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Investigation on the Quality of Aspirin Tablets Manufactured in Different Countries, by Applying The Methods Used in Pharmaceutical Technology

Çeşitli Ülkelerde İmal Edilmiş Aspirin Tabletlerinin Farmasötik Teknolojide Kullanılan Yöntemler ile Kalitelerinin İncelenmesi

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Aspirin has analgesic, antipyretic and anti-inflammatory actions and it is used for the relief of the less severe types of pain such as headache, neuralgia, neuritis, rheumatic joint pains, myaligas and in the treatment of acute and chronic rheumatic states.

Because of its easy availability, cheapness, low toxicity and the less side effects, it is the most commonly used of all analgesics (1, 2, 3, 4). It is reported that serious gastric effects and side effects as tinnutus and sensitivity are observed in patients who have been using aspirin for a long time. The mechanism of bleeding in gastrointestinal tract after administration of an aspirin tablet is quite complicated. The more often occurance of bleeding and erosion after administration of an aspirin tablet, observed in gastrointestinal tract in patients, who have low pH, are attributed to the stomach HCl. Even with the analgesic doses, aspirin inhibits the platelet function in the body and extends the bleeding time (2, 3, 5).

It is suggested that aspirin with milk and food reduces the irritating effect. Since it may cause metabolictic diseffects, aspirin is not recommanded for children below 1 year of age (1). Adults can take 0.3 to 1.0 g. and up to 4.0 g. daily. In the treatment of acute rheumatism, this can be increased even to 8.0 g. daily, in divided doses (6). In horses and cows 25 to 50 g., in sheep and pigs 1.0 to

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3.0 g., in dogs 0.25 to 1.0 g. and in cats 0.1 to 0.2 g. dosages are used (3).

Tablet form is the most used dosage form of aspirin among the other dosage forms of aspirin such as aspirin suppository and aspirin capsule.

Aspirin is the first recommended medicine in the case of indispositions in our country and also in many other countries. Presently, people can get aspirin tablets from any drugstore or grocer's without a prescription and know how to use it. However, he takes certain means for avoiding its side effects. For example, foreign aspirin tablets are usually preferred to domestic product. Because, it is believed to have less side effects. This causes domestic aspirin tablets to be cheaply available compared to expensive availability of foreign aspirin tablets.

43 persons were asked whether they preferred domestic or foreign aspirin tablets, and their reasons for preference. Most of the people who answered, were professional pharmacists and graduate students of pharmacy. 22 of them preferred domestic aspirin tablets, while the remaining 21 preferred foreign aspirin tablets.

The reasons of the preference for domestic aspirin tablets were contribution to domestic industry, the fact that domestic aspirin tablets have the same effect and prevent the unnecessary foreign currency payment. Those, who preferred foreign aspirin tablets, indicated that it might have been manufactured with better production techniques and better quality controls and as a result those factors caused better effects.

The question of "Which aspirin tablet is better?" and "Is the preference due to psychological reasons or is it because of better technology and hence better quality?" may be arised. These questions led us to make the present study.

In this study, the quality control methods, used in pharmaceutical technology, were applied to domestic and foreign aspirin tablets, and the results based on the experimental data. The results were compared with each other and with the limits stated in the pharmacopoeias, which were accepted as reference in this study.

EXPERIMENTAL

MATERIAL and METHODS

In tablet technology, appearance, porosity, color stability, mechanical strength (hardness, friability, fracture resistance, bending strength, and crushing strength), weight variation, content uniformity, disintegration time and dissolution rate (7, 8) are the most important factors used both during production steps and quality controls. Appropriate test methods, based on the above factors, are used (6, 9, 10, 11, 12, 13, 15) and the qualities of the tablets are determined according to the results.

Aspirin (ASA) tablets, used in the experiments, were obtained from Switzerland, W. Germany, England, France, Belgium, the U.S.A., Iran, and Turkey[1]. Among different types of aspirin tablets, like effervescent, buffered, sustained release and plain, only the last one was chosen to be tested.

