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Evaluation of The Pharmaceutical Quality of the Most Commonly Purchased Vitamin C(Ascorbic Acid) Formulations in COVID-19 Infection in South Africa

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Abstract

An extensive examination of available literature suggests that vitamin C plays a role in lessening, and in certain instances, eliminating specific symptoms associated with COVID-19, particularly those linked to vitamin D deficiency. This has resulted in an increase in the demand and consumption of over-the-counter dietary supplement vitamin C, - Ascorbic acid, both in the event of viral infection and for general wellness and health. Yet, despite numerous conducted clinical trials, there is limited substantiating evidence to endorse its regular or routine utilization. In South Africa, the regulatory authority SAHPRA has always been lenient with dietary supplement industry which has grown since the COVID-19 pandemic. The present study sought to evaluate the pharmaceutical quality of different Vitamin C formulations commonly purchased by consumers available on the market in South Africa. All the tests normally carried out during the pharmaceutical tablet and capsule manufacturing were performed. In addition, consumer advisory statements were closely examined. From the test results, tablets had friability of 15% and had only 18% of vit C as stated on the label which also contained confusing information. In contrast, the capsules passed all the manufacturing process test. Be that as it may, there is still need for SAHPRA to come up smart regulations to continue protecting the general public from poor quality over-the counter dietary supplement vit C products. For any dietary supplement product such as vit C, typically the customer cannot appreciate the processes involved in assuring quality of a product during its manufacture. Consumers expect quality of over-the-counter products such dietary supplements.

Key words: Ascorbic acid, Quality, Consumer advisory statement, Smart regulations

Introduction

Vitamin C, also known as L-ascorbic acid, Fig 1, is a vital water-soluble vitamin recognized for its antioxidant properties. It has been demonstrated to boost the immune system and has consequently been applied in addressing SARS-CoV-2 infection.

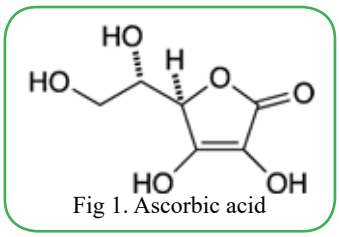

Fig 1. Ascorbic acid

Ascorbic acid serves as a co-factor and substrate for multiple enzymes, playing a vital role as a potent antioxidant in various metabolic reactions. It also plays a role in stabilizing vitamin E and folic acid while aiding in the absorption of iron. Vitamin C is crucial for treating scurvy resulting from its deficiency. However, while it is undeniably effective for this purpose, its history as a therapeutic remedy has been more uncertain and varied in its effectiveness beyond addressing scurvy [1].

Furthermore, it has been documented that the way vitamin C moves through the body is intricate [2]. Governed chiefly by a set of specific sodium-dependent vitamin C transporters (SVCTs), its absorption and removal are greatly influenced by the dosage. Additionally, the various types and levels of expression of these SVCTs in different tissues lead to a distinct distribution pattern, resulting in a wide range of vitamin C concentrations across organs at a stable state, varying from approximately 0.2 mM in muscle and heart tissues to as high as 10 mM in the brain and adrenal gland.

Ever since the WHO declared SARS-CoV-2 a pandemic in 2020, the virus has spread rapidly worldwide [3]. Sufficient evidence now indicates that vitamin C supports various cellular mechanisms within both innate and adaptive immunity, ultimately bolstering the overall strength of the immune system, Fig 2 [4].

Some argue that individuals with low vitamin C levels or severe respiratory conditions like COVID-19 might find value in using vitamin C. This is attributed to its favorable safety record, ease of administration, and the potential for quick and efficient production

at scale. As a result of rapid production scaling, the market in South Africa, since COVID-19, has seen a plethora of vit C supplements in many forms, tablets, capsule and gummies. Limited scientific evidence exists to favor one form of vitamin C absorption over another. In both experimental and clinical studies, whether low or high doses are used, the focus has largely been on ascorbic acid or its sodium form, sodium ascorbate, especially in COVID-19 patient research. Both natural and synthetic forms of this acid share identical chemical structures, displaying no discernible differences in biological activities or bioavailability [5].

