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Research Article

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Synthesis, Physico-chemical Control and Formulation of Acetylsalicylic Acid

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Abstract *Acetylsalicylic Acid (ASA)* is the first active pharmaceutical ingredient (API) obtained by synthetic drug chemistry ' Therapeutic Chemistry'. ASA is one of the most commonly used analgesic and antipyretic medication worldwide, having been in clinical use for over 100 years. We synthesized this active pharmaceutical ingredient in Therapeutic Chemistry laboratory of pharmacy department of Sidi Bel-Abbes and the yield obtained is 79.75 %. The physicochemical quality control of the synthesized ASA is carried out according to the requirements of the European Pharmacopoeia 8th edition. The synthesized ASA was formulated as capsules and its content is 100.92 %. This work is an application of "Drug chain" notion; it would be very interesting to introduce it as coordinated practical work of Therapeutic Chemistry and Galenic Pharmacy modules for the third-year pharmacy students and residents in post-graduate.

Keywords Acetylsalicylic Acid; Aspirin; Active Pharmaceutical Ingredient; Drug Chain; Non-Steroidal Anti-inflammatory; Physicochemical Quality

1. Introduction

Acetylsalicylic acid (ASA), better known by the trade name of *Aspirin*, is the active substance in many medicines with analgesic, antipyretic, anti-inflammatory and antiplatelet properties [1]. It is one of the most commonly used analgesic and antipyretic medication worldwide, having been in clinical use for over 100 years [1,2]. ASA is a non-steroidal anti-inflammatory agent which binds to and acetylates serine residues in cyclooxygenases, resulting in decreased synthesis of prostaglandin, platelet aggregation and inflammation [3]. In high doses, *ASA* can cause moderate to marked serum aminotransferase elevations occasionally with jaundice or signs of liver dysfunction, and in lower doses in susceptible children with a febrile illness aspirin can lead to Reye syndrome [4,5,6]. In 1897, Felix Hoffmann, a German chemist who works for the Bayer laboratories, was the first to obtain pure *ASA* and to carry out its industrial production. The patent for *ASA* (figure 1) was filed by the Bayer Company in 1899, under the trade name *"Aspirin"* [1,7,8].

In this article, we synthesize the ASA as an active pharmaceutical ingredient (API), we control its physicochemical quality according to requirements of the European Pharmacopoeia eighth edition (Eur Ph 8th Ed) and we formulate it as capsules which have been controlled.

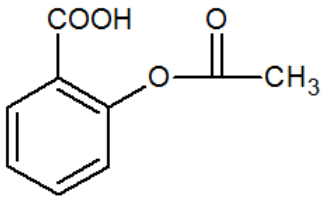

Figure 1: Chemical structure of ASA [1,8]

2. Materials and Methods

2.1. Synthesis of ASA

2.1.1. Salicylic Acid acetylation by acetic anhydride

7 mL acetic anhydride was introduced into dry Erlenmeyer flask 125 mL using funnel; 5 g of salicylic acid was added while rotating Erlenmeyer to dissolve the salicylic acid in acetic anhydride. Four drops of sulfuric acid were added as catalyst to speed up reaction rate. The Erlenmeyer flask was immersed in water bath set at 60 °C for 15 to 20 minutes [9,10].

2.1.2. Isolation of impure ASA by crystallization

The Erlenmeyer was removed from water bath and allowed to cool while stirring occasionally. Then, we gradually added 75 mL cold water, while stirring violently. The precipitation of impure *ASA* was observed little by little. We placed Erlenmeyer in crystallizer to accelerate precipitation. At the end, we filtered impure *ASA* and dried it in oven [9,10].

2.1.3. Purification of impure ASA by recrystallization

The impure ASA precipitate was returned to its initial container, 15 mL ethanol 96 % was added and container was immersed in water bath set at 60 °C, while stirring the impure ASA was gradually dissolves. 38 mL hot water at 60 °C was added and the mixture was stirred well until completely clear. Subsequently, the container was covered with parafilm and allowed to cool for 24 hours. The pure *ASA* was filtered and dried in oven and the amount obtained was weighed in order to calculate the synthesis yield [9,10].