The following test methods were conducted on the tablets according to the U.S.P. XVIII and B.P. 1973. Since, U.S.P. XVIII gives the description of the quality control methods comprehensively, it is chosen a basic pharmacopoeia for our experiments in this study. B.P. 1973 was chosen as a second basic pharmacopoeia, because, some of the methods described there, are easy to be applied. However, the procedure and the limits of the hardness and friability tests for tablets do not appear in the pharmacopoeias, we performed tests according to the literature (16), and we compared the results with each other.

Thickness and Size of the Tablets (6) - The thickness and the diameter of the tablets were measured with a callipers[1] on the ten tablets of aspirin, manufactured in the above countries. The mean values are shown in Table I.

Weight Variation of the Tablets (13) - The weights of twenty tablets of each country were determined according to the method described in the U.S.P. XVIII. The results are shown in Table II.

1 Turkey I and Turkey II represent the plain tablets of two different manufactories in Turkey.

2 Callipers, NSK, Nippon Sokutei, Hyogo Japan.

RESULTS

Table I. Some Physical Properties of the Tablets.

Country of Manufacture	Tablet Form	Mean Tablet Thickness cm	Mean Tablet Diameter cm	% Wt.Loss at 100 r. p.m.	Mean Tablet Hardness kg
Turkey I	Convex Face	0.5105	1.2100	1.35	13.350
Belgium	Convex Face	0.4995	1.2205	1.50	13.625
France	Flat Face	0.3415	1.2850	1.02	10.975
U.S.A.	Convex Face	0.4370	1.0450	1.30	9.175
W.Germany	Convex Face	0.5140	1.2185	1.58	8.535
Switzerland	Convex Face	0.5200	1.2225	1.54	7.750
Turkey II	Flat Face	0.4850	1.2055	4.94(4)*	6.175
Iran	Convex Face	0.5215	1.2155	1.52	5.550
England	Convex Face	0.3845	1.1380	2.62	4.695

* The number of the capped tablets.

Table II. Weight Variation of the Tablets.

Country of Manufactüre	Mean Weight g	Standard Deviation ∓ mg	Relative Deviation %
Turkey I	0.6177	17.6	2.8
Turkey II	0.5419	11.0	2.0
Belgium	0.6176	12.0	1.9
France	0.5684	8.7	1.5
England	0.3877	5.4	1.4
U.S.A.	0.4007	5.3	1.3
Iran	0.6246	4.9	0.8
W. Germany	0.6214	5.2	0.8
Switzerland	0.6292	4.0	0.6

Content Uniformity (6) - Acetylsalicylic acid (ASA) content of each aspirin tablet was determined according to the method described in B.P. 1973. The test was repeated on three tablets and then the mean was calculated. The results are shown in Table III.

Table III. Content Uniformity of the Tablets

Country of Manufacture	ASA Quantity per tablet		Standard Deviation ∓ mg	Relative Deviation %
	On Label mg	Found mg		
U.S.A.	300	351.9	1.5	0.5
England	324	323.1	1.0	0.3
Turkey II	500	499.7	9.8	2.0
France	500	500.0	6.4	1.2
Belgium	500	503.2	1.1	0.2
W.Germany	500	505.2	1.5	0.3
Turkey I	500	505.6	4.9	0.9
Switzerland	500	506.9	0.6	0.1
Iran	500	512.3	3.9	0.8

Salicylic acid Content (6) - The tests for comparison of salicylic acid (SA) were performed according to the B.P. 1973. The color of the solutions prepared from the tablets, were compared with the color of the standard solutions. The colors of the English and Turkish I samples were darker than the color of the standard solution.

Disintegration Test (13) - Disintegration times were determined with a disintegration tester[1] according to the conditions specified in the U.S.P. XVIII. The tablets, manufactured in England, in Turkey I, in W. Germany, in Switzerland, in the U.S.A., in Iran, in Turkey II, in France, and in Belgium, disintegrated in 8, 9, 5, 13, 14, 15, 15, 15, 19 and 22.5 seconds respectively.

