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# Analysis of Naproxen 500 mg Caplets from Different Brands Available in the Iraqi Market: A Comparative In-vitro Study

**Amal F. Al-Dulaimi[1,*], Zahraa Hussein Ali[2], Sarah Ahmed Waheed[1]**

*[1]Department of Pharmaceutical Chemistry, College of Pharmacy, University of Mosul, Mosul, Iraq.*
*[2] Department of Pharmaceutics, College of Pharmacy, University of Mosul, Mosul, Iraq.*

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*** CORRESPONDING AUTHOR:**
Amal F.Al-Dulaimi
amal-aldulaimi@uomosul.edu.iq

## ABSTRACT

Naproxen, a non-steroidal anti-inflammatory drug, has been used widely for its analgesic, antipyretic, and anti-inflammatory activities. Based on that, this medication has many brands available in the Iraqi market. These numerous brands confuse doctors and patients about which is the best in terms of good quality and the exact quantity of active ingredients. Accordingly, this research is conducted to perform an *in-vitro* comparative study to evaluate different brands of naproxen caplets available in Iraqi market (as whole and splitted caplets), with a price evaluation. With regard for the intact caplet investigations, the weight, size, friability, and content uniformity values of the caplets of all tested brands were acceptable, while the caplets' hardness results were above the limits, especially for brands B and D. The disintegration times of these brands were within the limits, except for brand C that exceeded the limits with a large margin. Concerning the dissolution rate inspection, all brands fell within the pharmacopeial limits, but in the case of the 5-min drug release percentage comparison, which was linked straightly to the onset of action, brands A and B were superior. A similarity factor study revealed that brands A and B were similar regarding their dissolution profiles, while brands A and C were the most dissimilar. On the other hand, the splitted caplet investigation included weight, weight variation and uniformity, average accuracy percentage and content uniformity percentage analysis. The results of most of them occurred within acceptable limits. One of the most important parameters that directly affect patient compliance with the medication is the price and how it is linked with the effectiveness. On this matter, the best price: effectiveness ratio was found in brands E and B.

## 1. Introduction.

Naproxen is a non-steroidal anti-inflammatory drug (NSAID). It acts by non-specific reversible inhibition of cyclooxygenase enzymes (COX1 and COX2). It is used to relieve pain and inflammation in different conditions like toothache, headache, osteoarthritis, acute gout, post-surgical, and gynecological pain[1–3]. Naproxen is available in various dosage forms; the caplet form, which came from merging the properties of capsule and tablet, is an oval-shaped, smoothly coated tablet. The oblong shape made the caplets more favorable than ordinary tablets due to their easy swallowing[4]. Naproxen caplets are solid dosage forms with a middle splitting line that present in most of manufactured brands. Dividing the naproxen 500 mg caplets into two halves is necessary to make the dose suitable for children (especially when 250 mg tablets are not available). The most professional way to divide a caplet into two halves is through the use of tablet splitter device. Breaking the caplets by hand or through using a kitchen knife would not ensure the equal division of the caplets. The unequal splitting leads to variations in weight and content uniformity, which could lead to either toxicity or under-therapeutic activity of the dosage form in children[5].

The pharmaceutical formulations undergo quality control studies inside the drug factories and even after their release into markets to ensure the effectiveness, potency, and safety of the active pharmaceutical ingredients (APIs). In drug factories, there is a special unit for standardization and quality control that conducts many *in-vitro* studies on each batch of pharmaceutical products before transferring them to the packaging and marketing units and repeats these tests at specific periods during the product's shelf life to ensure that they meet all the GMP (Good Manufacture Practice) requirements[6,7]. According to WHO reports, developing countries are suffering from higher percentages of fake and substandard drugs due to the lack of strong regulations that confirm the safety and quality of the marketed medication[8]. There is lack of the presence of a neutral side that conducts quality control studies on the medications traded in markets[9]. Caplets quality control include same pharmacopeial official and non-official tests that are applied on conventional tablets[10].

Patient compliance with the therapeutic regimen is the cornerstone of obtaining the desired therapeutic outcome[11]. In this field, the medication price is vital to patient adherence to the treatment[12]. The price-effect is more obvious in chronically used medication[13]. Naproxen is an NSAID, so it could be used more frequently as analgesic and anti-inflammatory[13]. Thus its price has direct effect on its use by the patient.

This study aimed to evaluate the different brands of naproxen caplets available in the Iraqi market. The evaluation includes quality control studies on whole and split caplets, along with a price-effect evaluation.

## 2. Materials and Methods

### 2.1.Materials

Seven different brands of marketed naproxen 500 mg caplets were purchased from local pharmacies in Mosul, Iraq. The seven naproxen brands were coded from A to G. The name, code, manufacturer, and batch number of each brand were included in **Table (1)**.

