-salicylic acid samples which yield increases with increasing concentration of methanol or ethanol. **Figure 11** shows that by increasing the content of isopropanol in binary mixtures with water, recrystallization yield decreases. A slight decrease in the yield of acetyl-salicylic acid produced using 30% strength of the binary mixture, which continues by the application of the 70% and 100% isopropanol content that gives the lowest yield. The reason may lie in the fact that isopropanol is the alcohol who have a longer and more ramified hydrocarbon chain relative to the methanol and ethanol, thus it is a less polar. In support of this fact is that the isopropyl by its dielectric constant (18.2) close to the limits of non-polar solvents[15] thus, the electrostatic forces between the molecules are larger, but the solubility is reduced. Using binary mixture of n-butanol/water and isobutanol/water in different percentages for recrystallization, the yield of obtained samples decreases with increasing percentage content of alcohol. Using binary mixture acetone /water as is seen from the diagram, 50% solution have the best influence to yield of recrystallized aspirin. Using toluene as the non-polar solvent for recrystallization, yield of recrystallization of acetylsalicylic acid is decreased[14].

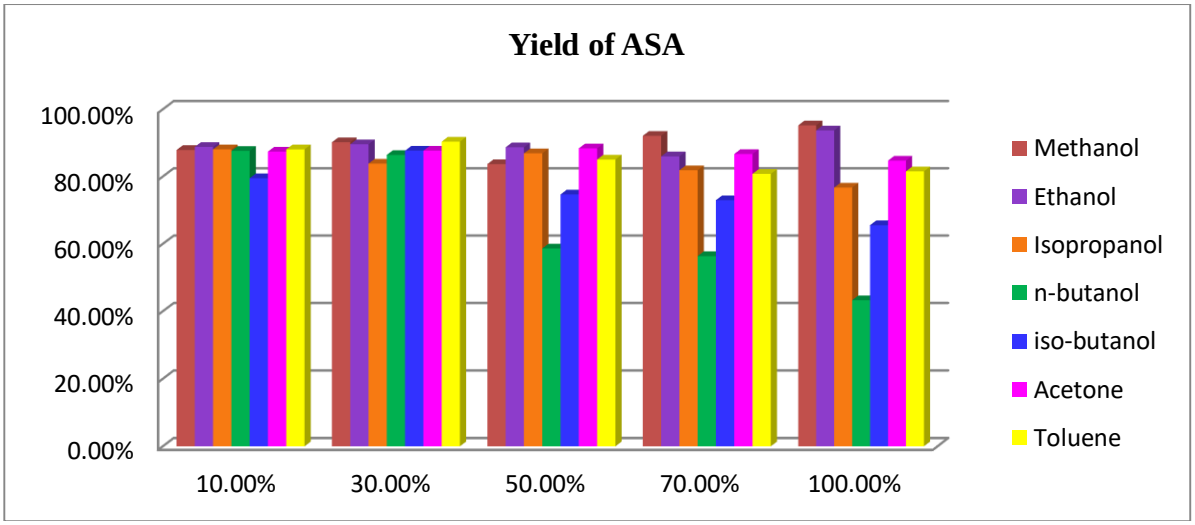



**Figure 11:** Effect of different solvents to the yield of the synthesized acetyl-salicylic acid

The FTIR spectar of the synthesized samples of acetyl-salicylic acid (**Figure 12.)** show peaks in 1630 cm-1, which can identify as an ester group of molecules aspirin. The spectrum shows the presence the maximum of absorbance in the area of 1625-1590 $cm^{-1}$ who belonging to C=C bond in benzene ring. Weak vibration in 2800-2600 $cm^{-1}$ belonging to the OH-group of carboxylic acid. Absorption peak which occurring at 2954.2 cm-1 is belong to C-H bond which is present in the molecule of aspirin[12]. Peak in 3200 $cm^{-1}$, derives from the phenolic OH groups of residual molecules of salicylic acid who represents impurities in the product. Interpreting the IR spectra of the obtained samples of acetylsalicylic acid after the first recrystallization from methanol and ethanol and comparing by software with the IR spectrum of the standard of acetyl-salicylic acid was found matching IR spectra over 90%. By comparing the percentage of crude FTIR correspondence of acetyl-salicylic acid (74,5%), it is seen that recrystallization increase the purity of the product. Using of different concentration of methanol and ethanol for recrystallization synthesized acetylsalicylic acid leads to characteristic changes in the FTIR characterization of the samples.

