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Product quality evaluation of marketed veterinary Ivermectin formulations in Addis Abeba

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Abstract

Objectives: To assess the prevalence of substandard products, a quality study based on the United States Pharmacopeia (USP) standards was conducted on the veterinary medicinal product ivermectin.

Methods: From September 2020 to January 2021, a cross-sectional quality analysis was carried out on 19 samples of pharmaceutical products. These samples were obtained from all veterinary retail outlets in Addis Ababa, Ethiopia. The analysis included organoleptic assessment for packaging-related information and physical appearance, as well as high-performance liquid chromatography (HPLC)-based physicochemical analysis for identity, assay, packaging uniformity, and HLB ratio. The procedures followed were in accordance with the USP recommendations. The quality analysis took place at the national veterinary drug quality test center.

Results: The quality analysis has revealed the presence of substandard products for uniformity of packaging (15.8%), API assay (15.8%), and filling to a volume (16.67%). However, both sampled products demonstrated the expected API, recommended physical appearance, and consistent packaging information. The prevalence ratio values for all H1B1a/(H1B1a+H1B1b) chemical species were greater than 0.95.

Conclusion: The findings from this study clearly indicate the alarming presence of substandard veterinary pharmaceutical products. This highlights the need for strengthening the regulatory surveillance system.

Keywords: Ivermectin, Quality Analysis, Substandard Drugs, Ethiopia.

Introduction

Ivermectin, an antiparasitic and wormicide agent, has been in existence since it was introduced to the global market in 1981. It is derived from a class of chemicals known as avermectins, which are generated by Streptomyces avermitilis, a gram-positive mycelial bacterium. Ivermectin is the 22,23-dihydro derivative of the actinomycete-produced macrocyclic lactone avermectin B1. This compound is highly effective at low dosages against various roundworms and arthropod parasites. Its pharmacological activity is attributed to its ability to enhance the transmission of a neurotransmitter called γ-aminobutyric acid (GABA) in the nervous system. Initially, it was used in many countries for the treatment and prevention of parasites in cattle, horses, and sheep.[1,2] In 1987, following its initial marketing for veterinary purposes, ivermectin was subsequently approved for use in human medicine.[3] Ongoing research endeavors have since revealed its noteworthy anti-inflammatory and antiviral characteristics.[4] Notably, a recent report highlighted the utilization of topical application of ivermectin by healthcare professionals as a prophylactic measure against COVID-19.[5]

Avermectins are a group of compounds that share structural similarities with antibacterial macrolides and antifungal macrocyclic polyenes.

These compounds have a 16-membered macrocyclic lactone backbone, which undergoes further substitution with a hexabydrobenzofuran unit (C-2 to C-8a), a disaccharide substituent at C-13, and a spiroketal unit (C-17 to C-28). The actinomycete Streptomyces avermitilis produces four pairs of closely related compounds through fermentation: avermectin AI, A2, B1, and B2.

The A-compounds have a 5-methoxy substituent, while the B-compounds have a 5-hydroxy substituent. Furthermore, the 1-compounds have a 22,23-double bond, which is generated by dehydrating the 2-compounds' axial 23-hydroxy group.[6] Ivermectin, a medicinal product, is composed of two chemically modified avermectins. These avermectins contain a minimum of 80% 22, 23-dihydroavermectin-B1a and more than 20% 22, 23-dihydroavermectin-B1b. This highly lipophilic substance can dissolve in most organic solvents, but it is almost insoluble in water, with a concentration of only 0.0004% m/v.[7]

Antimicrobial resistance occurs when a segment of an infectious agent is capable of surviving standard doses of a product that is effective against other groups of its kind.[8] This phenomenon is a result of various social and administrative factors that contribute to the emergence and spread of resistance. The degree of antimicrobial consumption is a known factor that affects the evolution of microbial agents.[9] Additionally, the use of low-quality medicines that result in subtherapeutic levels has been identified as a common factor in the development of resistance.[10,11] Moreover, the administration of antimicrobial agents in veterinary medicine to animals bred for commercial food production has been linked to the dissemination of antimicrobial resistance to human pathogens.[9] The worldwide prevalence of substandard drugs in both human and veterinary products has been well documented.[12] Furthermore, the emergence of resistance to anthelmintic drugs,[13,14] including ivermectin, in helminth parasites in veterinary medicine has been reported in several regions, including the United States, Ghana, and Cameroon, raising concerns about the possibility of a similar trend in human parasites.[14,15] Approximately 10% of medications in developing nations are either substandard or counterfeit.[16] While various types of pharmaceutical products have been found to be affected, the available evidence indicates that anti-infectious agents, specifically antibiotics and antiparasitic agents, are the most commonly counterfeited products in developing countries.[17]

The monitoring of product quality is crucial in order to mitigate the development of drug resistance, with substandard products being a significant contributing factor. This is particularly important in urban areas, where the product is extensively utilized for its efficacy against ectoparasites and worms.

