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IN VITRO COMPARATIVE STUDY OF PHARMACEUTICAL QUALITY OF DIFFERENT BRANDS OF DICLOFENAC SODIUM TABLETS AND AMPULES BEFORE AND AFTER EXPIRY DATE

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ABSTRACT

The objective of this study was to assess the pharmaceutical quality parameters of expired and unexpired diclofenac sodium coated tablets and ampules. Appearance, weight variation, hardness, content uniformity, TLC analysis, and dissolution profile were evaluated for expired and unexpired coated tablets, whereas for ampules, only appearance, content uniformity, and TLC analysis were assessed. The physical properties did not differ between expired and unexpired diclofenac sodium coated tablets and ampules. The content uniformity and TLC tests showed no degradation of diclofenac after the expiry date in both forms (tablets and ampules), as all values were within the USP limits. The dissolution profiles of expired and unexpired tablets were similar (f1 less than 15 and f2 more than 50). Diclofenac sodium preparations retained their pharmaceutical quality characteristics after the expiry date.

KEYWORDS: Diclofenac sodium, expiry date, TLC, dissolution.

1. INTRODUCTION

The expiry date (EXP) of a drug is the last day by which the manufacturer guarantees that the drug will retain all of its properties when stored under ideal storage conditions such as temperature, humidity, and exposure to light. Since 1979, the Food and Drug Administration (FDA) has required drug manufacturers to label all drugs with expiry dates.[1,2,3] The expiry date of pharmaceutical preparation is determined by stability testing. It ensures the maintenance of physical, chemical, and bacteriological stability throughout the drug's shelf life.[4,5] After this date, the drug may no longer be safe or effective. The expiry date of medicines is from 1 to 5 years from the date of manufacture.[6,7,8]

There have been few efforts to assess the quality of drugs beyond their expiry date. Quality assessment of 122 drugs (more than 3,000 batches of drugs) has led to the extension of the expiry date for 90% of the investigated drugs (an average extension of 5 years).[9,10] A study on expired drugs was conducted in Serbia in 2020. This study compared the dissolution profiles and some physical characteristics of 10-years expired immediate-release tablets of lamotrigine with unexpired tablets. The results showed that there was no statistical difference in physical parameters between expired and unexpired tablets, but there was a difference in the dissolution profiles.[11] Another study conducted in Poland in 2009 compared the results of the in-vitro dissolution and content uniformity tests of metoprolol tartrate and propranolol hydrochloride tablets before and after the expiry date. The finding showed that there was no statistical difference between the results of expired and unexpired tablets.[12]

Diclofenac is the most widely used nonsteroidal anti-inflammatory drug for the treatment of chronic inflammation and degenerative joint diseases such as rheumatoid arthritis and osteoarthritis. It is available in the form of sodium and potassium salts.[13,14] Few studies have focused on the physical and chemical changes of the diclofenac drugs after their expiry date. For example, one study investigated possible changes in chemical and physical parameters every six months for two years after the expiry date of some analgesic drugs, including diclofenac. The tested analgesic drugs remained chemically and physically stable for two years after their expiry date.[15] The purpose of this study was to compare the pharmaceutical quality characteristics of different commercial brands of diclofenac sodium tablets and ampules before and after the expiry date.

2. MATERIALS AND METHODS

2.1. Chemicals and samples

Diclofenac sodium standard (99% purity) was provided by Pan Drugs Ltd (India). Potassium dihydrogen phosphate was obtained from Titan Biotech (India). NaOH and HCl were purchased from Sham Lab (Syria).

Two commercial dosage forms of diclofenac sodium were tested (enteric-coated tablets and ampules). Expired and unexpired samples were obtained from local pharmacies. The investigated enteric-coated tablets (strength 50mg) belong to two different Syrian companies (brand A and brand B). Ampules (75mg/3ml) belong to a single Syrian company (brand C). Table 1 provides label information for the studied brands of diclofenac sodium.

Table 1: Code, manufacturing date, expiry date, and testing time of different brands of diclofenac sodium.

Dosage form	Brand	code*	Manufacturing country	Date of manufacturing	Expiry date	Time of testing
Enteric coated tablets 50 mg	A	An	Syria	2-2022	2-2026	Before the expiry date
		Ae	Syria	3-2017	3-2021	2 years post the expiry date
	B	Bn	Syria	2-2022	2-2025	Before the expiry date
		Be1	Syria	6-2019	6-2022	One year post the expiry date
		Be2	Syria	6-2015	6-2018	5 years post the expiry date
Ampules 75 mg	C	Cn	Syria	11-2022	11-2025	Before the expiry date
		Ce	Syria	3-2020	3-2023	7 months post the expiry date

*n: unexpired medication, e: expired.