For the construction of naproxen calibration curve, a pure naproxen sample was obtained from (Pioneer Company for the pharmaceutical industry in Al-Sulaymaniyah, Iraq). Absolute ethanol, absolute methanol, potassium dihydrogen phosphate, and sodium hydroxide were from (Scharlau, Spain).

All required instruments and research stages were conducted in the Pharmaceutics department, Pharmacy College, Mosul University.

**Table 1. The name, code, manufacturer, and batch number of 500 mg naproxen caplets.**

| Name | Code | Manufacturer | Packet price in USD | Number of caplets in one packet | Batch number |
|---|---|---|---|---|---|
| Naproxen | A | Glenmark, India | 4.5-5.5 | 30 | 19215276 |
| Napron | B | Pioneer, Iraq | 2.5-3.0 | 20 | 211203A |
| Inaprol | C | Bilim, Turkey | 2.5-3.5 | 20 | 22014001A |
| Nopain | D | Hikma, Jordan | 3.5-3.75 | 10 | 9444A |
| Naproxen | E | Wockhardt, UK | 3.75-4.0 | 28 | 2101070 |
| Naprorex | F | Delorbis, Cyprus | 4.5-5.5 | 20 | 20682 |
| Axen | G | Julphar, UAE | 4-5 | 20 | 0018 |

**1.2. Methods.**

**2.2.1 Evaluation of Whole Caplets.**

All evaluation tests and acceptable limits depend on information mentioned in British Pharmacopoeia and/or U.S. Pharmacopoeia[14,15] .

**2.2.1.1 Caplets Width, Length and Thickness.**

The width, length, and thickness of ten caplets from each brand were measured in (mm) through the use of an electronic digital caliper (Adoric). The results were expressed as mean ± S.D. (standard deviation), and all the resulted values should not deviate from their mean by more than 5%[16].

**2.2.1.2 Caplets Weight and Weight Variation.**

The weight of each caplet gives an idea about its dose uniformity. To perform this test, twenty randomly selected caplets from each brand were individually weighed using an analytical balance (Adam Equipment, PW 124). Then, the average weight for each brand was calculated[17].

As all caplets having weights occur within the range of (more than 324 mg), the requirements of this test were: no more than two of the caplets` weights deviate from the average weight by more than 5%, and no individual caplet`s weight deviates from the average weight by more than 10%[14].

**2.2.1.3 Caplets Hardness.**

The force required to break one caplet longitudinally was measured by a YD-1 hardness tester (Lpmie). To perform this test, ten caplets were selected randomly from each brand, and their individual hardness was measured in N (Newton), which was then converted to Kg (1N= 0.102 Kg). The caplets harness average values were calculated and compared to the acceptable range from 4 to 12 Kg[18].

**2.2.1.4 Caplets Friability.**

The resistance of caplets to weight loss and abrasion during handling was measured by a CS-3 friability tester. To perform this test, ten caplets from each brand were selected randomly, weighed, and placed in the drum of the apparatus. The drum was sealed, and the apparatus was run at the rate of 25 rounds per min (RPM) for 100 revolutions. At the

end of the revolutions, the drum was opened, and the 10 caplets were de-dusted and reweighed. The friability percentage was calculated according to equation (1)[14], and the acceptable percentage should not exceed 1%[18].

$$Caplets\ friability\ \% = \frac{intial\ weight - final\ weight}{intial\ weight} * 100\% \quad (1)$$

**2.2.1.5 Caplets Disintegration Time.**

The time required for the caplet to disintegrate and pass through the basket mesh was measured by the disintegration apparatus (BJ-2). To perform this test, six caplets from each brand were selected randomly and placed separately in each of the six baskets of the apparatus. Then, these baskets were immersed in a 900 mL vessel filled with disintegration media (distilled water). The temperature of the disintegration medium was set at 37 ± 0.5 °C. The time was measured in minutes and it should not exceed 15 min[19] .

**2.2.1.6 Caplets *In-vitro* Dissolution Profile Study.**

***Determination of Naproxen λ max and Calibration Curve.***

The λmax of naproxen was determined through the preparation of 1000 µg/mL naproxen stock solution in methanol. After that, 10 mL of the stock solution mentioned above was diluted with methanol up to 100 mL and scanned between 200- 400 nm by a UV-visible spectrophotometer (Thermo Fisher Scientific).

To construct the calibration curve, serial dilutions were prepared from the stock solution (10, 20, 40, 60, 80, 100, and 110 µg/mL), and they were analyzed at naproxen λmax (which is 331 nm)[20].