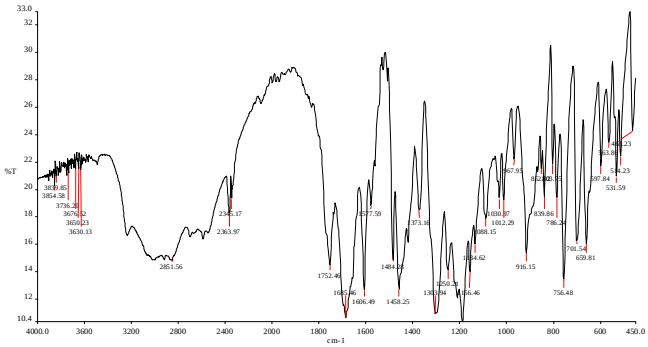


Figure 12. The FTIR spectrum of crude acetylsalicylic acid synthesized from a commercial salicylic acid

**Figure 13** shows that 50% of the binary mixture of methanol and ethanol with water have the most notable effect on a FTIR characterization, wherein the methanol have the lowest and the ethanol gives the highest maximum correspondence. 70% aqueous mixture and pure solvent methanol and ethanol have a similar FTIR characterization that is not significantly different from the lower percentage relationship. This percentage ratio have the most conspicuous increase in hydrocarbon chain, or hydrophobic parts which is resulting in clearer qualitative ribbons in the FTIR spectrum when is using ethanol as a solvent. This is supported by the value of the dielectric constant of ethanol (22.4) and methanol (32.6), which show that ethanol with a lower dielectric constant and long hydrophobic chain, in 50% mixture with water, better balances the polar effect water, which favors the amphiphilic character of aspirin and results in better FTIR characterization and better yield. Results of FTIR characterization of acetyl-salicylic acid clearly show that the 30% and 50% binary mixtures of isopropanol and water is most optimal in the course of recrystallization of acetylsalicylic acid.

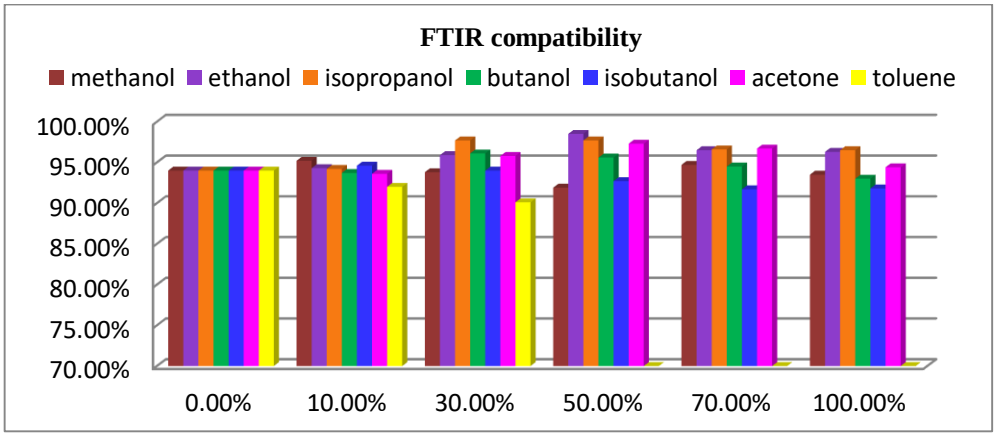
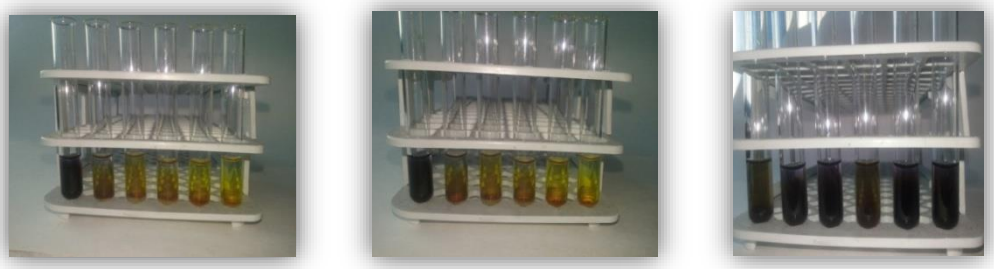