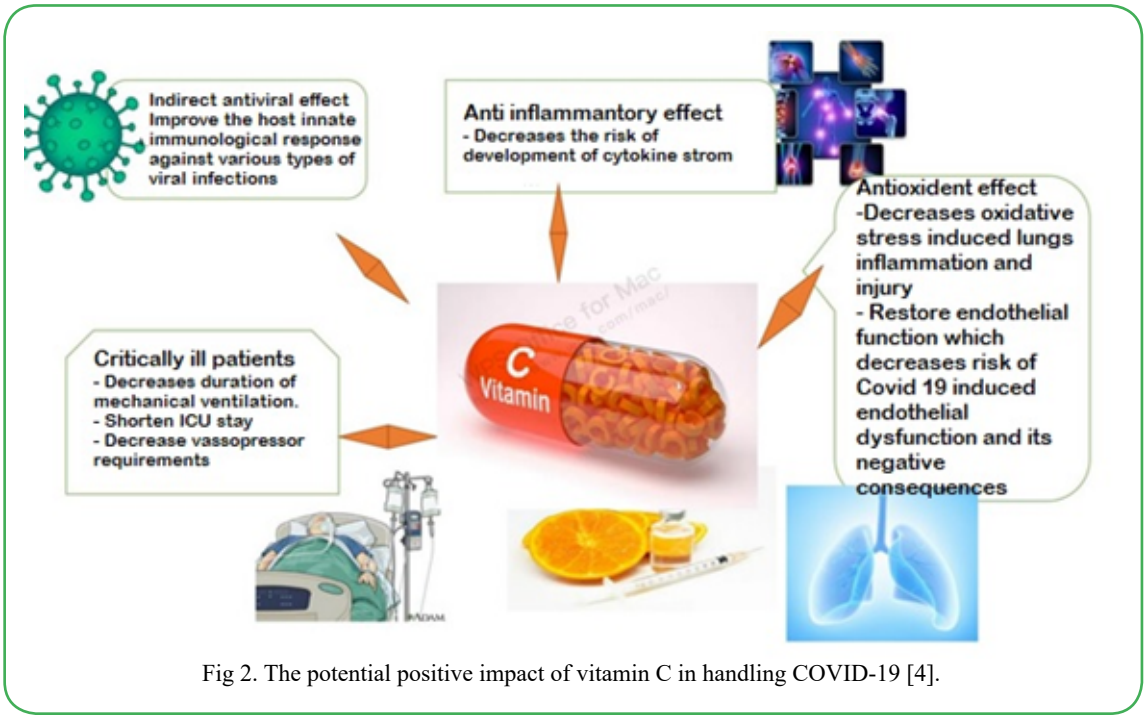

Fig 2. The potential positive impact of vitamin C in handling COVID-19 [4].

Supplements such as vit C usually do not have patent protection because they are classified as food and not medicines. Therefore, although both supplements and pharmaceuticals might be used for therapeutic purposes, only pharmaceuticals have strict regulatory regime. The manufacturing processes used for health supplements in South Africa are a bit more relaxed and the processes are regulated under the Medicines and Related Substances Act, Act 101 of 1965, Category D Medicines administered by the South African Health Products Regulatory Authority [6]. This means that there is no guarantee that all the Vitamin C products are produced according to the Good Manufacturing Practice (GMP) and are of good and acceptable standard. However, their category of distribution is pharmacy outlets as nutritional products or complementary health products and available over the counter for consumers.

We therefore carried out a study to evaluate the pharmaceutical quality of different Vitamin C formulations as a COVID-19 supplements available on the market in South Africa. The objectives the study were 1) to identify the most common vit C formulations on the market, 2) to characterize the physical properties of the vit C products, 3) to determine the amount of vit C contained in the products and 4) to evaluate the in-vitro release properties of vit C from the products.

