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Determination of the active ingredient amounts of expired albendazole drugs

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Abstract

In this study, it was aimed to determine the active ingredient amounts of 24 expired and 3 unexpired antiparasitic drugs containing the active ingredient albendazole using UV-Vis and RP-HPLC techniques. The drugs were prepared using methanol (MeOH) and 1 N HCl (70:30, v/v) mixture. The quantitative analyses of albendazole were carried out at 338 nm in the range of 1.562-75 µg mL-1 (R^2=0.9997) in UV-Vis. In RP-HPLC, separations were achieved using Nucleosil 100-5, C18 column (250 x 4.6 mm, 5µm) in isocratic elution. 0.02 M phosphate buffer (pH 3.0) and MeOH mobile phase (30:70, v/v) were used at a flow rate of 1.0 mL min-1. Detections were conducted in the same concentration range (R^2=0.9998) using a PDA detector (210 nm). The results obtained using both techniques were evaluated by taking into account the studies in the literature. In this study, it was determined that the loss of active ingredient in veterinary drugs containing different albendazole active ingredient examined decreased over time and that some drugs containing albendazole active ingredient on the market may have less active ingredient amount than the acceptable limit values.

Keywords: Albendazole, expired drugs, RP-HPLC, UV-Vis spectrophotometer

Introduction

Albendazole (ABZ) is a benzimidazole derivative compound with high efficacy at low doses and a wide spectrum of anthelmintic effects, used in veterinary and human drug in the treatment of parasitic infestations caused by helminths [1,2]. ABZ is used in human drug, especially in diseases caused by Enterobius, Ascariss, Ancylostoma, Necator, Trichuris, Taenia, and Trichinella spiralis. In veterinary drug, it is used against Bunostomun, Cooperia, Haemonchus, Nematodirus, Oesophogostomus, Trichostrongylus, Strongyloides, and Dictyocaulus species in ruminants; Strongylus, Strongyloides, Dictyocaulus, Parascaris, Oxyuris, and Anoplocephala species in horses; lungworms, heartworms, ascarids, hookworms, and stripworms in dogs and cats; Ascaridia, Heterakis, Kapillaria, Amidostomum, Trichostrongylus, and Hymenolopis species in poultry. It is also extremely effective against Strongylus vulgaris larvae migrating in the adventitia layer of the artery. ABZ is widely used because it has a wide anthelmintic spectrum and is inexpensive [3].

Shelf life, or in old terms "Expiration", is defined by the World Health Organization (WHO) as the last date that drugs can be used [4]. Shelf life is calculated from the accelerated degradation results obtained by exposing drugs to stress conditions. Many factors influencing its shelf life are taken into consideration while determining the expiration date of the drugs [5,6].

Since they constitute a significant part of health expenditures, the rational use of drugs is of great importance in terms of more efficient use of limited resources [7,8]. The date stated on the drugs is the date by which the manufacturer guarantees the safety and full potency of the drug. The actual expiration date at which the drug will remain safe and effective is a matter open to debate.

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Since 1979, the FDA has required pharmaceutical companies to post expiration dates on prescription and over-the-counter drugs. Aside from drugs such as insulin, nitroglycerin, and liquid antibiotics, whose active ingredients are known to become less stable over time, many other drugs may have a longer shelf life than stated on the label. As a result of the investigations, it was determined that drugs, some of which were produced at least 40 years ago (including antihistamines, painkillers, and diet pills), were able to maintain their full potential despite this long period [9-11].

However, the uses of poor quality and substandard drugs are increasing worldwide. This situation is an inevitable result of inadequate controls in many countries [12]. The presence of substandard drugs can pose an economic threat to the public, as well as health problems in living beings. In order for the drugs used to be effective, they must have sufficient active ingredient content and the necessary physical properties [13]. If the amount of active ingredient of a drug is not within the standard acceptance range, it is not safe for living beings. For example, with drugs containing insufficient amounts of ABZ, some undesirable situations such as failure to achieve the desired treatment, the need for repeated treatment causing additional costs, or the development of a resistant parasite population in the long term may ocur [14].

In this study, the active ingredient amounts of 24 expired and 3 unexpired anthelmintic ABZ veterinary drugs were analyzed using UV-Vis and RP-HPLC with PDA techniques. The results obtained from both techniques were evaluated by comparing them with the results of other studies in the literature.