***Determination of Dissolution Rate Percentage.***

The dissolution rate study is one of the most important tests that should be performed on caplets, as it reflects the *in-vivo* dissolution rate of the caplets inside the G.I.T. To perform this test, six caplets from each brand were selected randomly; each caplet was settled in one of the six vessels of a U.S. type 2 paddle apparatus (OLABO\ BK-RC6). The dissolution media used for the test consisted of 900 mL of phosphate buffer solution (PH = 7.4). The dissolution medium was prepared by dissolving 13.608 g of potassium dihydrogen phosphate in 1 L of D.W. and 6.8 g of sodium hydroxide in 1 L of D.W. separately. After that, the two solutions were mixed, and the pH of the resulting solution was checked through a sensitive pH meter (Eco Tester pH 2®). The dissolution apparatus was set at 37 ± 0.5 °C temperature and 50 RPM paddle rotating speed. After starting the test, 5 mL samples were withdrawn and replaced with fresh dissolution media at (5, 10, 15, 30, and 45 min) intervals, respectively. The drawn samples were filtered through a membrane filter (0.45µm, Chromafil Ao-20/25®). The filtrate was properly diluted and analyzed at naproxen λ max by a UV-visible spectrophotometer (Thermo Fisher Scientific). The percentage of naproxen dissolution was calculated. To be acceptable, no less than 80% of the labeled amount should be released within 45 min[14,15].

***Determination of Similarity Fit Factor ($f_2$).***

The comparison between different naproxen brands caplets in dissolution profile was done through the study of the similarity fit factor ($f_2$) by applying equation (2)[19].

$$f_2 = 50 \times \log\left\{\left[1 + \sum_{t=1n}(R_t - T_t)^2/n\right]^{-0.5} \times 100\right\} \quad (2)$$

Where:

n represents the number of sample point,

$R_t$ represents the percentage of dissolution for the brand caplets at time t and,

$T^t$ represents the percentage of dissolution for the reference brand caplets at time t.

The dissolution profile of the brand caplets is considered to be similar to the reference brand if $f_2$ higher than 50[19].

**2.2.1.7 Caplets Content Uniformity.**

The content uniformity refers to the amount of naproxen found in each caplet. This content should be uniform from one caplet to another and from batch to batch and should be kept within a narrow range compared to the labeled amount on the caplet leaflet[9].

To perform this test, ten caplets were selected randomly from each brand. Each of these caplets was weighed, crushed, and dissolved in 500 mL of methanol, separately. Then, about 1 mL of the resulted solution was filtered through a 0.45 µm membrane filter and diluted with methanol up to 10 mL, which was measured at naproxen λmax. From the measured drug concentration, the exact weight of naproxen as well as the percentage of naproxen weight in each caplet were calculated by equation (3)

$$Naproxen\ weight\ percentage = \frac{\text{the exact weight (mg)}}{\text{the labeled weight (500 mg)}} * 100\% \quad (3)$$

The naproxen weight percentage should be within the 85%-115% range. If one caplet was outside the above-mentioned range but within the 75%-125% range, the content uniformity test should be repeated for another 20 caplets, and no single caplet could have a weight percentage outside the two mentioned ranges[14].

**2.2.2 Evaluation of Splitted Caplets.**

The device that was used to cut the caplets into two halves was a common plastic tablet cutter available in the Iraqi market. The plastic cutter dimensions were 85 mm in length and 38.5 mm in width in the middle. The thickness of the cutter metal blade was about 1 mm. Each caplet was placed inside the cutter parallel to the x-axis and pushed to the closest point of the cutter. When the cutter was closed, the metal blade of the cutter would go down at the splitting line of the caplet, cutting it into two approximately equal pieces.

**2.2.2.1 Splitted Caplets Weight and Weight Variation and Weight Uniformity.**

The measurements of splitted caplets weights and the calculations of weight variation were performed in a way similar to that applied on the whole caplets [21]. The splitted caplets weights were compared with the average weight. The individual weight of each splitted caplet should not deviate from its corresponding average weight by a percentage specified in pharmacopeia (according to the average weight of splitted caplets)[22]. If the average weight was less than 324 mg, the requirements for this test are: no more than two of the splitted caplets weights should deviate from the average weight by more than 7.5%, and no one individual caplet weight should deviate from the average weight by more than 15%. On the other hand, if the average weight was more than 324 mg, the requirements for this test are changed to be: no more than two of caplets weights should deviate from the average weight by more than 5%, and no one individual caplet weight should deviate from the average weight by more than 10%[14]. The evaluation of splitted caplet weight in some references depends on the calculation of the weight uniformity with the RSD% (relative standard deviation) rather than weight variation. The limitations of this test were that for 20 splitted caplets, only one caplet may deviate from the average weight by 15% but not outside the 75%-125% range from the average, and the RSD% should not exceed 10%[23,24].

In addition, the percentage of the caplet-division accuracy was calculated according to equation (4)

$$The\ accuracy\ percentage = \left\{1 - \frac{W/2 - H}{W/2}\right\} * 100\% \quad (4)$$

Where:

W represent the whole caplet weight,

H represent the splitted caplet weight[24].

The requirement of the accuracy percentage test is to keep the percentage within ± 5%, that is to say, the accuracy percentage should be kept between 95% and 105%[25].