Materials and Method

Vitamin C tablets and capsules were acquired from two South African pharmacies. The study utilized several pieces of equipment, including a Vernier caliper supplied by Fragram in South Africa, a hardness tester supplied by Schleuniger in Switzerland, a Friabilator supplied by Roche in the USA, a Disintegrator supplied by Pharma Test in Germany, a weighing balance (College B154) supplied by Mettler Toledo in South Africa, a Dissolution tester supplied by Hanson Research SR8-Plus in the USA, and a UV spectrophotometer supplied by Biobase in China. All the equipments were available in the Department of Pharmacy, University of Limpopo, South Africa.

(a) The methods was in two parts;

Simulated client methodology which involved going into selected pharmacy outlets, namely chain pharmacies and independent pharmacies, in Polokwane City, Limpopo Province, South Africa. Observation of what vit C products were on the shelves was made, noting the information for consumers on their labels. This was followed by engaging with pharmacy managers or the responsible pharmacists and then purchasing the most common sought after vit C product.

(b) Experimental procedure

Vit C (Ascorbic acid) comes in different dosage forms which include tablets, capsules, gummies, etc. The study focused on the most commonly purchased vit C formulations, which were tablets and capsules and they happened to belong to a particular brand. A total of 60 tablets were purchased, divided into 3 lots of 20 tablets each. The physical characteristics namely: dimensions, weight, hardness, friability, disintegration and quantity of vit C of these tablets were assessed. As well, a total of 60 capsules were purchased, divided into 3 lots of 20 capsules each. The physical characteristics namely: weight, disintegration and quantity of vit C of these capsules were assessed.

(i) Measurement of dimensions

Using a Vernier caliper, the dimensions of the tablets (specifically thickness, length, and diameter) were assessed. Ten tablets were chosen for measurement, and their individual thickness, diameter, and length were recorded.

ii) Weight variation test

Twenty tablets were chosen at random and individually weighed, while for capsules, the contents of 20 capsules were weighed individually. The average weights and standard deviations (SD) for both tablets and capsules were computed. The individual tablet weights were compared to the average tablet weight, and similarly, the individual capsule contents' weights were compared to the average capsule content weight. To pass the weight variation test, no more than two dosage units could exceed the defined percentage limit, and no dosage unit should differ by more than two times the

percentage limit [7]. For tablets or capsules weighing less than 0.3g, a 7.5% weight deviation from the mean was considered acceptable, whereas for tablets or capsules weighing 0.3g or more, a 5% weight deviation from the mean was acceptable.

iii) Hardness test

The hardness of ten separate tablets was gauged using a hardness tester [7]. The mean hardness of these ten tablets was computed, and a 5% deviation from this mean was determined. Meeting the hardness criterion meant that no more than 2 out of the ten tablets in the sample were allowed to fall beyond the 5% deviation range.

iv) Friability test

Twenty tablets chosen randomly underwent weighing, and their individual weights were noted. These tablets were then subjected to a Roche friabilator, rotated at a speed of 25 rpm for 100 revolutions. Post-rotation, the tablets were taken out, any fragments or chips were removed, and the tablets were weighed again, following the USP method [7]. The percentage of loss was calculated using the following equation:

$$\%\ Friability = \frac{\text{Initial weight of tablets} - \text{Final weight of tablets}}{\text{Initial weight of tablets}} \times 100$$

Tablets successfully meet the friability test criteria if the percentage of friability remains below 1%.

v) Disintegration test

The disintegration test followed Chartuvedi et al, [8] method. A Pharma Test® disintegration tester equipped with 5 glass tubes (measuring 77.5 ± 2.5 mm in length and 21.5 mm in internal diameter) featuring a mesh at the base was utilized. The tablets or capsules were inserted into these glass tubes, which were then immersed in a simulated disintegration environment maintained at 37 ± 2ºC within a one-liter vessel. The method involved an up-and-down movement spanning 5 to 6cm at a rate of 30 cycles per minute. During the upward motion, the dosage forms remained 2.5 cm below the liquid surface and did not approach closer than 2.5 cm from the bottom of the beaker during their descent. The duration taken for each dosage form to disintegrate was recorded.