2.2. Equipment

Equipment used in this study included a UV spectrophotometer (Erweka DT128, Germany), a sensitive electronic weighing balance (Sartorius CPA225D, Germany), a digital pH meter (Sartorius PT-10, Germany), a friability apparatus (Erweka TAR120, Germany), a disintegration test apparatus (Erweka ZT222, Germany), a dissolution test apparatus (Erweka DT128, Germany).

2.3. Preparation of the calibration curve of diclofenac sodium in phosphate buffer (pH 6.8)

10mg of diclofenac sodium powder was dissolved in 100mL of phosphate buffer solution (pH 6.8) to obtain a stock solution of concentration (0.1mg/mL). The stock solution was then diluted with phosphate buffer to obtain solutions with concentrations ranging from 0.006mg/mL to 0.024mg/mL. The absorbance of the solutions was measured with a spectrophotometer at 276nm, using phosphate buffer (pH 6.8) as the blank.

The average absorbance values were plotted against the corresponding concentrations to obtain a calibration curve (Figure 1). The value of the coefficient of determination for the obtained linear curve was 0.9993T, demonstrating good linearity for diclofenac sodium over the studied range (0.006-0.024mg/mL). The linear regression equation was: y=29.33x+0.0046.

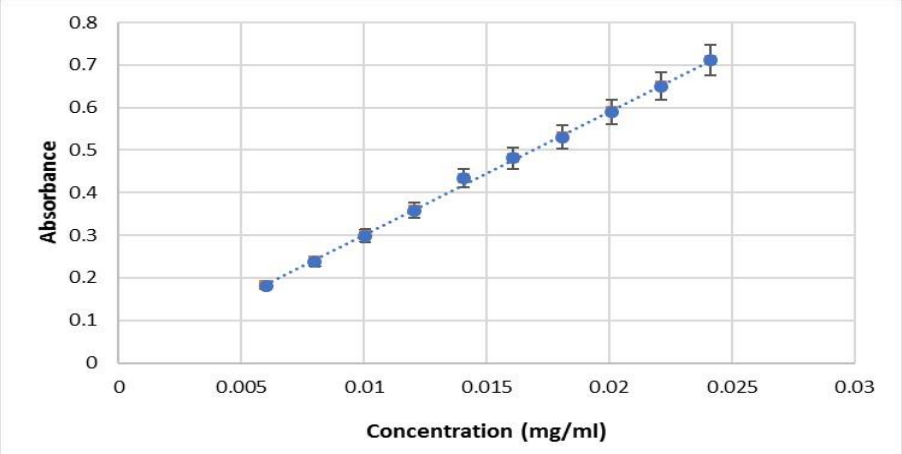

Figure 1: Calibration curve for diclofenac sodium in phosphate buffer (pH 6.8).

2.4. Pharmaceutical quality tests

Several tests have been performed on diclofenac sodium coated tablets, including appearance, weight variation, hardness test, disintegration test, content uniformity, TLC analysis, and dissolution test. The ampules were only tested for external appearance, TLC analysis, and content uniformity.

2.4.1. Weight variation

Twenty coated tablets of brand A and brand B were randomly selected and weighed individually. The mean weight, standard deviation (SD), and weight variation percentages were calculated. According to USP, for tablets with an average weight between 130 and 324 mg,

a deviation of ±7.5 % from the average weight is acceptable.

2.4.2. Hardness test

This test was performed on ten coated tablets of each brand. The hardness value is expressed in kg/cm^2. The average and standard deviation of tablet hardness were calculated. The minimum acceptable hardness value is 4 kg/cm^2.

2.4.3. Disintegration test

The disintegration time of each brand was measured using six coated tablets. Each tablet was placed in one tube of the basket, immersed in a one-liter beaker containing simulated gastric fluid, and kept at 37°C for two hours. After two hours, the simulated gastric fluid was replaced with a phosphate buffer solution at pH 6.8. According to USP, coated tablets should not show obvious signs of disintegration within 120 minutes in gastric fluid, but they should disintegrate within 30 minutes in phosphate buffer.