2.2. Quality control of synthesized ASA

The control of synthesized ASA is carried out according to requirements of the Eur Ph 8th Ed [11].

2.2.1. Organoleptic characteristics and solubility

We checked appearance and odor of synthesized ASA, as well as its solubility in water and in ethanol 96 % according to requirements of the Eur Ph 8th Ed [11].

2.2.2. Melting point measurement

The melting point is a specific physical character of each solid substance; it plays an important role for its identification. The measurement was made using a device called: Köfler bench.

2.2.3. Characterization by chemical processes

A. Identification reaction of functional group

We test absence of phenol group in ASA and its presence in salicylic acid by the staining reaction with ferric chloride solution 2 %. In first tube we added 10 mg synthesized *ASA* and in the second 10 mg salicylic acid. 1 mL ferric chloride solution 2 % was added in each one; we agitated and observed the coloration [11].

B. Deacetylation reaction

0.2 g synthesized ASA with 4 mL calcium hydroxide was heated to boiling for 3 minutes. We allowed solution to cool, 5 mL dilute sulfuric acid was added, filtration and drying of solution at 100 °C. Finally, the melting point of obtained product was determined [11].

2.2.4. Identification by thin-layer chromatography

The mobile phase was prepared from cyclohexane and ethyl ether (75:25). Three solutions of synthesized ASA, standard ASA and salicylic acid were prepared by dissolution 0.5 mg in 3 mL ether **[11].**

2.2.5. Content determination by ultraviolet spectroscopy

Standard solution prepared by dissolving 0.25 g standard ASA in 25 mL acetonitrile and test solution by dissolving 0.25 g synthesized ASA in 25 mL acetonitrile. The absorbance lectures were taken at wavelength λ: 275 nm [11].

2.2.6. Loss on drying

0.1 g ASA is placed in watch glass and it is drying at 105 °C in oven until constant mass [11].

2.3. Formulation of synthesized ASA as capsules form

30 capsules were prepared according to below formula:

Acetylsalicylic acid ……50 mg

Caffeine ……15 mg

Excipient (lactose) …….. SQF 01 capsule [12].

The apparent volume of ASA and caffeine weighed was reported on the capsule filling table "Abacus", the capsule number was determinate graphically by extrapolation and the diluent amount "lactose" required was calculate.

2.4. Control of conceived capsules

2.4.1. Mass uniformity

15 conceived capsules were weighed each one, on the other hand, 15 empty capsules were weighed. The powder mass contained in 15 conceived capsules, the average of 15 obtained values and the limit deviation were calculated [13].

2.4.2. Content uniformity

The ASA content determination is carried out by ultraviolet spectroscopy. Standard solution: 0.25 g standard ASA in 25 mL acetonitrile. Test solution: 0.408 g powder of conceived capsule in 25 mL acetonitrile **[13].**

2.4.3. Disintegration time

This test was not carried out because the conceived capsules are made of plastic **[13].**

3. Results and Discussion

3.1. Synthesis of ASA

The different steps of *ASA* synthesis are illustrated in **Figure 1 and** 2.

Figure 1: Salicylic acid acetylation and isolation of impure ASA by crystallization

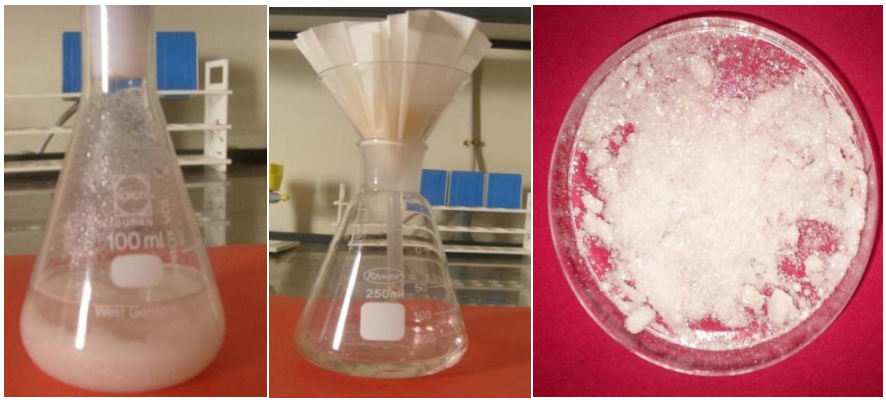

Figure 2: Purification of impure ASA by recrystallization and drying

The calculated synthesis yield of ASA is 79.75 %.