vi) Quantity of Vitamin C in dosage units

The quantity of Vitamin C present in the products was determined following a specific method by [9]. Initially, one tablet was crushed and dissolved in a 50/50 v/v mixture of methanol and water within a 100ml volumetric flask, creating a labeled stock solution. Similarly, for capsules, the contents of one capsule were emptied and dissolved in the same 50/50 v/v mixture in a 100ml volumetric flask to generate another labeled stock solution. Using a syringe, a 5 ml volume was extracted from the stock solution, filtered, and placed into a 100ml volumetric flask. This flask was then filled up to the mark using the 50/50 v/v mixture of methanol and water, labeled as sample A. The absorbance of this sample was measured at 258 nm. This procedure of withdrawing 5ml samples from the stock solution and diluting was replicated to create sample B and sample C.

To create standard solutions, 100mg of ascorbic acid was precisely weighed and transferred into a 100ml volumetric flask. The volume was adjusted to reach the flask's mark using a solvent mixture of methanol and water (50/50 v/v), achieving a concentration of 1000 µg/ml. Serial dilutions were subsequently prepared from this stock solution, resulting in solutions of 3, 6, 9, 12, and 15 µg/ml concentrations of ascorbic acid. These solutions were prepared in triplicate, and their absorbance was measured at 258 nm [10]. The quantity of vitamin C present in the dosage forms was then calculated and compared to the acceptable range, typically between 95% to 105% of the stated amount of the active ingredient.

Ethical clearance was obtained from the University of Limpopo, Ethics Committee, number TREC/302/2021: UG.

Results and Discussion

Following close examination and studying of the information labels of the vit C formulations which included tablets, capsules and caplets (coated tablets), it was interesting to note that it appeared that, some companies were not aware that Medicines Control Council was replaced by SAHPRA. From this result it was therefore reasonable to conclude that the industry was not submitting samples of their information labels to SAHPRA for registration as expected. As matter of fact, in 2022 SAPHRA issued guidelines aiming to offer precise instructions on safety and efficacy standards for Health Supplements, a subset of complementary medicines in South Africa. The objective was to establish stringent evidence criteria for safety and efficacy, safeguarding public health and sustaining consumer trust. Simultaneously, these guidelines aimed to outline a well-defined process for registering health supplements. The guidelines were to be read with other documents such as the Complementary Medicines: Quality and Complementary Medicines - Guidance on Specified Substances [6]. Maybe SAHPRA needs to put more effort in making sure that the industry follows the established guidelines. It is important to state that a clear understanding and appreciation of nutrition supplements in the regulatory system will certainly decrease the misconception in establishing the policy for nutrition supplements such as vit C. Generally, the industry considers supplements as nontoxic and scientifically proven to provide health benefits, including disease treatment and prevention. In fact, it can be stated that supplements have led to the new era of medicine and health, in which the food industry has developed into a research oriented sector [11].

If indeed the industry has developed into a research-oriented sector, products labelling on some of the products that were studied would not contain misleading information.

There was one product, for example, with the following information on its container label

'This medicine is not intended to diagnose, treat, cure or prevent any disease. This medicine has not been evaluated by SAHPRA'

Another version of the advisory statement said the following;

"This registered medicine has not been evaluated by SAHPRA for quality, safety and intended use"

This statement is certainly confusing to any discerning consumer in South Africa because to any ordinary person a medicine, refers to any substance or combination of substances utilized or claimed to be fit for use, produced or marketed for the purpose of diagnosing, treating, alleviating, altering, or preventing disease, irregular physical or mental conditions, or their related symptoms in humans or animals. In addition, the consumer is not even sure about the possibility whether the product is not adulterated and misbranded since no evaluation has been carried out.