**2.2.2.2 Splitted Caplets Content Uniformity.**

To perform this test, the same steps used to find the content uniformity of whole caplets

were applied on splitted caplets except for the volume of the solvent and the labeled weight in the naproxen weight percentage equation, were changed to 250 mL and 250 mg, respectively[50,22].

**2.2.3 Evaluation of Naproxen Caplets Price.**

Evaluation of naproxen caplets price of different brands was performed through statistical analysis using Minitab statistical software for Windows (version 19. Minitab, Ink) to compare the brands price per packets and per caplets with each other.

**2.2.4 Data Statistical Analysis.**

All the data that collected in this research were statistically expressed as mean ± standard deviation (S.D). They had been tabled by the Microsoft Excel 2010 program and analyzed by one-way (ANOVA) test followed by the Tukey test using Minitab statistical software (version 19. Minitab, Ink) for Windows. If the *P*-value ≤ 0.05, the difference was considered to be statistically significant otherwise, it was considered to be insignificant.

## 3.Results and Discussion

### 3.1. Evaluation of Whole Caplets.

This study was conducted on only five bands of naproxen caplets 500 mg, as brand F and brand G caplets were film-coated; hence, they were neglected. The brands included within the study immediately released 500 mg caplets, and they were investigated while they were within their shelf lives. All the details of the used brands were illustrated in **Table (l).**

All the measurements of caplets' width, length, and thickness are included in **Table (2).** They were within the accepted limits (mean ± 5%) (16). Statistically, all the differences in the dimensions among the various naproxen caplets brands were significant (*P*-value < 0.05). However, these variations could be neglected since all the readings were within the pharmacopeial limits. Regarding the thickness of the caplets (which is the most important dimension of the caplet, as it has a direct relation with the compression forces and material compactibility), it is worth mentioning that brand C had the smallest thickness while brand D had the largest one (5.88 mm and 7.02 mm, respectively).

In general, the biggest size caplet was brand D.

**Table 2. The width, length, and thickness of the different naproxen brands.**

| Code | Width (mm) | Length (mm) | Thickness (mm) |
|---|---|---|---|
| A | 7.27± 0.01 | 15.97±0.01 | 6.25±0.07 |
| B | 7.16±0.03 | 18.23±0.03 | 6.47±0.02 |
| C | 7.08±0.01 | 18.65±0.04 | 5.88±0.03 |
| D | 8.38±0.01 | 21.42±0.03 | 7.02±0.03 |
| E | 8.79±0.03 | 18.07±0.01 | 6.1±0.02 |

* All the readings are expressed as mean ± SD (n = 6).

The weight and weight variation measurements of the different naproxen brands are included in **Table (3)**. The average weight and weight variation measurements were within the accepted pharmacopeial limits. As all caplets weight variation range were within ± 5% of the mean, there was no need to calculate the variation to ± 10% of the mean.

The calculated average weights of the tested naproxen brands were increasing in the following order: A < B < C < E < D. All of these increments

were statistically significant (*P*-value < 0.05) except for the difference between brand B and C, which was statistically insignificant (*P*-value ≥ 0.05). The highest average weight was measured in brand D, which demonstrated the biggest size as mentioned earlier. The average weight of brand D was about one and a half to two times greater than that of the other brands. These relatively large caplets with average weights that surpass 1000 mg tend to cause discomfort and swallowing difficulties for the patients [26]. In addition, the amount of excipients in brand D were greater than the amount of API, and they were greater than those included within the caplets of the other brands. This fact might be linked to a higher production cost of this brand D and its subsequent higher market price.

**Table 3. The weight and weight variation results of the different naproxen brands.**

| Code | Average weight (mg) | The accepted weight variation range in mg (mean±5% of the mean) | The measured weight variation range in mg (minimum weight - maximum weight). | Pharmacopeial acceptance |
|---|---|---|---|---|
| A | 539±7.093 | 512.05-565.95 | 522-551 | Accepted |
| B | 694.7±6.974 | 659.965-729.435 | 680-709 | Accepted |
| C | 699.4±7.701 | 664.43-734.37 | 687-709 | Accepted |
| D | 1139.8±15.095 | 1082.81-1196.79 | 1120-1170 | Accepted |
| E | 748.1±4.656 | 710.695-785.505 | 740-756 | Accepted |

*All values were calculated as mean ± S.D. (n = 20).

The hardness results of the tested naproxen caplet brands were above the accepted pharmacopeial limits (which should be 4-10 kg), as shown in **Table (4)**. Furthermore, the hardness of brands B and D could not be even measured as they exceeded the measurement capacity of the used hardness apparatus. The hardness readings of the remaining brands under investigation range from 16.282 kg (for brand A) up to 18.473 kg (for brand C), with no statistical difference between their values (*P*-value ≥ 0.05). The hardness of caplets may affect disintegration time, as too hard caplets disintegrate slowly. The hardness values are related to the compression forces and/or the type and amount of the excipients included (27).