Material and Methods

Instruments

Quantitative ABZ ($C_{12}H_{15}N_3O_2S$) measurements in tablet dosage forms were carried out using a UV-Vis spectrophotometer and RP-HPLC techniques. Absorbance measurements were performed using a double-beam UV-Vis spectrophotometer (AE-S90-MD Model) with a spectral band width of 1 nm using quartz cells with a 1.0 cm path length at 338 nm. Chromatographic analyses were performed on an Agilent 1100 RP-HPLC system using Nucleosil 100-5, C18 chromatographic column (250 x 4.6 mm id, 5 µm particle size) at 30°C. The injection loop volume was 20 µL. An isocratic mobile phase containing 0.02 M phosphate buffer (pH 3.0) and MeOH in a ratio of 30:70 (v/v) was used at a flow rate of 1.0 mL min^{-1} with a diode-array detector (PDA) set at 220 nm. A pH meter (inolab WTW pH 730) was used to adjust the pH of the mobile phase. Sonication was carried out using a Wisd Wise Clean (Daihan) ultrasonic bath sonicator. Samples were centrifuged using a Hettich Centrifuge (Universal 320, Hettich Lab Technology) at 4000 rpm. An ATX 224 (Shimadzu) analytical balance (Capacity: 220 g and precision: ±0.1 mg) was used for the weighing.

Chemicals and Materials

ABZ was purchased from Sigma-Aldrich, USA. MeOH and HCl (37%) were obtained from Merck (Darmstadt, Germany). Ortho-phosphoric acid (H_3PO_4, 85%) and sodium dihydrogen phosphate dihydrate ($NaH_2PO_4 \cdot 2H_2O$) used for the mobile phase were acquired from Merck (Darmstadt, Germany). The solutions were prepared using the Direct-Q5 UV water purification system (18.2 MΩ cm, Merck Millipore). Samples were filtered through a polytetrafluoroethylene (PTFE) membrane filter with a pore size of 0.45 µm purchased from Isolab. The drugs used in the study with an expiration date of less than 1 year were obtained from veterinary clinics before expiration dates. Other drugs stored in a dark environment and protected from heat, light, and moisture were obtained from Van Yüzüncü Yıl Üniversity, Faculty of Veterinary Medicine.

Method

Preparation of standard solutions: A standard stock solution of ABZ in the concentration of 1000 µg mL^{-1} was prepared using MeOH:1 N HCl (70:30). Working standard solutions of ABZ in the range of 1.562-75 µg mL^{-1} were prepared using 100 µg mL^{-1} solution in MeOH:1 N HCl (70:30) prepared from 1000 µg mL^{-1} ABZ stock solution. Analyzes of the prepared solutions (n=3) were carried out with two different UV-VIS and RP-HPLC techniques.

Pharmaceutical formulation preparation: 5 tablets were finely powdered for each drug containing different amounts of ABZ active ingredient. Three parallel samples of 10 mg of each drug were weighed and made up to 25 mL with MeOH:1 N HCl (70:30, v/v) [15] in 50 mL conical centrifuge tubes. The drug samples were sonicated in an ultrasonic bath for 30 min and centrifuged at 4000 rpm for 10 min. Samples were filtered through a 0.45 µm PTFE membrane syringe filter and the supernatants were then transferred to another centrifuge tube. Drug samples were prepared with MeOH:1 N HCl (70:30, v/v) to contain 20 µg mL^{-1} ABZ from each supernatant sample obtained. Samples were analyzed three times using UV-Vis and RP-HPLC methods. 1.5 mL glass vials were used for RP-HPLC analysis.

UV-Vis Absorption Measurements: Absorbance measurements of ABZ for standard and drugs were performed using a double-beam UV-Vis spectrophotometer. A quartz cell of 1.0 cm was used in the measurements. A calibration curve was constructed using ABZ standards prepared in a mixture of MeOH and 1 N HCl (70:30, v/v) in the 1.562-75 µg mL^{-1} range for UV-Vis. The calibration curves were found to be linear for seven standard samples with a coefficient of determination (R^2) of 0.9997 ($y=0.0316x+0.0291$, $\lambda max=338$ nm). The obtained calibration curve is given in Figure 1. The drug solutions containing 20 mg L^{-1} of ABZ in MeOH: HCl (70:30, v/v) solvent were measured on the UV-Vis spectrometer at 338 nm.