From these observations, there is an urgent need to revisit advisory statements (Table 1) on labels that are on dietary supplement products such as vit C. SAHPRA has to come up with smart regulations in consultation with everyone in the industry from the manufacturers, distributors, healthcare providers and consumers. From the results it would also appear that those manufacturing, distributing and selling vit C products were not knowledgeable about South African regulations regarding dietary supplements in general.

Within the capsule was zinc ascorbate, where the recommended daily allowance (RDA) stands at 11 mg/day for adult men and 8 mg/day for adult women. It is advised that the upper limit (UL) of zinc intake for adults should not surpass 40 mg/day. Dietary zinc deficiency is quite common in South Africa where it is about 47.8% among children [12]. However, continuously consuming zinc above the tolerable upper intake level (UL) of 40 mg/day for adults may lead to a deficiency in copper over time.

Formulation	Ingredients and quantity	General information on the label	Specific directions for use
Vitamin C Capsules	Vitamin C (1000mg) Selenium (25 mg) Zinc (54 mcg)	Should not be used by pregnant women and lactating women. Discontinue if you experience any adverse reactions. Do not exceed recommended daily dosage	Take 2 capsules daily, with or after meals or as prescribed by a healthcare practitioner
Tablets	Vitamin C (500mg) Citrus Bioflavonoids (10mg)	The recommended daily dosage for women is 75mg and 90 mg for men. Discontinue if you experience possible side effects	Take one or two tablets each day with a glass of water after a meal

Table 1 Consumer advisory statements on the container label of the most commonly purchased formulation that were investigated

Bioflavonoids in the tablets are thought to increase vit C bioavailability [5, 13] vit C with small amounts of its metabolites and ascorbyl palmate which is likely to be hydrolysed in stomach to ascorbic acid and palmitic acid. There appeared to be no liposomal encapsulated vit C available in the pharmacy. On some of the vit C product labels it was stated that they contained minerals such as calcium, magnesium and sodium as aspartate salts. Mineral salts derived from vitamin C are perceived as less likely to cause digestive discomfort compared to ascorbic acid, which can lead to gastrointestinal upset in certain individuals. Ascorbates, therefore, are considered "buffered." and do not cause any problems [14].

The results of the dimensions and shapes tests performed to check the consistency of the tablets in terms of length, width, and thickness, are shown in Table 2 below.

Tablets	Length (mm)	Width (mm)	Thickness (mm)
Average	13.29 ± 3.75	5.805 ± 1.045	5.805 ± 1.045

Table 2: A table of the length, width, and thickness of the most commonly purchased vit C tablets.

Thickness = The thickness of the all the individual tablets sampled fell within the acceptable ± 5% range from the mean. Thickness is the result of both filling amount of granulation and the compaction pressure during manufacturing. There is no thickness limit provided by USP because tablet thickness is by and large controlled by the in-house specification and related to the disintegration rate and hardness

Width = All the sampled individual tablets' widths remained within the acceptable range, not deviating more than ± 5% from the mean width.

Length = All the sampled individual tablets' lengths remained within the acceptable range, not deviating more than ± 5% from the mean length.

From all the measurements that were taken, none exceeded a ± 5% deviation from the mean. It can therefore be concluded that tablets were of consistent thickness, width and length. This then indicated that Good Manufacturing and Laboratory Practices were followed in making the vitamin C products as far as the above dimensions were concerned Currently there appears to be no SAHPRA guidelines specifically for prototype dietary supplement formulation which, however, should be the same for pharmaceutical tablets. For a dietary supplement to be well-crafted, it necessitates incorporating evidence-supported ingredients to ensure the product's effectiveness. Currently the decision about the formulation of a dietary supplement appears to be between a brand owner and the manufacturer in some cases. In addition to the above measured dimensions that were tested in the study due to the ingredients used, weight variation of the product had to be investigated, the results of which are shown in Table 3.