Objectives

The objective of this study was to evaluate the quality of the veterinary product ivermectin available on the market, employing quality assessment procedures based on the United States Pharmacopeia (USP) standards.

Methods

From September 2020 to January 2021, a cross-sectional study was carried out in Addis Ababa, Ethiopia, focusing on post-marketing surveillance for the quality of veterinary product ivermectin. The study encompassed ten sub-cites and 117 districts, as reported in reference.[18]

Nineteen samples of various ivermectin products were obtained from veterinary pharmacies. Each encounter yielded a sufficient amount of sample for analysis. The collected samples included injectable and oral liquids, as well as a combination tablet containing ivermectin and clorsulon. To ensure proper identification and handling, each sample was appropriately labeled and treated in accordance with the recommendations provided by the respective manufacturer. For the analysis, a high-performance liquid chromatography (HPLC) system equipped with a UV-Vis detector (Shimadzu-CTO-20AC) was utilized. The analytical setup involved the use of acetonitrile, hydrochloric acid (37%), methanol, sulfuric acid (98%), and a reference standard of ivermectin (USP). All reagents and chemicals employed in the analysis were of analytical grade and met the required purity standards.

The physical characteristics of a sample were thoroughly inspected using a checklist recommended in the USP and other relevant references.[19,20] The analysis was carried out using a HPLC system equipped with a UV-Vis detector (Shimadzu-CTO-20AC) using the techniques indicated in the USP.[20] The parameters of identity, content assay, H1B ratio, packaging uniformity, and filling volume were assessed using this method. To evaluate the uniformity of mass among tablets of each brand, twenty tablets from a specific sample were individually and collectively weighed. The differences between the masses of the individual tablets and the mean mass of the twenty tablets were then compared. For injectable preparations, the fill volume was determined by evaluating ten vials from each sample. Furthermore, the regulatory registration status of the samples was confirmed by cross-referencing with the national list of veterinary medications registered.[20,21]

In the present investigation, the data collection approach employed did not involve the use of human or animal subjects, thereby rendering ethical clearance unnecessary. The study was conducted in accordance with the Declaration of Helsinki. Institutional Review Board and institutional approval was obtained.

The continuous variables were expressed as the mean ± SD, and the categorical variables were presented as a percentage and frequency. All statistical analyses were performed with SPSS (version 16.0, SPSS Inc, Chicago, IL, USA). A "P-value" less than 0.05 was considered significant.

Results

Tables 1 and 2 present the results of the organoleptic assessment conducted on the packaging, including primary and secondary packaging integrity, label, and packaging insert, as well as the evaluation of the product's overall appearance. In the meantime, Tables 3 and 4 outline the drug's physicochemical quality criteria, such as identification tests, package weight fluctuation, filling capacity, and assay, which relate to the amount of active pharmaceutical substances present. The drug's organoleptic and physicochemical characterization was carried out in line with World Health Organization (WHO) and USP criteria.[20,22]

The purpose of the identity test is to verify the existence of ivermectin in every sample of ivermectin that undergoes a quality test. This is accomplished by comparing the retention duration of the samples in the chromatographic response to that of the reference standard [Tables 2, 3, and 4]. It was confirmed that all samples indeed contained the anticipated active pharmaceutical ingredient, ivermectin.