2.4.4. Content Uniformity

For coated tablets (50mg), ten randomly selected tablets of each brand were powdered separately and then dissolved in 100ml of phosphate buffer (pH 6.8). Samples were then filtered and further diluted to obtain suitable concentrations for analysis using a UV spectrophotometer at 276nm. Drug content was estimated using a previously prepared calibration curve. According to USP, samples will pass the test if the diclofenac sodium content is between 90 and 110% and the acceptance value AV is 15 or less.

For ampules (75mg/3ml), ten ampules of brand C were randomly selected. 1mL from each ampule was taken and diluted with phosphate buffer before measuring the absorbance. According to USP, samples will pass the test if the diclofenac sodium content is between 95 and 105% and the acceptance value AV is 15 or less.

2.4.5. Thin Layer Chromatography

Thin layer chromatography (normal phase) was performed on TLC silica gel plates (10×10cm). The solutions of pharmaceutical samples and the standard of diclofenac sodium were spotted on the TLC plates by a capillary tube. The mixture of cyclohexane: chloroform: methanol: and glacial acetic acid (6:3:0.5:0.5, v/v) was used as the mobile phase to separate the degradation products from diclofenac sodium.[16] The TLC plates were developed for about 30min and then dried at room temperature. The detection of product degradation was performed by UV lamb and by heating at 110°C after spraying the plates with a stable solution of vanillin-sulfuric acid reagent. The retention factors (Rf) of pharmaceutical samples were compared with the standard.

2.4.6. Dissolution Study

The dissolution USP apparatus II was used to study the dissolution profile of six coated tablets of each brand. The dissolution test was first carried out in the acidic phase (0.1N HCl medium) for two hours and then changed to the basic phase (phosphate buffer pH 6.8) for 45min. The temperature was maintained at 37±0.5°C and the rotation speed at 50rpm during the test.

10 ml of dissolution samples were withdrawn (at 60, 120min in HCl medium and at 5, 15, 25, 35 and 45min in phosphate buffer) and immediately replaced with the same volume of fresh medium. Each sample was diluted appropriately and analyzed using a spectrophotometer at 276nm. The release rate of diclofenac sodium was determined at each time point.

According to USP, tablets must resist the HCl medium for two hours and at least 75 % of the tablet content must be released in the phosphate buffer medium within 45 minutes.

3. RESULT AND DISCUSSIONS

Diclofenac sodium is available on the Syrian market in the form of coated tablets, creams, and ampules used alone or in combination with other drugs. This work aimed to study the pharmaceutical quality characteristics of several brands of diclofenac sodium after the expiry date and compare them with those of unexpired dosage forms of the same brands. Two commercial dosage forms were tested (coated tablets and ampules). Two brands of coated tablets and one brand of ampules were studied. The tested expired samples included samples seven months beyond their expiry date (ampoules of brand Ce), one year beyond their expiry date (tablets of brand Be1), two years beyond their expiry date (tablets of brand Ae), and 5 years beyond their expiry date (tablets of brand Be2).

The investigated quality characteristics of unexpired and expired coated tablets included appearance, weight variation, hardness, content uniformity, disintegration time, TLC analysis, and release rate. For unexpired and expired ampules, the assessed quality characteristics included only appearance, TLC analysis, and content uniformity.

3.1. Diclofenac sodium coated tablets

The studied unexpired and expired coated tablets of diclofenac sodium for brands A and B showed uniform color and a continuous coating layer.

The average weight of coated tablets of brands A and B was between 197mg and 265mg. Both unexpired and expired coated tablets for the two brands showed uniformity of weight since the percentages of weight variation were within the acceptance weight variation limit (±7.5%) according to USP (Table 2).

Table 2: Lowest/highest value of weight variation percent of brands A and B.

Brand	Code	Average weight (mg) 20 tablets	Lowest value of weight variation %	Highest value of weight variation %
A	An*	197.21	- 1.985%	2.32%
	Ae*	210.195	- 2.043%	2.618%
B	Bn	267.598	-3.298%	1.985%
	Be1	269.725	-4.421%	4.995%
	Be2	264.095	-2.156%	3.1%

*n: unexpired medication, e: expired.