Batch	Mean weight (mg)	Number of tablets outside the allowable percentage range	Number of tablets outside double the percentage allowed
1	735.405	0	0
2	733.86	1	0
3	735.56	2	0

Table 3: Weight variation of the tablet batches

At most, only two tablets had weights outside the allowable range, and not even one of the weights was outside double the range acceptable. Thus, a conclusion can be made that the tablets were of similar weights. Typically, fluctuations in weight often signify corresponding variances in the active ingredient. Throughout tablet manufacturing, it is essential to consistently measure the tablet weight to guarantee the accurate presence of the active ingredient. Uniformity, it is assumed, also ensures consistency of dosage units during compression. Weight variation test is necessary to guarantee that the consumer takes a precise vit C dose, normally confirmed by other tests such as the disintegration and dissolution tests.

In the case of the vit C product in capsules, the average weight of the powder of all the three batches was 641.775 mg, 647.22 mg and 657 mg respectively, as shown in Table 4 below.

None of the powder weights from either of the batches were outside the allowable range, ±5% from the average weight of the batch. This indicates the uniformity of the weights of the powder within the capsules. Furthermore, this indicates the reliability of the filling in process of the capsules [15].

Batch	Mean weight (mg)	Number of tablets outside the allowable percentage range	Number of tablets outside double the percentage allowed
1	641.775	0	0
2	647.22	0	
3	657	0	0

Table 4: Weight variation of the contents of the capsules

The results obtained for the tablets and capsules would seem to suggest that while it might have been important to weigh the vit C tablets and capsules, the results had to eventually be linked to the dissolution results. The products claimed to contain at least 500 mg of ascorbic acid which was difficult to confirm equally for the end user.

Hardness of tablets was done to help forecast resistance to breaking and crumbling during storage, transportation, and handling prior to customer consumption. Results obtained from the hardness test are depicted in Table 5.

1st batch		**2nd batch**		**3rd batch**	
Tablets	Hardness (kpa)	Tablets	Hardness (kpa)	Tablets	Hardness (kpa)
Tablet 1	11.48	Tablet 1	10.56	Tablet 1	12.34
Tablet 2	13.40	Tablet 2	12.10	Tablet 2	12.23
Tablet 3	15.07	Tablet 3	11.09	Tablet 3	12.56
Tablet 4	8.59	Tablet 4	10.59	Tablet 4	10.59
Tablet 5	12.92	Tablet 5	12.30	Tablet 5	12.42
Tablet 6	11.89	Tablet 6	11.45	Tablet 6	11.55
Tablet 7	11.10	Tablet 7	12.90	Tablet 7	10.87
Tablet 8	12.40	Tablet 8	11.80	Tablet 8	11.55
Tablet 9	11.72	Tablet 9	10.50	Tablet 9	10.12
Tablet 10	12.45	Tablet 10	11.21	Tablet 10	11.40
Average	12.102 ± 3.98	Average	11.45 ± 3.54	Average	11.563 ± 3.576

Table 5: The hardness of the tablets

The first batch had five tablets that were outside the allowable range from the mean. The second and third batches respectively had six and seven tablets that were outside the permissible range. As a result, it can be concluded that the tablets did not have consistent hardness, thereby compromising the quality of the tablets. In essence the tablets failed the quality test. For tablets with greater hardness than the required, this means that breaking the tablets requires greater force, and so the pills may take longer to disintegrate or may even fail to disintegrate and release ascorbic acid in the intestines. When this happens it means that ascorbic acid will take longer to enter the blood circulation and worse if the dose is low, this may mean that the active constituent will take longer to reach the blood stream or that the user may even be under dosed [16].

Disintegration which is related to thickness, denotes the duration needed for tablets to disintegrate into particles within specific conditions. The results of disintegration test of the dosage forms are shown in Table 6 for tablets and Table 7 for capsules.

Tablet no	Time (minutes)
1.	< 1
2.	< 1
3.	< 1
4.	< 1
5.	< 2
6.	< 2

Table 6: Disintegration time of the tablets

From the obtained results, it was observed that all the tablets disintegrated within the required time which, to an extent, contradicted the hardness results. These results obtained should, however, be interpreted with caution when it comes to what actually happens in the stomach.