Table 1. Packing information and labels available, Physical characteristics of the injectable liquid (Ivermectin + Clorsulon), liquid Ivermectin for oral drench and oral tablet ivermectin) preparations

Product Sample	Strength (mg/unit)	Uniformity of shape/ appearance	Uniformity of volume/ size	Uniformity of color	Breaks, cracks and splits	Embedded surface spot or contamination
1	5 mg#	Yes	Yes	Yes	No	No
2-15	10mg/ml	Yes	Yes	Yes	No	No
16	10 mg +100 mg /ml	Yes	Yes	Yes	No	No
17-19	0.8 mg/ml*	Yes	Yes	Yes	No	No

	Container and closure	Medicine strength (mg/unit)	Dosage statement	Batch/ Lot No	Manufacture & expiry date	Storage information	Leaflet or package insert
1-17	Yes	Yes	Yes	Yes	Yes	Yes	Yes

*liquids for oral drench; $ oral tablet

Table 2. Retention times of different brands of Ivermectin as comparison with the standard

Product Sample	Dosage form	Sample RT		Standard/USP RT		Difference		Remark
		H2B1a	H2B1b	H2B1a	H2B1b	H2B1a	H2B1b	
1	Tablet	8.572	7.175	8.573	7.174	0.001	0.001	Negligible
2	Injectable	8.573	7.176	8.572	7.177	0.001	0.001	Negligible
3	Injectable	8.573	7.176	8.571	7.173	0.002	0.003	Negligible
4	Injectable	8.574	7.176	8.576	7.178	0.002	0.002	Negligible
5	Injectable	8.573	7.176	8.572	7.177	0.001	0.001	Negligible
6	Injectable	8.574	7.177	8.576	7.179	0.002	0.002	Negligible
7	Injectable	8.574	7.178	8.577	7.179	0.003	0.001	Negligible
8	Injectable	8.573	7.178	8.571	7.174	0.002	0.004	Negligible
9	Tablet	8.572	7.175	8.573	7.174	0.001	0.001	Negligible
10	Injectable	8.573	7.176	8.572	7.177	0.001	0.001	Negligible
11	Injectable	8.573	7.176	8.571	7.173	0.002	0.003	Negligible
12	Injectable	8.574	7.176	8.576	7.178	0.002	0.002	Negligible
13	Injectable	8.573	7.178	8.571	7.174	0.002	0.004	Negligible

14	Injectable	8.572	7.175	8.573	7.174	0.001	0.001	Negligible
15	Injectable	8.573	7.176	8.572	7.177	0.001	0.001	Negligible
16	Injectable	8.573	7.176	8.571	7.173	0.002	0.003	Negligible
17	Oral Drench	8.574	7.178	8.577	7.179	0.003	0.001	Negligible
18	Oral Drench	8.573	7.176	8.571	7.173	0.002	0.003	Negligible
19	Oral Drench	8.573	7.178	8.571	7.174	0.002	0.004	Negligible

RT: Retention Time

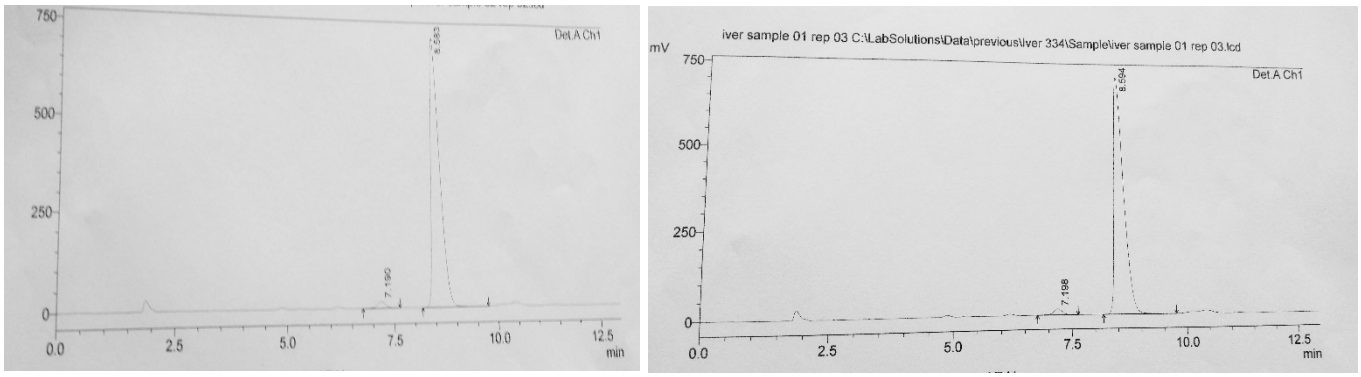

Figure 1. Chromatograph of USP standard solution (Right) and one of test sample (injectable) preparation with Ivermectin API (Left)

The data presented in Table 3 and 4 provides information on the filling in volume of injectable and oral drench and tablet ivermectin preparations for each sample. Upon analysis, it was observed that out of the 18 injectable samples, 3 (16.67%) did not meet the specifications outlined in the official Pharmacopoeia (20) limit.

