



## **Controlled Release of Bi-Layered EGCG Tablets Using 3D Printing Techniques**

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### **Authors' contributions**

*This work was carried out in collaboration between both authors. Author SKS designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors PB and SKS managed the analyses of the study. Author PB managed the literature searches. Both authors read and approved the final manuscript.*

### **Article Information**

DOI: 10.9734/JPRI/2020/v32i3931019

#### Editor(s):

(1) Dr. Sung-Kun Kim, Northeastern State University, USA.

#### Reviewers:

(1) Nirmal Hiteshkumar Shah, India.

(2) Mohd Affendi Mohd Shafri, International Islamic University Malaysia, Malaysia.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/63586>

**Original Research Article**

**Received 01 October 2020**

**Accepted 05 December 2020**

**Published 07 January 2021**

### **ABSTRACT**

Epigallo-catechin Gallate (or EGCG) is a polyphenol which is withdrawn from green tea and is commercially available as Epigallocatechin gallate. Epigallo-catechin gallate is known to have been used as dye and food colorants, but it also has many medicinal properties like anti-inflammatory, anti-microbial, anti-diabetic, anti-obesity, and anti-cancer. Keeping these medical properties in mind, in the present research paper, a 3D printing technique evolving a desktop based 3D printer to extrude tablets along with the active drug ingredient and other excipients that are used as binders and disintegrants. The method adapted in the formulation of a 3D printed tablet in this research makes the tablet suitable for immediate and sustained release and does not affect its certain physical and mechanical properties such as hardness, friability, and weight variation. The tablets which are extruded from the 3D printer are the bi-layer tablets with controlled release. With the involvement of the 3D printer, the cost of printing the bi-layered tablets have found to be very low which makes the method cost efficient. The output bi-layer tablet has been developed using various analysis and specified standard apparatus and method so that the set standards of the tablet does not get affected. The immediate release and the

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sustained release methods were studied separately. The final stage of the research completes when the 3D printed tablets with set time intervals for the initial and sustained release and without changing the set mechanical properties of the tablet are obtained.

**Keywords:** Bi-layer tablets; EGCG; 3D printer.

## 1. INTRODUCTION

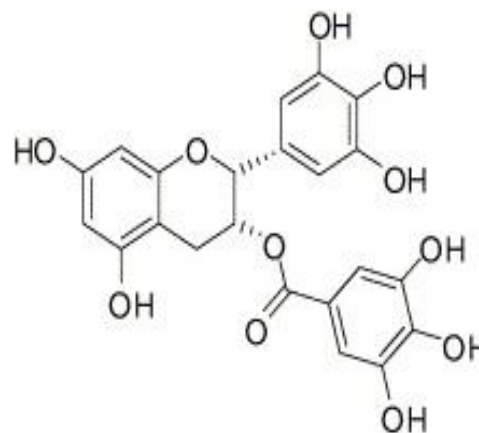
Polyphenols like Epigallocatechin Gallate can be extracted from green tea has various health related benefits for human body mechanisms/ physiological processes. The potential benefits of EGCG comprises effects against inflammatory disease, cancer, diabetes, stress and also benefits in cardiovascular disease and have antioxidant properties. The chemical structure of Epigallocatechin Gallate can be seen in Fig. 1.

There are various types of catechins found in tea phenol which includes epi-catechin (or EC), epigallo-catechin (or EGC), epi-catechin-3-gallate (or ECG), and the epigallo-catechin-3-gallate (or EGCG). Their structures can be seen in Fig. 2, among all these catechins the majority found catechin is EGCG. It is prominent to about 60-75% in the green tea [2]. Other benefits include, study of diseases like Parkinson's disease, stroke, obesity, and disease of Alzheimer [2-4].