**Figure 13:** Effect of different concentrations of various solvent to FTIR characterization of the synthesized acetyl-salicylic acid

Colorimetric method shows that the samples after recrystallization from isopropanol, were absent impurities such as salicylic acid, so we can conclude that the isopropanol gives satisfactory parameters in terms of purity of obtained samples. (**Figure 14.)**



*Isopropanol* *acetone* *toluene*

**Figure 14:** Verification the purity of recrystallized acetylsalicylic acid by colorimetric method

Each alcohol consisting of hydrocarbon chain and it is non-polar and has OH group which is a polar. Increasing length of hydrocarbon chain decreasing the polarity of alcohol and reduce their capability of construction of hydrogen bonds and water solubility. By increasing the nonpolar part (hydrocarbon chain) and weight, alcohol molecules are tightly packed together and that require more power to overcome the bonds between molecules. Starting from the alcohol with four or more carbon atoms, the aqueous solubility decreases because of hydrophobic interaction hydrocarbon chains become stronger than the interaction of hydrophilic hydroxyl groups.

**Characterization of acetylsalicylic acid obtained from a natural sources:** The main component in the synthesis of aspirin is salicylic acid. The natural way of getting salicylic acid is isolation from oil of wintergreen, which contains 99% of methyl salicylate. Salicylic acid which obtained by the hydrolysis reaction from oil of wintergreen is used in the synthesis of acetyl-salicylic acid. Characterization of acetyl-salicylic acid obtained by recrystallization from various solvents involves the examination of the influence of polarity and chain length of solvent on the purity and yield of the resulting products. The use of methanol and ethanol in the form of mixtures with water in various concentration, which is used for recrystallization of aspirin obtained from isolated salicylic acid, resulting in formation of samples where is FTIR percentage characterization increased with increasing content of alcohol in binary mixtures and it is visible on **Figure 15.**

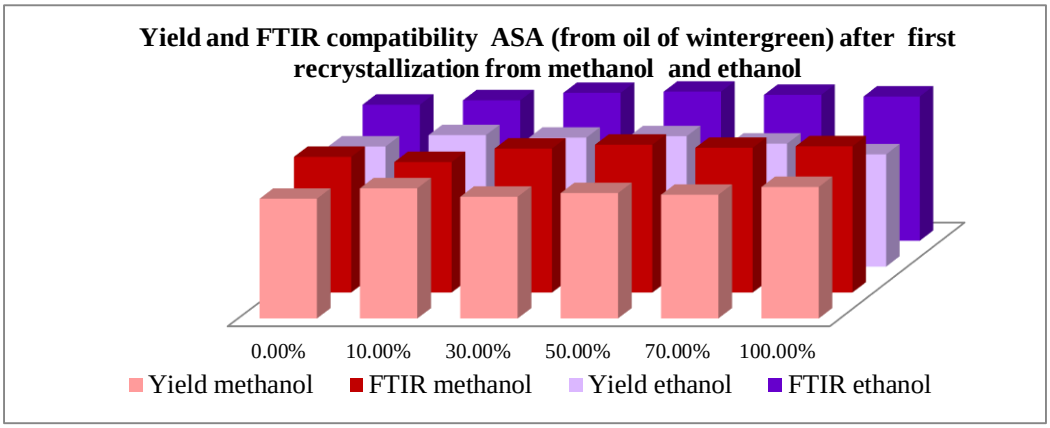



**Figure 15:** The effect of different percentage ratio of methanol/water and ethanol/water to FTIR characterization recrystallized acetylsalicylic acid (oil of wintergreen) after first recrystallization

Considering the amphiphilic character of the acetyl-salicylic acid, the use of the binary mixture of ethanol/water (30%, 50%, 70%) have the optimal effect on the preparation of pharmaceutical active compound with high purity and FTIR compatibility. Double recrystallization with pure methanol and ethanol it is obtained a high purity of pharmaceutically active compound with high percentage of FTIR correspondence which is 98.2% shown in **Figure 16**.