The hardness of tablets affects their disintegration and dissolution. As the hardness of the tablet increases, disintegration time and dissolution time increase. All diclofenac sodium coated tablets (expired and unexpired) had a hardness value higher than 4kg/cm^2 (minimum required hardness value) (Figure 2). Expired and unexpired diclofenac sodium coated tablets for brand A had approximately the same values of hardness (An: 14.5±2.33kg/cm^2, Ae: $14.1 \pm 1.9 kg/cm^2$), while the hardness of the expired coated tablets for brand B had higher values (Be1: 19.3±1.5kg/cm^2, Be2: $14.4 \pm 1.6 kg/cm^2$) than the unexpired tablets (Bn: 8.8±1.3kg/cm^2).

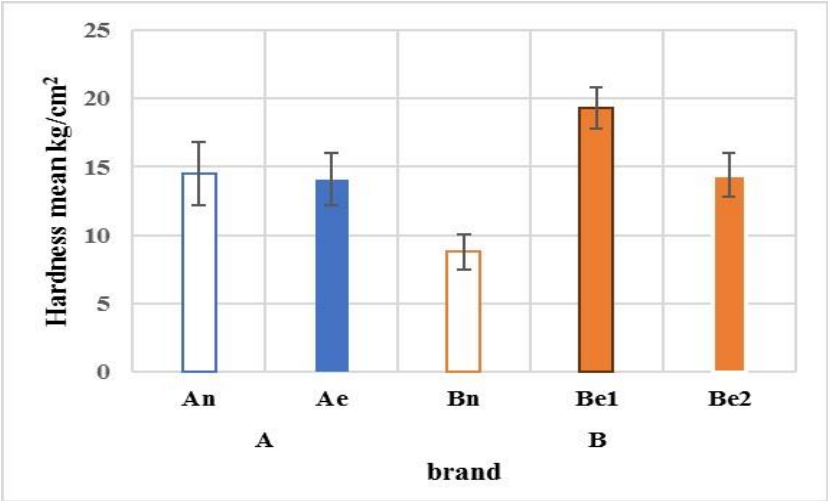

Figure 2: Hardness results of coated tablets brand A and B (n: unexpired, e: expired). Results are expressed as mean ± SD (n=10/brand lot).

The first important step for most tablets toward the solution is the disintegration or breakdown of the tablets into smaller particles. Therefore, the disintegration of the tablet is necessary for the absorption of the active molecules.[17]

All tested diclofenac sodium coated tablets (6 tablets) of brands A and B did not disintegrate in the acidic medium after 2 hours, but they completely disintegrated in the basic medium. The measured disintegration times of all diclofenac sodium coated tablets (expired and unexpired) were below the maximum USP limit of 30min in the basic medium (Figure 3). Disintegration time ranged from approximately 16.5min for brand B to 20min for brand A. This finding demonstrated no difference in disintegration time between the expired and the unexpired diclofenac sodium coated tablets for the same brand.

Many factors affect tablet disintegration time, including the hardness value of the tablets. Increasing the hardness of the tablets leads to an increase in the disintegration time.[18] It is worth noting that there was no linear relationship between the previously obtained hardness values of tested coated tablets and their times of disintegration. The expired coated tablets of brand B (Be1 and Be2) had the highest hardness values and had approximately the same time of disintegration as the unexpired tablets of the same brand (Bn), but lower time of disintegration as compared to both the expired and unexpired coated tablets of brand A. These findings may be due to the difference of the type and amount of excipients including disintegrants and binding agents used in the formulation of diclofenac sodium coated tablets and compression forces, which affect the tablet disintegration time.[19,20] A study investigated the effect of tablet hardness on its disintegration time. Tablets were manufactured with different hardness values using different wet binding agents. The results showed that the increasing of tablet hardness had no effect on the tablet disintegration time.[21]

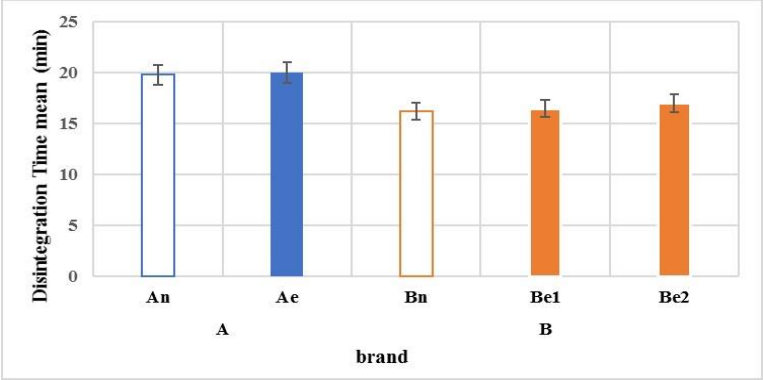

Figure 3: Disintegration time of coated tablet brand A and B in phosphate buffer pH 6.8 (n=6). Results are expressed as mean ± SD (n=6/brand lot).