Dissolution Rate (13) - Dissolution rate of ASA tablets were determined with a dissolution rate tester[1] according to the U.S.P. rotating basket method. The dissolution medium consisted of 900 ml of 0.1 N HCl. The test was conducted at 55 r.p.m., and at 37∓0.5 °C. Although for ASA tablets, the agitation intensity corresponding to the in vivo dissolution rate, is suggested to be 55∓10 r.p.m. (17), the experiments were conducted at 50 r.p.m. Because the Erweka Dissolution Rate Tester could not be set to 55 r.p.m. The absorbance of the samples, which were taken from the medium at 5, 15, 30, 45, and 60 minutes, were measured with a spectrophotometer[1] at 276 nm for ASA, and 303 nm for SA. The amonut of ASA and SA containad in each sample were calculated from the concentration versus absorbance plots (Fig. 2 and Fig. 3) The test was repeated on three tablets of each country and the mean was calculated. The results are shown in Tables IV. 1 - IV. 9.

Hardness of the Tablets (16) - Hardness of the tablets were determined with a hardness tester[1] according to the literature (16). The results are shown in Table I and in Fig. 3.

Friability (16) - Friability of the tablets were determined with a friabilator[1] with a speed of 27–28 r.p.m., according to the method described in the literature (16). Ten tablets of each country were

[3]Disintegration Tester, Erweka, Type ZT 2.

[5]Ultraviolet Spectrophotometer, Pye Unicam SP 1700, Unicam Instruments Limited, Cambridge.

[6]Monsanto Hardness Tester, Monsanto Chemicals, St. Louis 4, Missouri.

[7]Roche Friabilitor, Erweka.

weighed and then were tested. The tablets were weighed again after 100 revolutions. The percent loss of the tablets were calculated from the difference of the two weighings. The results are shown in Table I.

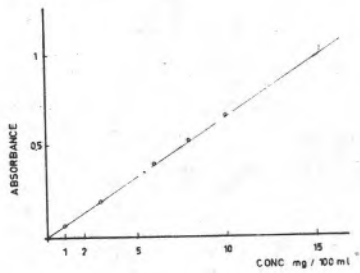

Fig. 1. Aspirin standard calibration curve.

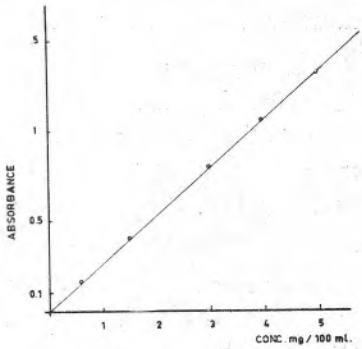

Fig. 2. Salicylic acid standard calibration curve.

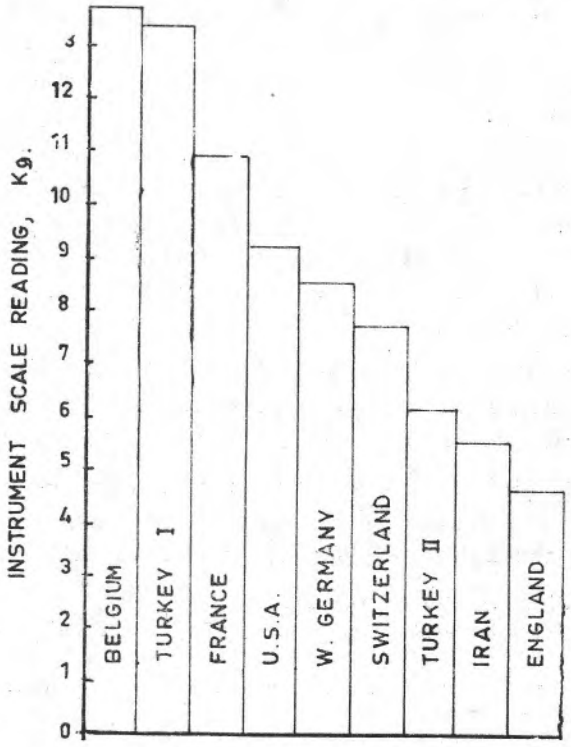

Fig. 3. Hardness of Aspirin plain tablets.