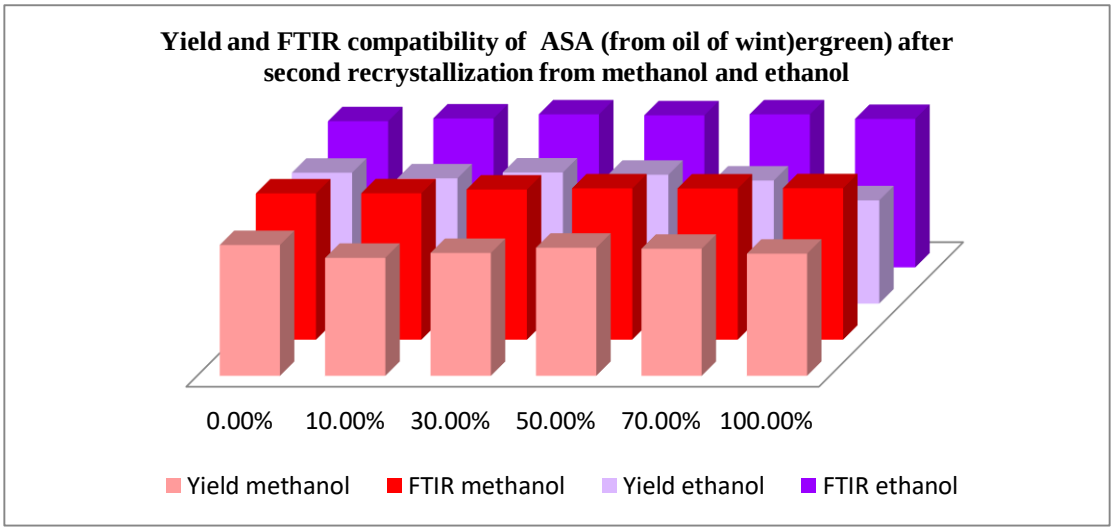



**Figure 16:** The effect of different percentage ratio of methanol/water and ethanol/water to FTIR characterization recrystallized acetylsalicylic acid (oil of wintergreen) after second recrystallization

In support of this is results obtained by determining the melting point and examining the presence of salicylic acid using iron (III) chloride. (**Figure 17.)** Salicylic acid as the main impurity of acetyl-salicylic acid in the presence of reagents, gives purple color. It can be noticed that the impurities present in the samples when is used binary mixtures with a higher content of water compared to alcohol (10% and 30% binary mixture) for recrystallization

**a** **b**

**Figure 17:** Colorimetric test of purity of acetyl-salicylic acid (from oil of wintergreen) recrystallized from a) methanol and b) ethanol

In addition, the measured values of the melting point of these samples are slightly lower compared to the reference value, which also confirms the presence of impurity. **Figure 18** show the linear increase of the melting point which is approaches the reference value of melting point by increasing the content of methanol in a binary mixture.