Content uniformity determines the degree of conformity of the amount of active molecules between the pharmaceutical dosage form units. The average content of diclofenac sodium was 98.86% for An, 102.57% for Ae, 100.29% for Bn, 92.21% for Be1, and 100.34% for Be2 (displayed as a percentage of the quantity stated on the label) (Figure 4). The content of diclofenac sodium in each unexpired and expired tablet of brands ranged from 90% to 110%. The calculated AV was 10.10 for An (before the expiry date), 11.84 for Ae (2 years post the expiry date), 14.13 for Bn (before the expiry date), 14.90 for Be1 (one year post the expiry date), and 8.47 for Be2 (5 years post the expiry date). All studied brands (unexpired and expired) met the USP specifications. These results indicate that diclofenac sodium is stable and did not degrade after the expiry date. This consequence is in agreement with the study conducted to investigate the change in the active ingredient of diclofenac sodium tablets over a period of two years post the expiry date. The results of content test of these drugs met the USP requirements, which indicate that they retained their potency after expiry date, and diclofenac sodium was stable and did not degrade.[15]

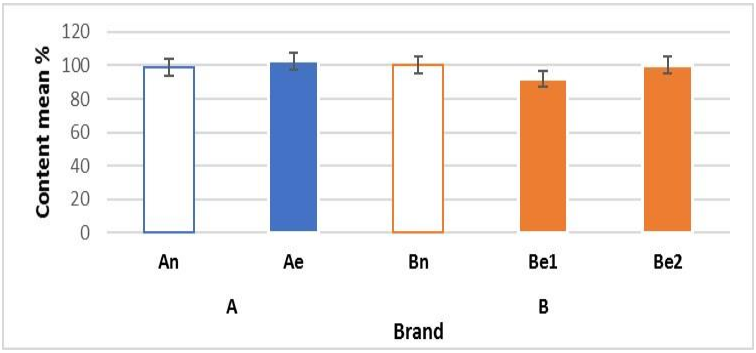

Figure 4: Results of content uniformity test for unexpired and expired coated tablets of two brands of diclofenac sodium (n: unexpired, e: expired). Results are expressed as mean ± SD (n=10/brand lot).

The results of the TLC analysis also showed that there were no degradation products of diclofenac sodium tablets. Where all spots of samples appeared in front of the standard spot, and the Rf values of the standard and samples were equal (0.5) (Figure 5).

Figure 5: Results of TLC analysis test for unexpired and expired diclofenac sodium coated tablets (Brand A). (S: diclofenac sodium standard, n: unexpired, e: expired).

Dissolution test is a measure of the concentration of drug released into the dissolution medium over time. This test simulates *in-vivo* drug dissolution and absorption. According to USP specifications, all six coated tablets of diclofenac sodium should not dissolute in HCl medium 0.1N in 2 hours, but they will release at least 75% of diclofenac sodium within 45min in phosphate buffer medium at pH 6.8.

The results showed that all samples (expired and unexpired) passed the test because they released 75% in less than 45 minutes (Figure 6). Time to release 75% was 26min for An (before the expiry date), 25min for Ae (2 years post the expiry date), 22min for Bn (before the expiry date), 24min for Be1 (one year post the expiry date), and 27min for Be2 (5 years post the expiry date). These results are in agreement with an *in-vitro* dissolution study on unexpired and expired metoprolol tablets available in community pharmacies of Poland. The test was performed using the apparatus 2 technique as described in the USP. The results showed that in vitro dissolution curves of unexpired and expired samples were almost identical and met the USP requirements.[12]