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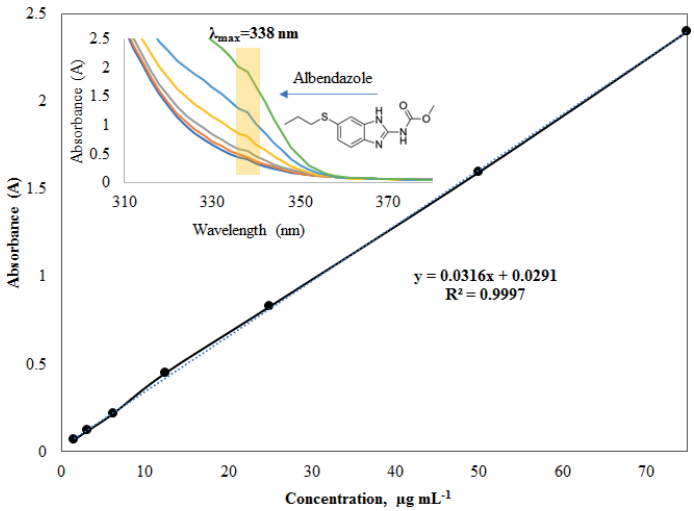

Figure 1. Calibration curve of ABZ in UV-Vis

HPLC Measurements: The RP-HPLC system equipped with a photodiode array detector (PDA) including a C18 column was used to quantify the ABZ drug. The measurements were performed at 30°C. The injection volume was set to 20 µL. 20 mM phosphate buffer (pH 3.0) and MeOH mixture (30:70, v/v) [16] were used in isocratic mode by keeping a 1.0 mL min^{-1} flow rate. Retention time was found to be 7.1 min at 220 nm. ABZ standards prepared with MeOH and 1 N HCl (70:30, v/v) solvent mixture were measured and the linear range was determined. The calibration curve was linear in the range of 1.562-75 µg mL^{-1}. The linear regression equation was y=142.21x+77.029 with a R^2 of 0.9998. The calibration curve constructed by plotting the RP-HPLC-determined peak area as a function of ABZ concentration is demonstrated in Figure 2. Chromatographic measurements of 20 mg L^{-1} ABZ drugs prepared with MeOH: HCl (70:30 v/v) solvent were carried out at 220 nm.

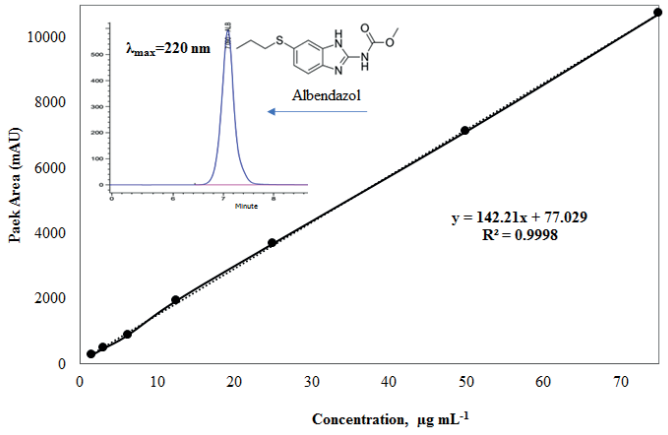

Figure 2. Calibration curve of ABZ in RP-HPLC

Results

Details regarding expired ABZ veterinary drugs are presented in Table 1. Also, the amounts and loss rates of active substances determined by applying both analytical techniques in the expired and unexpired ABZ drugs are shown in Table 2. According to Table 1, among the ABZ drugs studied, the majority of which have expiration dates over 10 years (between 13-16 years). Approximately 2 of the drugs are over 20 years old, 4 of them are over 30 years old, and 2 of them are over 40 years old. In addition, the expiration dates of 3 drugs have passed less than 1 year. The shelf life of these drugs varies between 1 year and 5 years. However, most drugs have a two-year shelf life. In addition to expired ABZ drugs, we also determined the amounts of ABZ active ingredients in 3 unexpired drugs that will expire in 2 or 3 years (Table 1) using both techniques to check the accuracy of the experimental results.