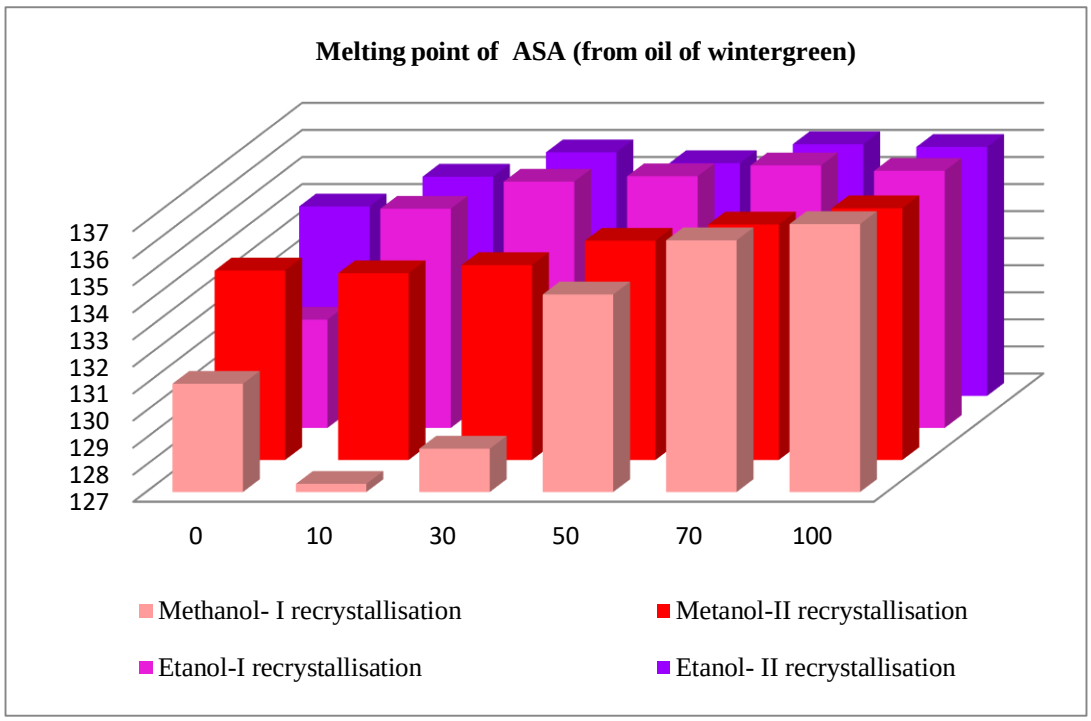



**Figure 18:** The effect of different percentage ratio methanol/water and ethanol/water to the melting point of the purified acetylsalicylic acid (from oil of wintergreen)

Considering the value of the melting point (which corresponds to a reference value of melting point of aspirin), a high percentage of overlap FTIR (synthesized sample with standard CRS) and a colorimetric method, it is seen that 30% binary mixture of ethanol and water, have an optimum influence on the purity of recrystallized samples. From the previous diagram it is seen that the use of binary mixtures that having the same and more part of methanol relative to water (50%, 70%, 100%) results in higher purity of the samples occurred due to the FTIR characterization, a colorimetric method and a melting point, so we can conclude that the this is the most suitable solvents for recrystallization acetyl-salicylic acids derived from renewable sources (oil of wintergreen).

However, comparing the FTIR characterization for crude products of synthesis, it can be noted that the synthesis of aspirin from salicylic acid derived from oil of wintergreen, produce a pharmaceutically active substance which without further purification have acceptable levels of purity of synthesized pharmaceutically active substances. This is supported by the FTIR analysis of crude sample and standard sample and it is shown in **Figure 19.**

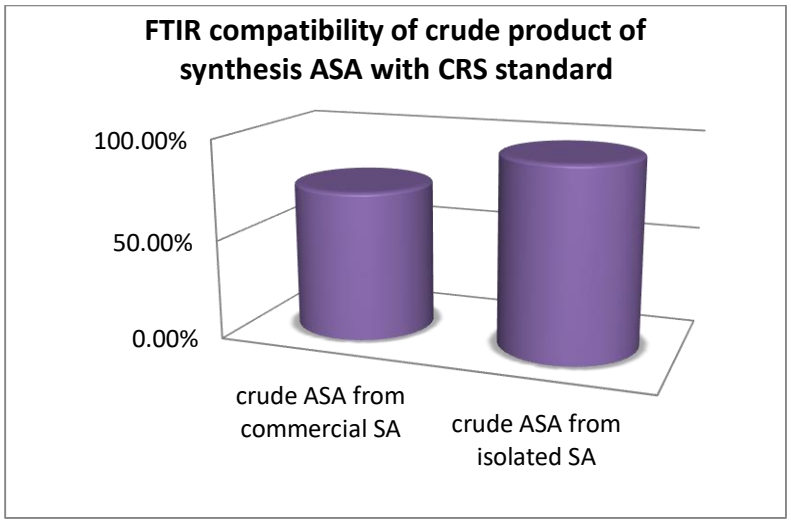
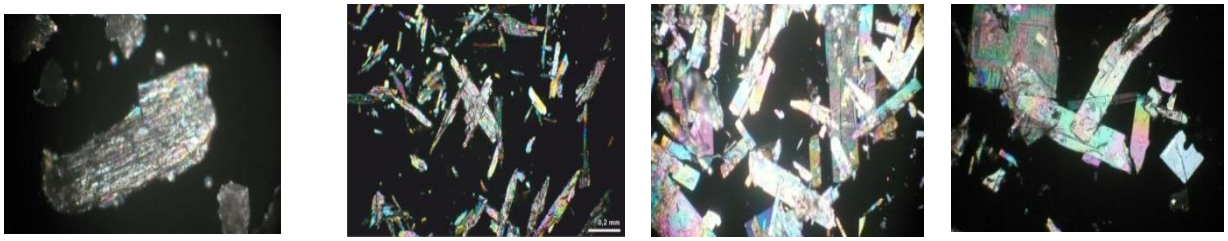