All the investigated naproxen caplet brands exhibited friability values within the accepted pharmacopeial limits (less than 1%), as shown in **Table (4)**. There was no statistical difference among the friability results of brands B, D, and E (*P*-value ≥ 0.05). In contrast, brands A and C displayed significantly higher friability results (*P*-value < 0.05). The caplets` friability might have a negative impact on the medication handling by the patient. Extremely friable caplets may suffer from chipping and capping when the caplet is to be splitted into two halves, leading to unequal doses.

The disintegration time of the different naproxen caplet brands varied widely, from 4.42 min for brand B to 31.57 min for brand C, as shown in **Table (4)**. The disintegration time of brands A, B, and E was fast occurring within less than 7 min (5.09, 4.42, and 6.07 min, respectively). The variations in the disintegration times among these three brands were statistically insignificant (*P*-value ≥ 0.05). On the other hand, the disintegration of brand C and brand D was extremely slow (31.57 and 14.5 min, respectively)

and significantly greater than those of the remaining brands under investigation (*P*-value < 0.05). For brand C, the disintegration result surpassed the pharmacopeial limits by one-fold. While for brand D, despite that the disintegration was within the limit, it was slow, which could be related to the large caplets size and confirmed by their very low friability.

**Table 4. Hardness, friability and disintegration time of the tested naproxen brands.**

| Code | The hardness in Kg (n=10) | The friability % (n=20) | The disintegration time in min (n=6) |
|---|---|---|---|
| A | 16.282±1.131 | 0.158%±0.039 | 5.09±0.92 |
| B | > 20 ±0.0 | 0.06% ±0.003 | 4.42±0.73 |
| C | 18.473±1.877 | 0.139%±0.026 | 31.57±3.60 |
| D | > 20 ±0.0 | 0.035%±0.00 | 14.50±0.65 |
| E | 16.573±3.153 | 0.054%±0.001 | 6.07±0.93 |

*All values were calculated as mean ± S.D.

The λ max of naproxen was found to be 331 nm, similar to the λ max mentioned in the U.S. pharmacopeia. The calibration curve of naproxen was constructed at 331 nm, as shown in **Figure 1**. The $R^2$ value was 0.997, and the correlation equation was y= 0.008x+0.093.

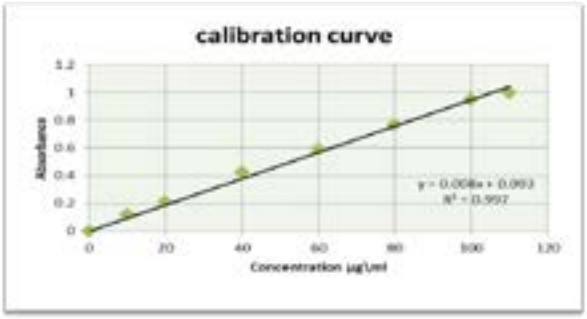


***Figure 1.*** *Naproxen calibration curve showing the $R^2$ value and the correlation equation.*

The measurements of caplets dissolution rate percentage are included in **Table (5)**, and all of them were within the accepted pharmacopeial limits. Upon comparing the percentage of drug release at the 5-min time point, it was found that there was no statistical difference between brands A and B (70.624% and 70.696%, respectively) with the highest release values (*P*-value ≥ 0.05). In contrast, brand E demonstrated an intermediate 5-min dissolution percentage of 50.407%, significantly lower than the previous two brands (*P*-value < 0.05). Finally, the brands C and D showed statistically the lowest 5-min dissolution percentages (23.438% and 22.988%, respectively) of the five investigated brands (*P*-value < 0.05). Since the 5-min dissolution percentage is usually linked to the onset of action of the medication, the obtained results indicated that the onset of action of the tested brands may occur in the following order (from slowest to fastest): D < C < E < A < B.

At the end of the experiment, all five brands under investigation manifested final dissolution rate percentages exceeding 81%. Brand D exhibited the greatest overall dissolution percent of 85.969%, while brand C had the lowest value of 81.621%. However, there were no statistical variations among their dissolution percentages at the 45-min time point (*P*-value ≥ 0.05).