Table IV. 1. Dissolution Rate of ASA Tablets Manufactured in the U.S.A.

Time min.	Average Cumulative Quantity Dissolved mg	Standard Deviation ∓ mg	Relative Deviation %	Percent Dissolved
5	75.9	12.9	16.9	25.3
15	151.6	20.0	13.2	50.5
30	224.1	10.2	4.5	74.7
45	269.1	2.0	0.7	89.7
60	3295.	4.3	1.5	98.4

Table IV. 2. Dissolution Rate of ASA Plain Tablets Manufacturad in England

Time min.	Average Cumulative Quantity Dissolved mg	Standard Deviation ∓ mg	Relative Deviation %	Percent Dissolved
5	76.8	4.3	5.6	25.6
15	136.5	16.8	12.5	45.5
30	214.4	17.9	8.4	71.5
45	259.3	15.5	6.0	86.4
60	285.5	10.7	5.3	95.2

Table IV. 3. Dissolution Rate of ASA Tablets Manufactured in Iran

Time min	Average Cumulative Quantity Dissolved mg	Standard Deviation ∓ mg	Relative Deviation %	Percent Dissolved
5	111.9	9.2	3.2	322.4
15	221.9	1.0	4.6	44.4
30	352.3	15.7	4.4	70.5
45	418.8	20.2	4.8	83.8
60	441.5	22.9	5.2	88.3

Table IV. 4. Dissolution Rate of ASA Tablets Manufactured in W. Germany

Time min	Average Cumulative Quantity Dissolved mg	Standard Deviation ∓ mg	Relative Deviation %	Percent Dissolved
5	117.9	19.0	16.1	23.6
15	215.7	29.9	13.9	43.1
30	339.1	44.7	14.2	67.8
45	395.5	40.0	10.1	79.1
60	433.4	40.4	9.3	86.7

Table IV. 5. Dissolution Rate of ASA Tablets Manufactured in Switzerland.

Time min	Average Cumulative Quantity Dissolved mg	Standard Deviation ∓ mg	Relative Deviation %	Percent Dissolved
5	83.3	8.7	10.4	16.7
15	186.9	11.1	5.9	37.4
30	333.5	18.8	5.6	67.7
45	408.4	22.3	5.3	80.7
60	432.3	14.6	3.4	86.5

Table IV. 6. Dissolution Rate of ASA Tablets Manufactured in Turkey I

Time min	Average Cumulative Quantity Dissolved mg	Standard Deviation ∓ mg	Relative Deviation %	Percent Dissolved
5	97.8	19.5	20.0	19.6
15	195.1	18.2	9.3	39.0
30	308.1	24.7	8.0	61.6
45	374.7	21.1	5.6	74.9
60	430.0	22.5	5.3	86.0

Table IV. 7. Dissolution Rate of ASA Tablets Manufactured in Belgium

Time min.	Average Cumulative Quantity Dissolved mg	Standard Deviation ∓ mg	Relative Deviation %	Percent Dissolved
5	107.4	8.1	7.6	21.3
15	197.6	16.0	8.1	35.5
30	310.1	32.7	10.5	62.0
45	377.6	49.7	13.0	75.5
60	429.1	9.5	2.2	85.8

Table IV. 8. Dissolution Rate of ASA Tablets Manufactured in Turkey II

Time min.	Average Cumulative Quantity Dissolved mg	Standard Deviation ∓ mg	Relative Deviation %	Percent Dissolved
5	103.8	14.6	14.0	20.8
15	198.8	18.8	7.4	39.8
30	306.8	25.3	8.3	61.4
45	361.3	28.3	7.8	72.3
60	407.1	26.7	6.6	81.4

Table IV. 9. Dissolution Rate of ASA Tablets Manufactured in France

Time min.	Average Cumulative Quantity Dissolved mg	Standard Deviation ∓ mg	Relative Deviation %	Percent Dissolved
5	77.4	9.7	12.6	15.5
15	164.7	18.2	11.0	32.9
30	289.2	20.4	7.0	57.8
45	366.3	10.9	4.3	73.3
60	405.7	4.3	1.1	81.1

DISCUSSION

Results obtained from the experiments are shown in Tables I, II, III, and IV.