Capsule no	Time (min and sec)
1.	7 min 52 seconds
2.	7 min 40 seconds
3.	7 min 45 seconds
4.	7 min 48 seconds
5.	7 min 50 seconds
6.	7 min 52 seconds

Table 7: Disintegration time of the capsules

Disintegration refers to the condition where no remnants persist on the screen of the testing device or cling to the lower surface of the disc, except for fragments of the capsule shell if a disc was utilized. Disintegration provides a critical safety data on drug bioavailability in the body.

As per [7], uncoated tablets are expected to disintegrate within a minimum of 5 minutes, while the majority typically disintegrate within a maximum of 15 minutes. If a single tablet fails to disintegrate within 30 minutes, the disintegration test is performed again using 12 more tablets. No fewer than 16 out of the 18 tablets examined must completely disintegrate within 15 minutes.

From the obtained results, it was observed that all the capsules disintegrated within the required time. However, in both capsules and tablets, the results of in-vitro release properties of Vit C obtained were not reliable, maybe because of the method used in the study. Therefore, the results would have to be interpreted with caution.

According to the reference standards, vit C tablets should contain at least 90% to 110% of the label claim [7]. The average amount of Ascorbic acid (Vitamin C) in the tablets was found to be only 91.55 mg (18.31%) of the stated 500 mg, as determined using the UV spectrophotometer at an absorbance of 258. In other words, the amount of vitamin C within the tablets did not correspond with what was written on the label and was even way below what was recommended for COVID-19 infection.

As seen from the results below, Table 8, percentage weight loss, friability, from three samples, each containing 20 tablets, was 4.05021%, 5.9646% and 4.5944% respectively. The amount of powder that fragmented from the tablets was greater than 1%, the limit, and thereby indicating that the tablets did not pass the friability test. This implies that the vitamin C tablets were susceptible to breakage, chipping, and capping whenever they were in motion, whether during transportation, packing, or handling. Furthermore, the vitamin C could be lost when the tablets fragment during handling, leading to lesser amounts of it delivered to the body [7]. The results obtained when testing the amount of ascorbic acid could also be explained by the poor friability test in addition to probably, poor quality assurance during the manufacturing processes.

	First batch	Second batch	Third batch
Mass of 20 tablets(g) before friability	16.9478	17.0021	16.8987
Mass of 20 tablets(g) after friability	16.1848	15.9880	16.1223
Mass lost(g)	0.7630	1.0141	0.7764
Percentage of mass loss %	4.5021%	5.9646%	4.5944%

Table 8: Results of the friability test

Conclusion

A robust dietary supplement quality system, DSQS is definitely critical to assuring dietary supplement products such as vit C are produced to fulfill the targeted standards of quality and performance. The DSQS needs to be the primary system assessed during SAHPRA inspections, playing a pivotal role in assuring SAHPRA of the suitable use of pertinent (science and risk-based) supporting information for decision-making. For any dietary supplement product such as vit C, typically the customer cannot appreciate the processes involved in assuring the quality of a product during its manufacture. Consumers expect that over-the-counter products such dietary supplements are of good quality which has been assured by any regulatory authority such as SAHPRA.

The SAHPRA has to remain steadfast in its commitment to ensuring that the risk of a low-quality dietary supplement, such as vit C product is kept to a minimum by ensuring that the product meets the claims made on its label: performance, lack of contamination, and availability. SAHPRA must place greater emphasis on cGMP, especially with the integration of Quality by Design (QbD). This involves scientifically demonstrating a commitment to precisely adhering to necessary limits right from the initial stages of dietary supplement production to the final packaging. This process significantly influences the attributes of the dietary supplement product, including dosage, safety, and efficacy. This can only be achieved through smart regulations.

Competing interests: The authors declare that they have no competing interests.

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