**Table 5. The results of the dissolution rate percentage for the investigated naproxen caplet brands.**

| Naproxen caplets dissolution rate percentage | | | | | |
|---|---|---|---|---|---|
| **Code** | **at 5 min** | **at 10 min** | **at 15 min** | **at 30 min** | **at 45 min** |
| A | 70.624 ±5.98 | 85.148 ±1.376 | 86.044 ±1.802 | 86.241 ±1.242 | 84.351 ±3.863 |
| B | 70.696 ±7.667 | 79.918 ±4.46 | 83.105 ±3.676 | 84.017 ±3.695 | 85.690 ±3.258 |
| C | 23.438 ±1.239 | 26.762 ±6.10 | 33.789 ±3.883 | 58.359 ±8.257 | 81.621 ±6.241 |
| D | 22.988 ±9.234 | 38.826 ±2.012 | 60.018 ±2.456 | 84.079 ±7.810 | 85.969 ±5.341 |
| E | 50.407 ±3.018 | 78.347 ±0.685 | 84.143 ±1.094 | 85.149 ±0.738 | 83.156 ±1.443 |

*All values were calculated as mean and S.D. (n = 6).

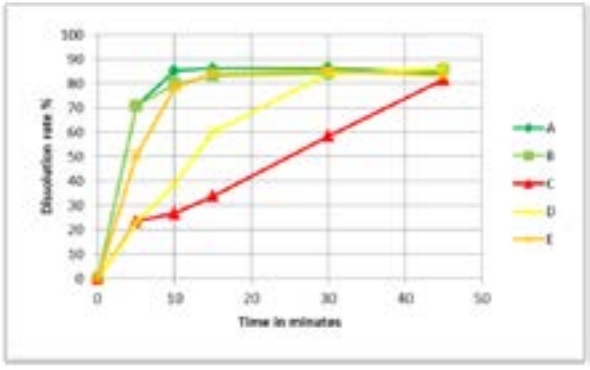


***Figure 2.*** *Naproxen caplets dissolution rate percentage.*

In general, the slowest overall dissolution rate was recorded in brand C, as shown in **Figure 2**. The dissolution rate study is the only *in-vitro* available method that is directly related to *in-vivo* drug release, absorption, and bioavailability[28]. The variation between different brands dissolution rate depends on the type of excipients, steps of addition, manufacturing methods, as well as other parameters[29].

The study of the similarity factor $f_2$ is beneficial in comparing different brands to each other as well as in comparing brand drugs to generics [30]. The calculations of the caplets` dissolution profiles similarity fit factors (f2) are included below in **Table (6)**. The higher the similarity factor, the more likely it is that the dissolution profiles of the corresponding brands are similar to each other. Accordingly, the two most similar dissolution profiles were for A and B caplets brands as their f2 was equal to 75.503 while the two most dissimilar profiles were for A and C caplets brands as their f2 was equal to 18.432. In addition, similar dissolution profiles were recorded for brands A, B, and E since their *f*2 was higher than 50. The dissolution profiles of the remaining brands were all dissimilar, with *f*2 less than 50.

**Table 6. The calculated similarity fit factors ($f_2$) of the different naproxen caplets brands.**

| The compared caplets brands | The similarity fit factor ($f_2$) |
|---|---|
| A with B | 75.503 |
| A with C | 18.432 |
| A with D | 24.775 |
| A with E | 50.760 |
| B with C | 19.668 |
| B with D | 26.138 |
| B with E | 51.692 |
| C with D | 37.934 |
| C with E | 21.905 |
| D with E | 30.878 |

The content uniformity percentages of different naproxen caplet brands under investigation were within the accepted pharmacopeial limits. There was no one caplet that expressed a percentage below 85% and above 115% of the labeled API amount in all of the tested brands. The highest content uniformity percentage was recorded in brand E, which was equal to 96.42%, while brand A demonstrated the lowest content uniformity with a value equal to 89.28%, as recorded in **Table (7)**. Statistically, there were no significant variations among the content uniformity results of the different naproxen brands included in the study (*P*-value ≥ 0.05). The importance of the content uniformity study is linked to the fact that it focuses on the assay of the real weight of pure API (by excluding the weight of other excipients) and comparing it to the labeled APIs` weight. This is distinct from the weight variation study, which depends on the weight of whole tablets, including the excipients[31].

**Table 7. The results of the content uniformity percentage for the investigated naproxen caplet brands.**

| Code | Content uniformity percentage | Caplets outside 85%-115% range | Caplets outside 75%-125% range |
|---|---|---|---|
| A | 89.28% ± 0.660 | None | None |
| B | 92.12% ± 0.456 | None | None |
| C | 94.06% ± 1.441 | None | None |
| D | 92.05% ± 1.210 | None | None |
| E | 96.42% ± 0.889 | None | None |

*All values were calculated as mean ± S.D. (n = 10).

### 3.2. Evaluation of Splitted Caplets.

The caplet splitting was done by using a plastic cutter device. This is the most efficient way that could be used to cut the caplets into two halves (5). Naproxen brands (A, B, C, and E) contained a splitting line in the middle of each of their caplets, facilitating their cutting. However, brand D caplets lacked this middle splitting line, and the absence of it might negatively effect the dose accuracy, especially if the splitted caplet is administered to the children. The best cutting of the naproxen caplets was observed in brand E with minimum to absence of powdering. The increase in chipping, cracking, and powdering during caplet cutting may lead to dose fluctuation with over-dose and under-dose delivery.