3.2. Quality control of synthesized ASA

3.2.1. Organoleptic characteristics and solubility

Appearance: the synthesized ASA is a white crystalline powder with acetic acid odor (figure 3).

Solubility: the solubility test showed that the synthesized ASA is partially soluble in water and completely soluble in ethanol 96 %.

Figure 3: Organoleptic characteristics of ASA

3.2.2. Melting point measurement

The measurement of melting point revealed an average value **143.2** °C; this value complies with standard of European pharmacopoeia which requires value 143 °C.

3.2.3. Characterization by chemical processes

A. Identification reaction of functional group

Tube A develops a yellow color which does not turn purple, therefore absence of phenol group contrary to tube B which develops a violet color. This test confirms that synthesized Acetylsalicylic Acid does not contain salicylic acid impurities (figure 4).

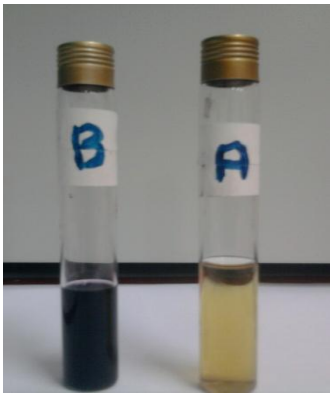

Figure 4: Identification reaction of functional group

B. Deacetylation reaction

After drying the product obtained in oven, its melting point obtained is 157.5 °C. This value complies with that required by the Eur Ph 8th Ed which must be between 156 °C and 161 °C. The melting point obtained corresponds to that of salicylic acid, which allowed us to deduce that the product obtained by this deacetylation reaction is salicylic acid (figure 5).

Figure 5: Deacetylation reaction

3.2.4. Identification by thin-layer chromatography

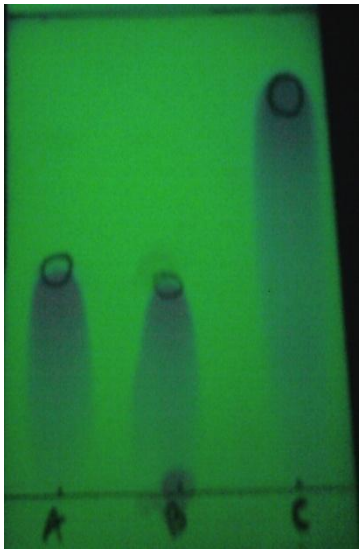

Figure 6: Identification by thin-layer chromatography

Two spots (A and B) of synthesized ASA and standard ASA were observed; they have the same fontal report which is 0.4. The spot corresponding to synthesized ASA is similar in position, coloration and dimensions to the spot of standard ASA. Spot absence at the same height as that of salicylic acid solution (C), so synthesized ASA is pure **(figure 6).**

3.2.5. Content determination by ultraviolet spectroscopy

After calculation, the pure ASA content is 99.75 %, value is included in interval [99.5 %-101 %] required by the Eur Ph 8th Ed.

3.2.6. Loss on drying

The loss on drying of synthesized ASA is 0.378 %, value lower than the required standard 0.5 %.

3.3. Formulation of synthesized ASA as capsules form

The apparent volume is 0.24 mL, after its extrapolation on the diagonal and the y axis, the capsule corresponding to the formulation of synthesized ASA is the capsule N° 3 (figure 7).