Table 1. Informations about the shelf life of drugs, their manufacturing and expiration dates, and the periods past their expiration dates.

Drug number	Manufacturing and expiration date (ED)	Drug shelf life	Time past ED (year/month)
1	07/2021-07/2023	2 year	5 month
2	07/2021-07/2023	2 year	5 month
3	03/2021-03/2023	2 year	9 month
4	05/2008-05/2010	2 year	13 year 7 month
5	05/2006-05/2010	2 year	13 year 7 month
6	02/2008-02/2010	2 year	13 year 10 month
7	08/2007-08/2009	2 year	14 year 4 month
8	06/2007-06/2009	2 year	14 year 6 month
9	06/2007-06/2009	2 year	14 year 6 month
10	02/2007-02/2009	2 year	14 year 10 month
11	02/2007-02/2009	2 year	14 year 10 month
12	05/2006-05/2008	2 year	15 year 8 month
13	05/2004-05/2008	4 year	15 year 8 month
14	05/2006-05/2008	2 year	15 year 8 month
15	04/2006-04/2008	2 year	15 year 9 month
16	06/2004-06/2007	3 year	16 year 6 month
17	10/1999-10/2003	4 year	20 year 2 month
18	01/1999-01/2003	4 year	20 year 11 month
19	08/1988-08/1989	1 year	34 year 4 month
20	05/1980-05/1985	5 year	38 year 7 month
21	05/1980-05/1985	5 year	38 year 7 month
22	05/1980-05/1985	5 year	38 year 7 month
23	06/1978-06/1983	5 year	40 year 6 month
24	06/1978-06/1983	5 year	40 year 6 month
25	03/2023-02/2026	3 year	new production
26	06/2021-05/2025	2 year	new production
27	10/2021-09/2025	2 year	new production

According to the experimental findings (Table 2), the percentages of active ingredient losses in expired ABZ drugs over the years have ranged from 30% to 96% and from 28% to 97% in spectrophotometric and RP-HPLC measurements, respectively. The active ingredient loss in expired drugs with an expiration date of less than 1 year is between 37% and 79% and 39% and

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79% according to spectrophotometric and RP-HPLC analysis results. It has been seen that the active ingredient losses of ABZ drugs with an expiration date exceeding approximately 13-16 years are between 30%-82% and 28%-80% according to spectrophotometric and RP-HPLC measurements, respectively, while in drugs whose expiration date exceeds approximately 20 years, these amounts vary between 81%-95% according to spectrophotometric and HPLC analytical measurements. In addition, the active ingredient losses in drugs with an expiration date of approximately 34-40 years are between 76%-96% and 74%-97% according to spectrophotometric and RP-HPLC results. In the 3 unexpired drugs examined, the amount of active ingredient was found to be 4-12% lower in UV-Vis and 5-14% lower in HPLC. The obtaining experimental results showed that the amounts of active ingredient of expired and unexpired ABZ drugs obtained from both techniques were very close to each other.

By the United States Pharmacopoeia (USP), the acceptable limit of the active ingredient amount of a drug (tablet) should be no less than 90% or more than 110% of what is stated on the label [17]. The amounts of active ingredient results obtained for expired and unexpired ABZ drugs were assessed taking into account the USP that states that the acceptable limit of the active ingredient amounts could be at most 10% less or more. The results indicated that all unexpired drugs analyzed using both techniques were outside according to the US pharmacopeia. In addition it was observed that two of unexpired ABZ drugs were within the pharmacopeia acceptable limit values, while one drug was lower than the acceptable limit (Table 2).

Table 2. Active ingredient amounts detected by UV-Vis and RP-HPLC techniques (n=3)