All the measurements of the splitted caplets' weight and weight variation are included in two **Table (8-A)** and **Table (8-B)**. The splitted caplet weight measurements had a higher deviation from the average weight when compared with the weight variation study of the whole caplets. In addition, two different pharmacopeial range limits (5%-10%) and (7.5%-15%) were used to study the splitted caplets` weight variation (14). The average weight of brand A was (274.005 ± 16.509) mg, which was less than 324 mg; therefore, for this brand, the applied limit should be (7.5%-15%). In contrast, the average weight of the other brands (B, C, D, and E) was higher than 324 mg; hence, the applied pharmacopeial limits were 5% and 10%.

**Table 8-A. The results of the weight variation study for the splitted caplets of the tested naproxen brands.**

| Code | Average weight (mg) | minimum weight-maximum weight (mg) | The accepted weight variation range in mg (mean±7.5% of the mean) | Number of splitted caplets outside the ±7.5% range | The accepted weight variation range in mg (mean±15% of the mean) | Number of splitted caplets outside the ±15% range |
|---|---|---|---|---|---|---|
| A | 274.005 ± 16.509 | 248.3-320.4 | 253.455-294.555 | 3 | 232.904-315.106 | 1 |
| B | 350.355 ± 27.394 | 306.8-390.5 | Not applicable | --- | Not applicable | --- |
| C | 352.22 ± 22.429 | 306.6-388.3 | Not applicable | --- | Not applicable | --- |
| D | 589.65 ± 46.582 | 506.7-666 | Not applicable | --- | Not applicable | --- |
| E | 376.66 ± 23.836 | 337.6-414 | Not applicable | --- | Not applicable | --- |

*All values were calculated as mean ± S.D. (n = 20).

**Table 8-B. The results of the weight variation study for the splitted caplets of the tested naproxen brands with the average accuracy percentage.**

| Code | Accepted weight variation range in mg (mean±5% of the mean) | Number of splitted caplets outside the ±5% range | The accepted weight variation range in mg (mean±10% of the mean) | Number of splitted caplets outside the ±10% range | The average accuracy percentage |
|---|---|---|---|---|---|
| A | Not applicable | --- | Not applicable | --- | 101.672% |
| B | 332.837-367.873 | 15 | 315.32-385.391 | 5 | 100.865% |
| C | 334.609-369.831 | 7 | 316.998-387.442 | 4 | 100.721% |
| D | 560.168-619.133 | 8 | 530.685-648.615 | 5 | 103.466% |
| E | 357.827-395.493 | 11 | 338.994-414.326 | 1 | 100.698% |

*All values were calculated as mean ± S.D. (n = 20).

The weight variation of splitted caplets of all naproxen brands under investigation was outside the pharmacopeial limits. Similar findings were reported in the results of previous research that investigated the efficiency of tablet splitting (5,24). The best results of weight variation were recorded in brand A, as the range of weight variation is very wide (7.5%-15%) due to their relatively small average weight of splitted caplets. However, the calculation of weight uniformity with the RSD% showed that all values of splitted caplets weight are within the limits as demonstrated in **Table (8-C)**. Only one splitted caplet in brand A was outside the 15% range from the average weight, but its weight was still within the 25% range from the average weight. All the RSD% of all splitted caplets were below 10%, with the highest percentage recorded in brand D, which was equal to 7.9%. while the average accuracy percentage of each splitted caplet brand was within the accepted range (95%-105%), as recorded in **Table (8-B)**. The highest recorded average accuracy percentage was for brand D, as it was equal to 103.466%.

**Table 8-C. The results of the weight uniformity study for the splitted caplets of the tested naproxen brands with the RSD%.**

| Code | The accepted weight uniformity range in mg (mean±15% of the mean) | Number of splitted caplets outside the ±15% range | The accepted weight uniformity range in mg (mean±25% of the mean) | Number of splitted caplets outside the ±25% range | The RSD% |
|---|---|---|---|---|---|
| A | 232.904-315.106 | 1 | 205.504-342.506 | 0 | 6.025% |
| B | 297.802-402.909 | 0 | 262.766-437.944 | 0 | 7.819% |
| C | 299.387-405.053 | 0 | 264.165-440.275 | 0 | 6.368% |
| D | 501.203-678.098 | 0 | 442.238-737.063 | 0 | 7.9% |
| E | 320.161-433.159 | 0 | 282.495-470.825 | 0 | 6.328% |

*All values were calculated as mean ± S.D. (n = 20).

The content uniformity percentages of splitted caplets from all the tested brands were within the 85%-115% pharmacopeial limits. Their values occurred in the range of (90.25%-98.34%) with no statistically significant difference among them (*P*-value ≥ 0.05). However, there were one and two splitted caplets outside the (85%-115%) limit for the brands C and D, respectively. Nonetheless, there were no caplets outside the 75%-125% pharmacopeial limits, as recorded in **Table (9)**. The administration of the splitted caplets from brands C and D to children might be associated with overdose and/or therapeutic failure as their content of API was not within the accepted limits.