Table 3. General information and filling to the volume results of different brands of Injectable and oral drench/syrup preparations of Ivermectin

Product	**Strength** (mg/ml)	**Vial x expected volume**	**Weight** (mg; mean ± %RSD) (n_1=10 and n_2=1)
1	10 mg/ml	10 x 50 ml	4995 ± 0.25
2	10 mg/ml	10 x 50 ml	5020 ± 1.00
3	10 mg/ml	10 x 50 ml	4985 ± 0.75
4	10 mg/ml	10 x 50 ml	4980 ± 1.00
5	10 mg/ml	10 x 50 ml	4975 ± 1.25
6	10 mg/ml	10 x 50 ml	4970 ± 1.50
7	10 mg/ml	10 x 50 ml	5010 ± 0.50
8	10 mg/ml	10 x 50 ml	4950 ± 2.50*
9	10 mg/ml	10 x 50 ml	4985 ± 0.75
10	10 mg/ml	10 x 50 ml	4955 ± 2.25*
11	10 mg/ml	10 x 50 ml	4965 ± 1.75
12	10 mg/ml	10 x 50 ml	4990 ± 0.50
13	10 mg/ml	10 x 50 ml	4970 ± 1.50
14	10 mg/ml	10 x 50 ml	4975 ± 1.25
15	10 mg/ml	10 x 50 ml	4957 ± 2.15 *
16	0.8 mg/ml	1 x 500 ml	399.6 ± 0.25
17	0.8 mg/ml	1 x 500 ml	398.8 ± 0.75
18	0.8 mg/ml	1 x 500 ml	399.60 ± 0.25
	Weight/tab	**Package**	**Weight variation**
19	5 mg/tablet	40 (10 x 4)	919.05 ± 1 %

* Do not meet USP recommended specification for Uniformity of Dosage Unit

Table 4 presents the results of the mass uniformity assay and packaging uniformity for each unit package. The filling-in package mass uniformity of single-unit packages of Ivermectin was tested in compliance with the specification limit specified by the official Pharmacopoeia (USP). Out of all the sample packages, 84.2% demonstrated values within the USP recommended specification of RSD 2. Additionally, all samples were found to have a H2B1a/(H2B1a+H2B1b) ratio greater than 0.95. However, the assay findings revealed that 15.7% of the samples had values outside of the USP recommended values. Furthermore, individual sample findings for RSD values were found to have higher values than the pooled sample assay values.

Table 4. Results of API-assay of the different products of Ivermectin brands and batches

Product	Preparations	Strength	Peak area (Triplicate inject)		H2B1a (H2B1a+H2B1b)	Assay (%LF; mean ± %RSD) (n_1=5 & n_2=20)	Content per blister or bottle (mg)
			H2B1a	H2B1b			
1	Tablet/bolus	5 mg/b	10857740	322917	0.971118245	97.28 ± 1.78	4.864
2	Injectable	10 mg/ml	11276290	300033	0.974082185	101.03 ± 1.62	50515
3	Injectable	10 mg/ml	9633342	117835	0.987915818	86.31 ± 0.59 #	43155
4	Injectable	10 mg/ml	11065341	315695	0.972261313	99.14 ± 1.82	49570
5	Injectable	10 mg/ml	11199277	248144	0.978323152	100.34 ± 1.09	50170
6	Injectable	10 mg/ml	11596620	239272	0.979784202	103.90 ± 1.84?	51950
7	Injectable	10 mg/ml	10064170	258093	0.974996471	90.17 ± 1.28 #	45085
8	Injectable	10 mg/ml	11174722	213173	0.981280737	100.12 ± 0.71	50060
9	Injectable	10 mg/ml	10931405	257964	0.976945617	97.94 ± 1.45	48970
10	Injectable	10 mg/ml	10666573	234815	0.978460082	95.62 ± 0.52	47810
11	Injectable	10 mg/ml	10388964	314328	0.970632587	93.08 ± 0.38 #	46540
12	Injectable	10 mg/ml	11596620	207382	0.982431213	103.90 ± 0.38	51950
13	Injectable	10 mg/ml	11518491	190617	0.983720622	103.20 ± 1.96?	51600
14	Injectable	10 mg/ml	11424735	188714	0.983750391	102.36 ± 0.49	51180
15	Injectable	10 mg/ml	11554207	184256	0.984303226	103.52 ± 1.51?	51760
16	Injectable *	10 mg/ml	11335445	248392	0.978557019	101.56±0.79,	50780
	IV + Clorsulon	100mg/ml	-	-	-	99.89±1.46 *	+499451
17	Oral drench	0.8 mg/ml	11040786	312184	0.972501997	98.92 ± 0.74	39568
18	Oral drench	0.8 mg/ml	11422503	309587	0.973611948	102.34 ± 1.71	40936
19	Oral drench	0.8 mg/ml	11312006	237124	0.979468237	101.35 ± 0.98	40540