**Figure 19:** FTIR characterization of acetylsalicylic acid (from commercial and isolated salicylic acid)

**The influence of the nature of the solvent on the morphology of acetyl-salicylic acid:** By using optical microscopy it is possible to investigate the impact of the type and nature of the solvent in the process of recrystallization on the morphological characteristics of acetyl-salicylic acid. Using of different solvents, at identical conditions of crystallization, it is possible to modify the crystalline form as a result of interaction of different solvent molecules and a surface of the crystal. Hydrogen bonds play an important role in the formation of crystalline forms of aspirin. In the crystalline state, aspirin molecules are connected in parallel chains, hydrogen bonding between the carboxyl groups thereof. The morphological appearance of the pharmaceutically active substance is changed depending on the nature of the solvent. Polar solvents such as methanol and ethanol, due to hydrogen bonding with acetyl-salicylic acid, causes growth of crystal along the x and y axis. (**Figure 20).** Therefore, aspirin is crystallized in the form of a rectangular plates[13].



**a** **b** **c** **d**

**Figure 20:** Morphological appearance recrystallized acetyl-salicylic acid a) in methanol b) in ethanol c) from isopropanol d) from acetone

Nonpolar solvents, inhibit the growth of crystals along the x-axis and facilitate its growth along the y-axis. As a result, occur a needle-shaped crystals of aspirin and it is shown in **Figure 21**.

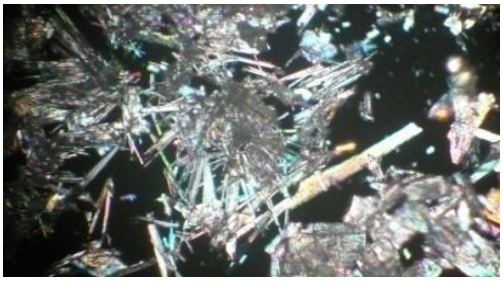


**Figure 21:** The morphological appearance of acetylsalicylic acid recrystallized from toluene

## CONCLUSION

- Acetyl-salicylic acid, the active pharmaceutical compound is one of the most accessible and the most used drugs in the treatment or the prevention of various diseases;
- Acetyl-salicylic acid occurs during the esterification reaction of salicylic acid with acetic anhydride, in the presence of sulfuric acid as a catalyst
- An alternative way of getting aspirin is from renewable sources, ie. hydrolysis of wintergreen oil it is isolated salicylic acid, which as the main crude material can be used for the synthesis of so-called ‘’natural aspirin’’
- Methods for characterization of crude products and by comparison with the standard, we can conclude that the synthesis from oil of wintergreen occurs aspirin with higher purity compared to the product obtained from commercial funds
- Using lower alcohols (methanol, ethanol, isopropanol) in the form of binary mixtures with water for recrystallization of crude aspirin, creating products whose purity increases with increasing concentrations of alcohol. Optimal binary mixture, when it comes to the methanol is 70% solution and pure methanol, in the case of applying ethanol the best results give the 50% of the binary mixture, while using isopropanol it is 30% and 50% solvent system. It can be concluded that decreasing the solvent polarity decreases the content of the acetyl-salicylic acid in optimal mixtures for recrystallization.
- Using binary mixture of n-butanol/water and isobutanol/water in different percentages for recrystallization, yield and FTIR correspondence obtained samples decreases with increasing percentage content of alcohol. Furthermore, branching chain of alcohol unfavorably affects to the FTIR correspondence of obtained samples.
- Based on the measured values of melting points, FTIR and colorimetric correspondence tests it is visible that the samples of acetyl-salicylic acid obtained in the process of recrystallization of the crude aspirin using acetone in 50% solution, show a satisfactory degree of purity
- The non-polar solvents such as toluene, are not suitable for recrystallization of acetylsalicylic acid
- Synthesizing the aspirin from wintergreen oil followed by purification using a binary mixture (methanol/water and ethanol/water) at different ratios, resulting in samples occurs in a lower yield compared to the samples obtained from the commercial salicylic acid

- Experimentally determined that the optimal ratio of the recrystallization of "natural aspirin" 50-70% solution of methanol and as well as pure methanol, while when it comes to ethanol, the best results are achieved by applying of 30% solution of ethanol.
- The influence of nature of solvent during recrystallization the morphology of crystals of aspirin, it can be concluded that polar solvents cause the formation of plate-like crystals and nonpolar solvents result in the formation of needle-like crystals.

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