Drug number	Amount of active ingredient given in the formula (mg/tbl)	UV-Vis			RP-HPLC-PDA			Compliance with US Pharmacopoeia limits
		Amount of active ingredient detected (mg/tbl)	Difference from formula (mg/tbl)	Loss rate (%)	Amount of active ingredient detected (mg/tbl)	Difference from formula (mg/tbl)	Loss rate (%)	
1	300 mg	85±10[a]	-215	72	79±5	-221	74	-
2	300 mg	62±5	-238	79	64±5	-236	79	-
3	1200 mg	755±52	-445	37	732±32	-468	39	-
4	300 mg	65±8	-235	78	63±5	-237	79	-
5	300 mg	105±8	-195	65	103±6	-197	66	-
6	1200 mg	468±12	-732	61	456±32	-744	62	-
7	300 mg	66±6	-234	78	70±5	-230	77	-
8	300 mg	54±1	-246	82	59±3	-241	80	-
9	300 mg	55±4	-245	82	60±6	-240	80	-
10	1125 mg	784±51	-341	30	810±60	-315	28	-
11	375 mg	145±18	-230	61	145±19	-230	61	-
12	1200 mg	408±17	-792	66	428±15	-772	64	-
13	300 mg	99±21	-201	67	99±19	-201	67	-
14	1200 mg	384±24	-816	68	380±7	-820	68	-
15	300 mg	64±2	-236	79	74±2	-226	75	-
16	600 mg	148±39	-452	75	146±27	-454	76	-
17	600 mg	116±3	-484	81	114±6	-486	81	-
18	76 mg	4±1	-72	95	4±1	-71	95	-
19	113 mg	27±1	-86	76	29±2	-84	74	-
20	152 mg	6±2	-146	96	5±3	-147	97	-
21	152 mg	9±4	-143	94	6±3	-146	96	-
22	152 mg	11±3	-141	93	9±5	-143	94	-
23	152 mg	6±1	-146	96	7±2	-145	95	-
24	152 mg	7±2	-147	95	6±3	-146	96	-
25	1500 mg	1439±25	-61	4	1420±38	-80	5	+
26	1125 mg	1028±26	-97	9	1035±59	-90	8	+
27	1200 mg	990±22	-210	12	967±45	-233	14	-

a: mean value ± Standard deviation, tbl: tablet

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Discussion

Parasite-related diseases that can cause important problems in terms of animal health in the livestock industry are tried to be controlled by using anthelmintic drugs. Albendazole is an antiparasitic drug widely used for this purpose. To achieve the required therapeutic impact with minimal side effects, it is critical that the drug's active ingredient amounts stays within acceptable levels. On the other hand, animals treated with ABZ drugs could fail to recover and become resistant due to the low concentration of the drug's active ingredient. There are studies showing that anthelmintic drugs could contribute to the emergence of drug resistance in organisms [18]. Also, a higher dose of the drug than the specified dose may not be safe for the health of living beings [14].

The expiration date stated on drug is the date on which the drug manufacturer guarantees the usefulness of the drug under conditions such as ideal temperature, humidity, light exposure, and packaging integrity. However, the actual expiration date at which the drug will remain safe and effective is a matter open to debate. Drug companies avoid giving guarantees to drugs that can be used for longer periods due to the high costs of stability tests. Thus, even after their expiration date, usable drugs are destroyed in vain and cause damage to the economy [11].

Upon examining the expiration dates of the drugs examined in this research, it is seen that some preparations have a 2-year shelf life, and some have a 3-or 5-year shelf life. Test results during the production phase need to be verified for long periods in the transition from the laboratory to pilot production [19]. However, these tests require a very long time and expense for drug manufacturers, which are commercial organizations. Therefore, even if the expiration date has passed, there may not be a significant change in the active ingredient amounts of the drugs. The application of analytical approaches based on the determination of the amounts of active ingredients in drugs on the market is important in terms of determining whether drugs contain the pharmacopeia limit values in terms of pharmaceutical effectiveness and their usability even if their dates have passed.

When we look at the amounts of active ingredients in the 24 expired antiparasitic veterinary drugs (except for the unexpired drugs) in our study, it is seen that all of them are outside the pharmacopeia limits. Although it has been determined that the loss of active ingredients has increased over the years, it has been determined that there is a serious loss of active ingredients in drugs that have barely expired.