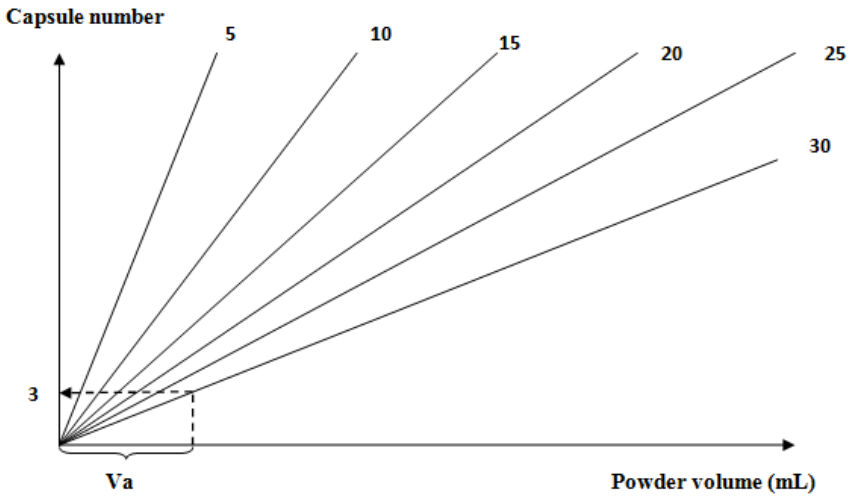

Figure 7: Extrapolation of apparent volume for capsule number determination

The diluent amount is 0.48 g for 30 capsules (figure 8) and the formula for all capsules is as follows:

Acetylsalicylic acid ……..1.50 g

Caffeine ……..0.45 g

Excipient (Lactose) ……...0.48 g

Figure 8: Different steps of capsules preparation

3.4. Control of conceived capsules

3.4.1. Mass uniformity

The mass uniformity results obtained are summarized in **table I.**

Table 1: Mass uniformity results.

	Mass			**Mass uniformity**		
				T = 10 %		
Capsules	**Empty Capsules (g)**	**Filled Capsules (g)**	**Powder per Capsule (g)**	**Discard (%)**	**T<Discard (%) <2T**	**2T <Discard (%)**
1	0.05	0.1369	0.0869	-4.5		
2	0.05	0.1389	0.0889	-2.3		
3	0.05	0.1449	0.0949	4.28		
4	0.05	0.1473	0.0973	6.92		
5	0.05	0.1385	0.0885	-2.75		
6	0.05	0.1417	0.0917	0.75		
7	0.05	0.1442	0.0942	3.5		
8	0.05	0.1358	0.0858	-5.7		
9	0.05	0.1344	0.0844	-7.25		
10	0.05	0.1339	0.0839	-7.8		
11	0.05	0.1457	0.0957	5.2		
12	0.05	0.1442	0.0942	3.5		

13	0.05	0.1422	0.0922	1.3		
14	0.05	0.1395	0.0895	-1.6		
15	0.05	0.1478	0.0978	7.5		
mp = 0.0910 g = 91mg				**Total Number of Capsules**	**0**	**0**
If mp > 300 mg Tolerance interval (T) = 7.5 % If mp < 300 mg Tolerance Interval (T) = 10 %				**Rules** **Decision Conformity**	**2 Capsules maximum** **CONFORM**	**None**

None mass deviates from the average mass by 10 %, and none mass also deviates by more than the double that percentage. According to the Eur Ph standards, the conceived capsules comply with the mass uniformity test.

3.4.2. Content uniformity

The ASA content in the conceived capsules is 100.92 %, value in accordance with the standards required by the Eur Ph [85 %-115 %].

4. Conclusion

The *ASA* was synthesized and the calculated synthesis yield obtained is 79.75 %. The physicochemical quality control of synthesized ASA is carried out according to the requirements of Eur Ph 8th Ed. The synthesized ASA was formulated as capsules and its content is 100.92 %. This work is an application of "Drug chain" notion, the pharmaceutical raw material denominate *ASA* was synthesized, controlled and formulated as capsules. As prospects, it would be very interesting to introduce this work as coordinated practical work of Therapeutic Chemistry and Galenic Pharmacy modules for the third-year pharmacy students and residents in post-graduate.

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