It is natural that an aspirin tablet, manufactured in a country, has to conform to its own pharmacopoeia. But we needed a competent reference in order to compare all the properties of the tablets in detail. Therefore we accepted the U.S.P. XVIII as the basic reference, since it contains almost all of the test methods and test limits extensively. We used B.P. 1973 as a second reference. Because some of the test methods described there, were simplier than the methods stated in the U.S.P. XVIII.

Considering that the sizes of the tablets containing 500 mg and 300 mg ASA have to be within ∓ 5 % limit of 12.5 mm and 10.5 mm respectively (6), when the results in Table 1 are observed, it can be accepted that, except for the English aspirin all of the tablets were within the limits specified by the U.S.P. XVIII.

The results of the weight variation of the tablets are observed in Table II, indicated that all of them were within the accepted limits, when the limits are set as ∓ 5 % of mean weight for the tablets heavier than 324 mg (6, 13). However, the greatest deviation was observed on the tablets manufactured in Turkey I, while the deviation was smallest for the tablets manufactured in Switzerland.

The test results of ASA content of the tablets, shown in Table III, indicated that the tablets manufactured in the U.S.A. have amounts greater than the limit, while all of the other tablets are within the ∓ 5 % limit of the amount stated on the label (11).

Considering the results both of SA content and dissolution rate of the tablets, it can be said that all of the tablets, except the tablets manufactured in England and in Turkey I, were in compliance with the pharmacopoeia (6).

The disintegration time for all the tablets tested, was less than the 5 minutes limit stated in the pharmacopoeia (13).

Data obtained from the dissolution rate tests of the tablets for the U.S.A., England, Iran, Germany, Switzerland, Turkey I, Belgium, Turkey II, and France are shown in Tables IV. 1 to IV. 9, and in Figures 4 and, 5, respectively.

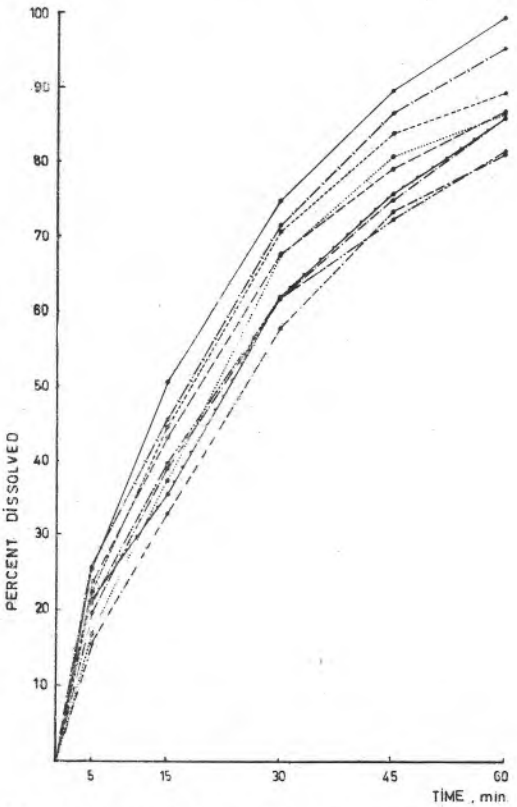

Fig. 4- Cumulative percent dissolved from Aspirin plain tablets manufactured in the U.S.A (——), in ENGLAND (—·—·—), in İRAN (·····), in W.GERMANY (— — —); in SWİTZERLAND (·····); in TURKEY I (— ·—·—); in BELGIUM (——·——); in TURKEY II (—·—·—) in FRANCE (— — —)