One of the important points that draws attention in this study is that the amounts of active ingredients contained in the drugs may be lower than stated. For example, when we evaluate the drugs containing 300 mg ABZ active ingredient; while the loss rates in the active ingredient results obtained with both techniques for drugs whose expiration date has exceeded 5 months vary between 72-79%, this difference has been found between 65-82% in the last 15 years. For the drugs containing 1200 mg of active ingredient whose expiration date has passed 9 months, these amounts were 37 and 39% for UV and HPLC, respectively, while the change in the 13-15 year period was determined as 61-68%. However, in another drug with an active ingredient amount of 1125 mg and an expiration date of 14 years, this value was determined as 30% in UV and 28% in HPLC, respectively. Another remarkable result is that in a drug containing 113 mg of ABZ active ingredient, 34 years after its expiration date, the loss was determined to be 76% and 74% for UV and HPLC, respectively. When we look at the experimental results obtained from unexpired drugs (3 drugs); it was observed that while two of them meet the pharmacopeia limits, one of them does not meet the required limit value.

In a study conducted by Hişmioğulları [20] on the active ingredient contents of some veterinary antibacterial drugs (aminoglycosides and sulfonamides) licensed in Turkey and the effect of some storage conditions, it was found that the detected amounts varied depending on the amount of active ingredient. It was also stated that the primary factors in the deterioration of the drugs are storage conditions, storage time, and the chemical properties of the active ingredients.

In the literature review, not many studies were found to determine the amount of active ingredient in expired drugs. But, Atasoy and Sonal [21] examined the amounts of active ingredients in 38 veterinary antibiotic preparations containing ampicillin, sulfadiazine-trimethoprim, and oxytetracycline depending on the elapsed expiration dates and found that 8 of them were outside the pharmacopeia limits. They reported that the loss rate in ampicillin samples was at most 15.83%, in Sulfadiazine-trimethoprim samples the loss rate was at most 62% for Trimethoprim, 80% for sulfadiazine, and the highest loss in the amount of active ingredient in oxytetracycline samples was 23%. In addition, the authors determined that there was no loss of active ingredient in drugs containing ampicillin with an expiration date of approximately 6 years, but there was a 15.86% loss of active ingredient in drugs with an expiration date of approximately 2 years. They stated that the rate of active ingredient loss was 23% in oxytetracycline preparations with an expiration date of approximately 8 years, while it was 17.5% in oxytetracycline preparations with an expiration date of approximately 9 months.

In a study conducted by Türel et al. [22] which is similar to our study, the active ingredient amounts in 16 illegal oxytetracycline drugs and 20 domestic drugs sold in Van were analyzed by HPLC. They concluded that four out of five expired drugs had levels of active ingredient less than the amounts stated on the label.

In addition to, Sharma et al. [23] conducted a study to investigate the chemical potency, physical stability, and effectiveness of analgesic agents over two years after the expiration date and stated that they maintained their chemical strength, physical

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stability, and analgesic effectiveness. They also expressed that a drug's expiration date is not an accurate reflection of its actual shelf life.

Cantrell et al [24] examined the active ingredient amounts of 8 drugs containing 15 different active ingredients in their original, unopened packages, with an expiration date of 28 to 40 years, and found that 12 active ingredient contents were found to be at concentrations of at least 90% of the labeled amounts, two active ingredients (aspirin and amphetamine) were found to be less than 90% of the labeled amount, and one active ingredient (phenacetin) was present in more than 90% of the labeled amounts in 1 drug tested, while less than 90% was present in another drug. According to these results they stated that many prescription drugs retain their full potency for decades beyond the expiration dates set by the manufacturer.

Conclusion

The study's conclusions indicate that some antiparasitic drugs containing the active ingredient ABZ in veterinary on the market may have less active component than the acceptable limit values. Although we observed that the amount of loss decreased over time in the different ABZ brands examined, the high amount of active ingredient loss in drugs with an expiration date of less than one year reveals this idea. However, in another ABZ drug whose expiration date has passed 34 years, the loss rate was found to be around 75%. This study reveals that the active ingredient contents of veterinary drugs in the legal market need to be monitored regularly.

Destroying expired drugs means eliminating a certain amount of the active ingredient without being evaluated. However, after it is determined whether the expired drugs maintain their stability, the route of administration of the remaining active ingredients can be changed so that they can be used for therapeutic purposes or re-evaluated as raw materials. For example, by checking the active ingredient amounts at regular intervals, the remaining amounts after the shelf life of the drugs can be used by giving to smaller-sized animals. Thus, bidirectional economic losses can be reduced as a result of utilizing the active ingredients, which are mostly imported drugs.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

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Ethical Approval
It does not require ethics committee approval.

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