Not within recommended range (reference range is 90–110% for the tablet preparation and oral drench and 95–105% for injectable preparations as USP recommended Specification)

*injectable 110 mg/ml Ivermectin Clorsulon combination (100mg/ml Clorsulon and 10mg/ml Ivermectin)

? individual sample values have ranges above upper USP recommended limit

Discussion

None of the samples in this specific evaluation of packaging accessories, including leaflet inserts, product labels, and overall physical appearance, exhibited any deviation from the desired criteria. This is in contrast to a study conducted in South Africa on seven solid dosage formulations of ivermectin, a human medicinal product, where it was found that none of the samples included a package insert or patient information leaflet. Additionally, 14% of the samples (1 out of 7) did not have the batch number, expiration date, or manufacturing date clearly indicated. These findings highlight the importance of labeling and packaging in the evaluation of Good Manufacturing Practices (GMP), market authorization, and surveillance against counterfeiting. Regulatory bodies recognize the significance of these aspects in ensuring the safety and efficacy of medicinal products.[23,24]

The present investigation has disclosed the values pertaining to routine quality parameters such as packaging uniformity, identity, and assay. All the samples analyzed in this study contained the expected active pharmaceutical ingredient (API). Similar findings have been reported in previous studies conducted on the human medicinal product Ivermectin in South Africa[23] and on a group of veterinary anthelmintics, including ivermectin, in the northwestern region of Ethiopia.[25] The assessment

conducted to identify any undeclared ingredients resulted in the detection of 10 undeclared APIs from 7 samples.[23] While it is crucial for quality assessment procedures to also consider the presence of undeclared contents in pharmaceutical products, the current study did not specifically address the assessment of undeclared active pharmaceutical ingredients. Studies assessing the presence of undeclared APIs in marketed products[26] have been conducted in various other countries around the world. The occurrence of undeclared products may be attributed to either defective manufacturing process control leading to contamination or intentional additions to enhance product performance. However, the deliberate addition of undeclared ingredients may not be a common finding in marketed veterinary products.

The latest analysis also revealed that 15.7% and 16.7% of the samples failed to satisfy the necessary USP values for both the declared API content and the uniformity in API packaging and unit package filling consistencies. Furthermore, individual unit package testing has indicated that additional samples, which were declared to be within the specification, actually had values above the USP recommended specification. This discrepancy may lead to an increased number of out-of-spec assay results. It is likely that the pooled sample testing technique indicated in the USP reference process altered this result. This disparity in test findings is worth noting.

The USP provides specific recommendations for assay values in different dosage formulations. For tablet and paste dosage formulations, the assay values should not be less than 90% and not more than 110% w/w. For liquid topical formulations, the assay values should not be less than 95% and not more than 105% w/v. As for veterinary injectable formulations, the assay values should fall within the range of 95% to 105%. In the northwestern part of Ethiopia, research on several veterinary anthelmintic medicines, including ivermectin,[25] indicated that the package uniformity and test results for all ivermectin samples met the USP requirement. However, it is important to note that this study utilized a small sample size for ivermectin, and a lower degree of compliance may be observed if the sample size is increased.

The assay values consider both the H2B1a and H2B1b chemical species, with H2B1a being the main component, constituting not less than 90% of the total (H2B1a+ H2B1b). In terms of packaging uniformity, the USP recommends that no two tablets should deviate by more than 5% and no single tablet should deviate by more than 10% w/w. Additionally, the unit package variation (RSD) (relative standard deviation) should not exceed 2%.[20] Ensuring uniformity is an important quality parameter that guarantees consistency among package units.