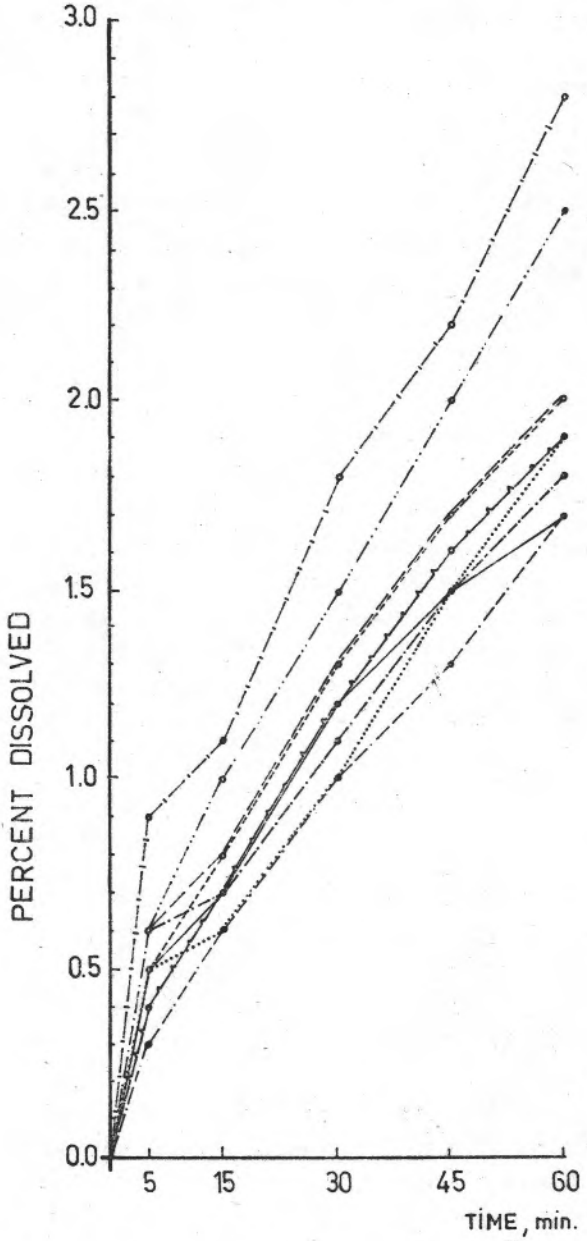

Fig. 5 – Cumulative percent of Salicylic acid dissolved from Aspirin plain tablets manufactured in the U.S.A (——); in ENGLAND (—·—·—); in IRAN (·····); in W. GERMANY (– – –); in SWITZERLAND (·····) in TURKEY I (–·–·–); in BELGIUM (—··—); in TURKEY II (– –) in FRANCE (–·–·–)

The percentage of ASA dissolved from the tablets were calculated as 15–30, 30–50, 55–85, 70–90, and 80–100 in 5, 15, 30, 45, and 60 minutes respectively.

According to the plots shown in Fig. 4, it can be said that percent dissolved of aspirin from the tablets manufactured in the U.S.A. and in England, were higher than the other countries.

According to the results of the hardness test shown in Table I, the values were quite different from each other. The tablets manufactured in England had the lowest value for hardness, while the tablets manufactured in Belgium were the hardest.

Friability test results, shown in Table 1, indicated that the tablets manufactured in Turkey II are the least resistive tablets. The tablets manufactured in England follow these. The rest of the tablets have quite close friability results.

Generally, it can be said that the domestic ASA tablets, in general showed in compliance with the pharmacopoeias in the quality control tests as with the foreign aspirin tablets. However, the results of the dissolution rate tests, which have a mean about the biological effects of the drug, indicated that the tablets manufactured in Turkey, followed the other countries.