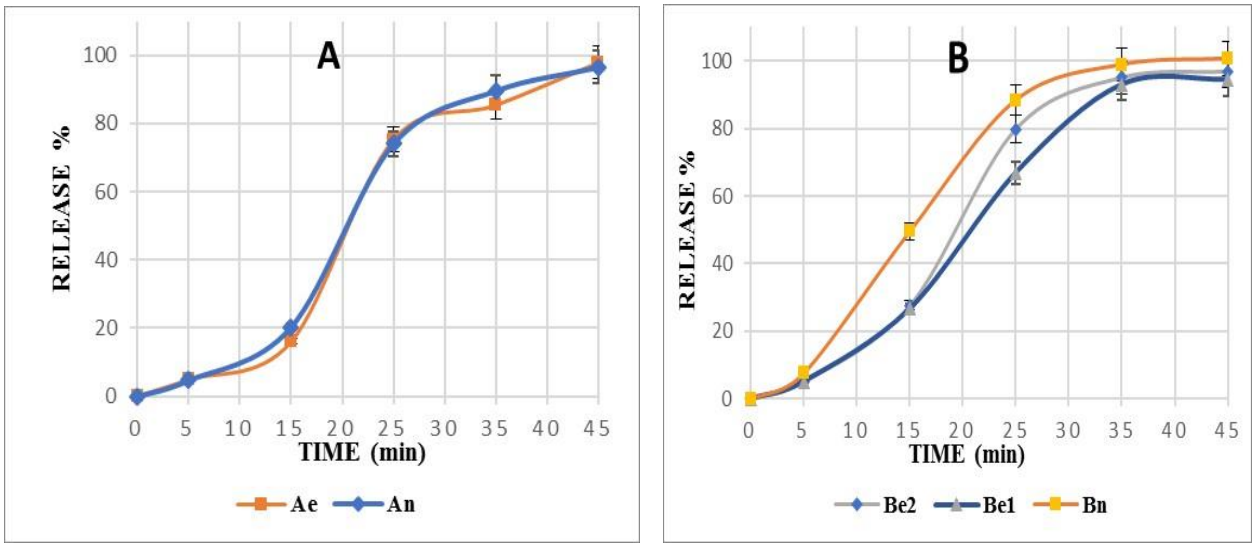

Figure 6: Dissolution profile for brand A: unexpired (An) and 2 years-expired (Ae), brand B: unexpired (Bn), one-year expired (Be1), and 5 years-expired diclofenac sodium coated tablets in phosphate buffer pH 6.8.

To compare the dissolution profiles of diclofenac sodium coated tablets, the difference factor (f1) and the similarity factor (f2) were used. Following FDA guidelines, two dissolution profiles are considered similar and bioequivalent, if the f1 value is between 0 and 15 and the f2 value is between 50 and 100. A high level of similarity between Ae (2 years post the expiry date) with An (unexpired) was found (f2: 88.24), as shown in Table 3. Whereas, a lower level of similarity for Be1 (one year post the expiry) and Be2 (5 years post expiry) with Bn, (f2 nearly 63). These results that the dissolution profiles of the expired diclofenac sodium coated tablets were comparable to those of unexpired tablets.

Table 3: Similarity factor (f2) and difference factor (f1) of dissolution profile comparison of expired and unexpired diclofenac coated tablets.

Brands	F1	F2
Ae and An	3.97	88.24
Be1 and Bn	11.35	63.57
Be2 and Bn	11.20	63.03

3.2. Diclofenac sodium ampules

Five ampules from unexpired (Cn) and 7 months post the expiry date diclofenac sodium samples (Ce) were selected and examined visually. The liquid was colorless and filled in a clear glass ampule with a red color ring on the neck. In addition, the liquid was clear and did not contain any undissolved particles that could be seen with the naked eye. The quality of the sealing was good, and the production date and the expiry date were labeled.[22]

The average content of diclofenac sodium was 100.78 % for Cn (unexpired) and 102.49 % for Ce (7 months post the expiry) date of label amount (Figure 7). Each ampule content of Cn and CE was between 95% and 105%. The calculated AV was 13.32 for Ce and 11.32 for Cn. All studied samples (unexpired and expired) met the USP specifications. These results indicate that diclofenac sodium was stable and did not degrade after expiry date in the ampule dosage form. The results of TLC analysis also showed that there were no degradation products of diclofenac sodium ampules (Figure 8). These findings

are in agreement with a study conducted to investigate the change in active ingredient of parenteral epinephrine post 2.5 years after expiry date, the result showed the studied ampules retained their potency after expiry date, and active ingredient was stable and did not degrade.[23]