**Table 9. The results of the content uniformity percentage for the splitted caplets of the investigated naproxen brands.**

| Code | Content uniformity percentage | Number of caplets outside 85%-115% range. | Number of caplets outside 75%-125% range. |
|---|---|---|---|
| A | 90.25% ± 4.468 | None | None. |
| B | 92.39% ± 3.323 | None. | None |
| C | 91.99% ± 8.719 | One caplet | None. |
| D | 91.66% ± 9.11 | Two caplets | None. |
| E | 98.34% ± 8.263 | None | None |

*All values were calculated as mean± S.D. (n = 10).

### 3.3. Evaluation of Naproxen Caplets Price.

Generally, the prices of the different naproxen caplets 500 mg brands in the Iraqi market are considered affordable. The prices of the different naproxen brands in USD are included in **Table (10)**. The difference among packets` prices is negligible with no significant statistical difference (*P*-value ≥ 0.05). One exception from this was the price of brand A, which had a significantly greater price than brands B and C (*P*-value < 0.05) but no statistical difference from the packet prices of brands D and E (*P*-value ≥ 0.05).

However, the observation was different after comparing the price per caplet for the different naproxen brands. Brand D demonstrated the

highest price per single caplet of about 0.35-0.375 USD. This price is approximately one-fold greater than the single caplet`s price from the other tested brands. Statistically, there were no significant variations among the single caplet price from the different naproxen brands except for brand D, which was significantly more expensive than the remaining brands (*P*-value < 0.05). As mentioned earlier, brand D caplets had the highest weight among the other brands. These relatively large caplets contain more than half of their weight as excipients, which may lead to additional manufacturing costs and, subsequently, to higher market prices.

After coupling the results of disintegration time, overall dissolution rate, and content uniformity of the whole and splitted caplets of all tested brands, it was found that the best results were recorded in brands A, B, and E. The designation of these three brands was fast (between 4 and 7 min). Also, their dissolution rate percentage at the first 5 min, which is linked directly to the onset of action (an important parameter in drug efficacy particularly for drugs with analgesic effects like naproxen) exceeded 50%. Besides, when observing the overall dissolution rate profiles as shown in **Figure (2)**, it could be noticed that there was a good similarity in the dissolution profiles among these three brands (which was confirmed by the similarity factor $f_2$ study). In the content uniformity study of whole and splitted caplets, no single caplets in brands A, B, and E were outside the (85%-115%) limits. For all these reasons coupled with the fact that these brands have a reasonable price/caplet, brands A, B and E were the best quality brands available in Iraqi markets. The order of these three brands in price/ caplet from the lowest to the highest price was E< B< A. By gathering the results of quality control with the lowest price, the best price: effectiveness ratio was obtained if the patient took brand E (0.134-143 USD/caplet) or brand B (0.125-0.150 USD/caplet).

**Table 10. Estimated prices of the different naproxen brands in the Iraqi market. The prices are expressed in USD per packet as well as per single caplet.**

| Code | Packet price in USD | The price per single caplet in USD |
|---|---|---|
| A | 4.5-5.5 \ 30 caplets | 0.150-0.183 |
| B | 2.5-3.0 \ 20 caplets | 0.125-0.150 |
| C | 2.5-3.5 \ 20 caplets | 0.125-0.175 |
| D | 3.5-3.75 \ 10 caplets | 0.350-0.375 |
| E | 3.75-4.0 \ 28 caplets | 0.134-0.143 |

## 4.Conclusion

The quality control study is important to ensure the effectiveness, and potency of the active pharmaceutical ingredients. In general, all the investigated brands of 500 mg naproxen caplets available in Iraqi markets are very good if they are used as whole caplets. They were subjected to pharmacopeial limits in different tests except in the hardness study, as all five brands were too hard. In addition, brand C caplet's disintegration time was so long that it exceeded the pharmacopeial

limit by more than one-fold. The most similar dissolution profiles were those of brands A and B. In a separate context, for caplet splitting, the presence of a middle line in the caplet facilitates its division. The absence of this splitting line in brand D may have a direct effect on the results of their splitted caplets. Unfortunately, the application of the weight variation test on splitted caplets leads to obtaining results out of the limits for all brands. On the other hand, the weight uniformity test and accuracy percentage calculation for all caplets were within the limits. Moreover, the content uniformity of splitted caplets of all brands was acceptable except for brand D. However, the use of splitted caplets in children should be restricted only when other alternatives are not available. The high weight of brand D, which came from the large amount of the added excipients, might have led to its higher price compared with other brands. The best price: effectiveness ratio was obtained if the patient took brand E or brand B.

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