These outcomes implied that aspirin tablets manufactured in the U.S.A. probably had technological superiority over the other aspirin tablets tested. However, it has to be stated that this impression was the results of the tests conducted on the plain tablets of aspirin which were randomly collected from the market. On the other hand, the quality of the aspirin tablets on the market depends largely on the technical facilites of the laboratories and factories manufacturing the aspirin tablets, and on the knowledge and experience of the personnel.

SUMMARY

Aspirin has analgesic, antipyretic and anti-inflammatory actions and it is used as the first recommended drug in the case of indispositions in our country and in many other countries.

The question of "Which aspirin tablet would you prefer, a domestic one or the one produced abroad?" was asked to forty-three

people. Most of them were professional pharmacist and graduate students of pharmacy. Twenty-two of them preferred domestic aspirin tablets, while the remaining twenty-one preferred foreign aspirin tablets.

The question of "Which aspirin tablet is better?" might be arised. The preference can be due to psychological reasons or due to better technology and hence better quality.

In the present study, we investigated the qualities of the plain tablets of aspirin manufactured in different countries to answer the above question experimentally.

The quality control methods used in pharmaceutical technology were applied to the plain tablets of aspirin which were obtained randomly from the markets in Turkey, in Iran, in Germany, in Belgium, in Switzerland, in France, in the U.S.A. and in England. The methods applied, were, the determination of size and thickness, hardness, friability, weight variation, content uniformity, salicylic acid content, disintegration time, and dissolution rate of the tablets.

The results obtained from experiments were compared with the limits in pharmacopoeias and with each other.

The results indicated that the plain tablets of aspirin manufactured both in Turkey and in the other countries, were generally in compliance with the pharmacopoeias. The aspirin tablets, produced in the U.S.A. seemed to be more conformable to the limits stated in pharmacopoeias.

ÖZET

Analjezik, antipiretik ve antienflamatuvar olarak etkiyen aspirin, ülkemizde ve diğer birçok ülkelerde rahatsızlık hallerinde ilk akla gelen ve çok kullanılan bir ilaçtır.

Yerli ve yabancı ülkelerde imal edilmiş aspirin tabletlerden hangisini ve niçin tercih ettikleri hakkında kırküç kişi üzerinde bir anket yapıldı. Anketi cevaplıyanların büyük bir kısmını asistan eczacılar ve eczane eczacıları oluşturuyordu. Anket sonucunda yirmiikisinin yerli, geriye kalan yirmi bir kişinin de yabancı kaynaklı Aspirin tableti tercih etmekte oldukları ortaya çıktı.

Acaba hangi tabletler daha iyiydi? Tercih nedenleri psikolojik sebeplere mi yoksa teknolojik üstünlükten ileri gelen daha iyi bir kalite farkına mı dayanıyordu?

İşte bu soruları deneysel olarak cevaplıyabilmek için yaptığımız bu çalışmada, çeşitli ülkelerde imal edilmiş basit aspirin tabletlerin kalitelerini belirlemeye ve elde edilen bulgulardan sonucu saptamaya çalıştık.

Türkiye, İran, Almanya, Belçika, İsviçre, Fransa, İngiltere ve Amerika Birleşik Devletleri piyasalarından sağlanan basit aspirin tabletler üzerinde farmasötik teknolojide kullanılan kalite kontrol yöntemleri uygulandı. Tabletler üzerinde başlıca, büyüklük ve kalınlık, sertlik, aşınma, ufalanma, ağırlık dağılımı, içerdiği etken madde miktarı, içerdiği salisilik asit miktarı, dağılma süresi ve çözünürlük hızı tayinleri yapıldı.

Yapılan deneylerden elde edilen bulgular birbirleriyle ve farmakope limitleriyle kıyaslandı.

Bulgular, Türkiye'de imal edilmiş aspirin tabletlerin diğer ülkelerin aspirin tabletleri ile birlikte genellikle farmakopelere uygun olduğu kanısını uyandırdı. Ancak A.B.D. aspirin tabletlerinin diğer ülkelerin aspirin tabletlerine kıyasla farmakope limitlerine daha yakın olduğu izlenimi bıraktı.

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