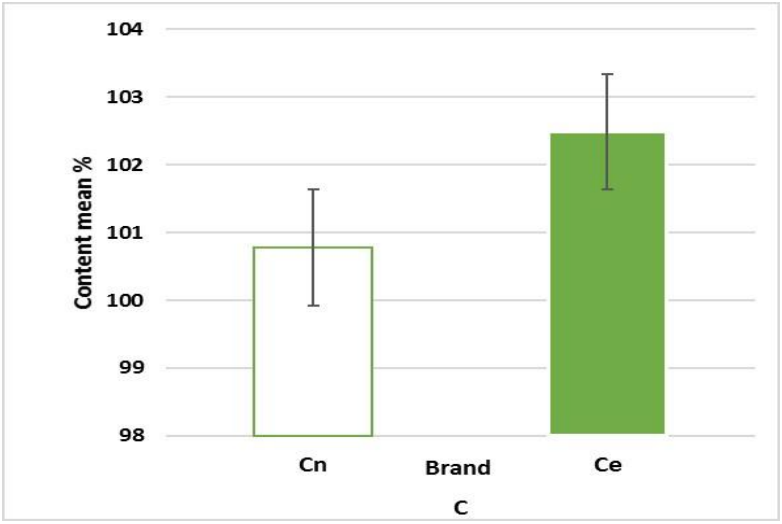

Figure 7: Results of content percent for unexpired and expired diclofenac sodium ampule (brand C). (n: unexpired, e: expired).

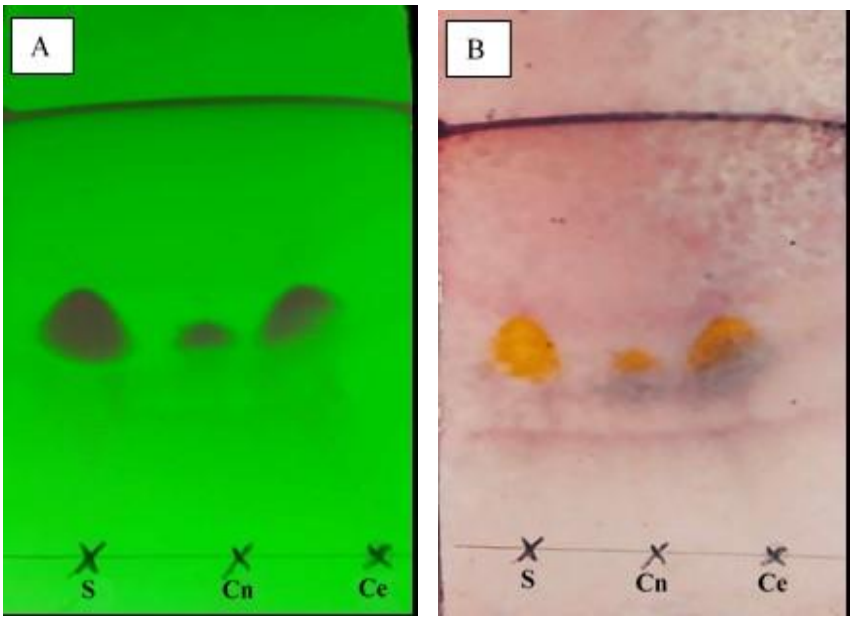

Figure 8: Results of TLC analysis test for unexpired and expired diclofenac sodium ampules (brand C) (A: UV lamp, B: Vanillin-Sulfuric acid reagent).

The study showed that there were no differences in physical and chemical properties between expired and unexpired diclofenac sodium preparations. The tested tablets (expired and unexpired) met the requirements for weight uniformity test, hardness test and disintegration test. According to the content and TLC tests results, the active substance did not destroy after the expiry date in both dosage forms (tablets and ampules), as all values were within USP limits. All studied tablets passed the dissolution test, which indicated there was no change in the drug's bioavailability after the expiry date. Difference factor (f1) and similarity factor (f2) values of all the tested brands of diclofenac coated tablets indicated that the release of the expired drug from all samples analyzed is similar to the unexpired drugs. Our study confirms that the labeled expiry date does not indicate the actual shelf life and the drug can remain effective after its expiry date. However, to confirm the clinical effectiveness of these preparations, it is necessary to conduct more studies and wide range of samples must be tested.

4. CONCLUSION

This study highlighted the importance of unexpired drugs. Unlike what is common, the drugs may be used after their expiration date because they maintain their

default specifications. Especially for drugs that are stable in different storage conditions, such as diclofenac.

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