The recent detection of filling volumes outside of the USP-approved range (of 2) in 23.1% of liquid formulation samples[20] is a particular finding from research on a marketed human ivermectin medication. This variation in filling volume may be attributed to inaccuracies in the filling machine or leakage during the manufacturing process. While this may have no influence on effectiveness or side effects when the required API assay value[27] and multidose packing in a single container are present, it may serve as a warning of other potential manufacturing quality issues. For single-dose vials, overfilling may result in unnecessary leftovers and contamination during administration, while underfilling may require additional vials to be opened to fulfill recommended dosages. The type of dissolution vehicle used may also contribute to variability in fill volume.[24]

Maintaining a certain amount of variability is critical to ensuring a treatment's theoretical effectiveness while minimizing the dangers associated with high toxicity or decreased efficacy due to inadequate API concentration. Subtherapeutic doses, which contain lower amounts of API, are more likely to contribute to the development of drug resistance. The phenomenon of anthelmintic resistance, particularly observed in the nematodes of domestic animals in warm and humid regions, has been attributed to inadequate therapeutic practices.[28] According to the published retrospective data, there was a 6.9% divergence from the 5-year laboratory data, but the WHO estimated a 10.5% variation. Additionally, a veterinary albendazole study conducted on samples from Addis Ababa revealed a 6% deviation from the USP recommendations.[29–31] It is important to note that the lower prevalence values of substandard samples may be attributed to the small and non-representative nature of the samples. Publications from the WHO tend to report lower deviations due to the average estimate derived from countries with stringent regulatory systems and developing nations.

The emergence of drug resistance resulting from the use of substandard drugs and underdosing in the treatment of various infectious diseases is a significant contributing factor to treatment failure.[32] Under-dosing plays a crucial role in the development of anthelmintic resistance as it allows the survival of heterozygous resistance worms due to subtherapeutic doses. Numerous experiments have demonstrated that under-dosing contributes to the selection of resistant or tolerant strains. Additionally, the variation in bioavailability among different host species is

also essential in determining the appropriate dosage. This finding is confirmed even more by indirect field evidence.[33] A concerning report reveals a high failure rate of over 80% in the performance of marketed veterinary anthelmintic products, including ivermectin, in north-west Ethiopia. The failure is attributed to parameters such as assay, friability, and dissolution, which were evaluated using the USP reference recommendation.[25] This study highlights the significant degree of failure in the performance of solid dosage formulations during dissolution.

The results of this investigation have raised a concerning issue regarding the presence of suboptimal drugs in the legal market, which can lead to a variety of interconnected problems. Firstly, the drug may not effectively treat the patient, particularly if farmers or animal attendants split the dose, as they often administer the drug themselves. This can result in treatment failure, compromising the welfare and productivity of the animals. Additionally, repeated treatment is necessary, incurring additional costs for the farmer or producer. Furthermore, suboptimal doses can lead to an increase in alleles that are important in the development of resistance, resulting in a more resistant parasite population against Ivermectin treatment in the long term. These consequences of subtherapeutic doses of drugs on the legal market will exacerbate the already existing issues of anthelmintic resistance and poor efficacy reported in various parts of the country. The clinical significance of drug resistance is particularly crucial for notorious parasites such as *H. contortus*, which can cause massive infections that can be fatal to the host.[34–36]

Conclusions

The analysis of selected quality assessment parameters indicated the prevalence of product quality problems in the market. Despite the fact that all of the products encountered were registered and there were no inconsistencies in accompanying documents or package labeling, the physicochemical parameter findings indicate the need to strengthen regulatory measures and conduct continuous post-marketing surveillance to reduce the impact of substandard products in veterinary practice

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Competing interests

The authors declare that they have no competing interests.

Abbreviations

Coronavirus disease 2019: COVID-19;
World Health Organization: WHO;
γ-aminobutyric acid: GABA;
United States Pharmacopeia: USP;
High-performance liquid chromatography: HPLC;
Good Manufacturing Practices: GMP;
Active pharmaceutical ingredient: API;
Relative standard deviation: RSD.

Authors' contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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None.

Availability of data and materials

The data used in this study are available from the corresponding author on request.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. Institutional Review Board approval was obtained.

Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

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