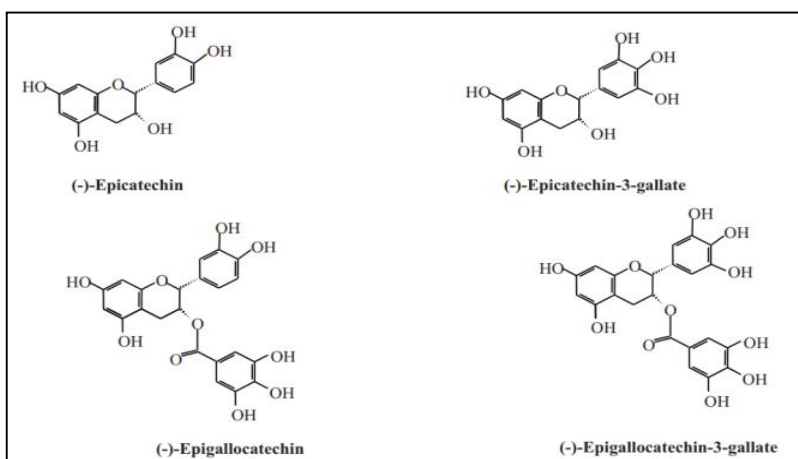
Many tea based products are entering in the market which provides an alternate means to the brewed teas. These include ready to drink tea beverages, various food supplements in the form of powder, food supplements, and tablets [6-8].

The aim of the experiment focuses on the getting an alternate and low cost method from that which

is used in the industries. So, the use of 3D printer in the experiment fulfills the desire of developing low cost bi-layered tablets. 3D dimensional printer is a device utilized for manufacturing solid tablets with the help of nozzles filled with constituent elements. These nozzles are capable of movement in three dimensional spaces to fabricate the tablet as an amalgamation of functionally active constituents. The resultant tablet displays controlled release of the constituents according to the chemical properties detected in the surroundings.



**Fig. 1. Structure of Epigallocatechin Gallate (EGCG) [1]**



**Fig. 2. Various catechins as green tea constituents with their chemical structures [5]**

The introduction of the first ever 3D printed drug approved by the FDA has raised this technology on next level on revolutionizing the health-care sector. The 3D printer related technologies are present in abundance in the fields of engineering, aerospace, construction, automobiles, dentistry, robotics, etc. but in the field of pharmacy its whole potential is yet to be discovered [9]. The powder based 3D printing applications has been expanded in the fields of pharmaceutical industries and tissue engineering technologies has over the years in between 1993-2003 which leads to the oral dosage forms in the pharmaceutical industries [10].

As per the study for the research, the use of 3D printer gives a method for developing low cost tablets and 3D printer is incorporated in the present research for extruding the initial and sustained release of the Epigallocatechin Gallate (EGCG) tablets. The 3D printed EGCG tablets will be cost effective and will provide benefits in the field of healthcare fulfilling the properties of EGCG that are against cancer, inflammation along with its antioxidant, anti-collagenase, and anti-fibrosis properties, also as the method provides completely natural tablet so it will be helpful for those people who are vegans and also as such it will not show any side-effects so it could be taken as supplement.

### 1.1 Research Questions

Can natural compounds be used to generate bi-layer tablets using 3D printer?

Can a method be available which with the production of bi-layer tablets is produced in a cost effective way?

Why HPMC is the prominent option for the controlled release of the drug for Hydrophilic Matrix Systems?

## 2. LITERATURE REVIEW

Epigallocatechin Gallate or Epigallocatechin-3-gallate (EGCG) has some properties which are against cancer, inflammation, and have some antioxidant, anti-collagenase, and anti-fibrosis properties [11]. Epigallocatechin Gallate or Epigallocatechin-3-gallate (EGCG) also has some applications which are related to a specific type of tissue. These applications are based on its effective properties which have been mentioned earlier. So, the applications are cancer treatment, treatment from oral diseases, and fortification of nervous system from the ailments like the disease of Alzheimer, Parkinson's, and Huntington's [11].

Studies also suggest that EGCG which is the green tea extract decreases U.V. [12]. The schematic figure showing applications and properties is shown in the Fig. 3.

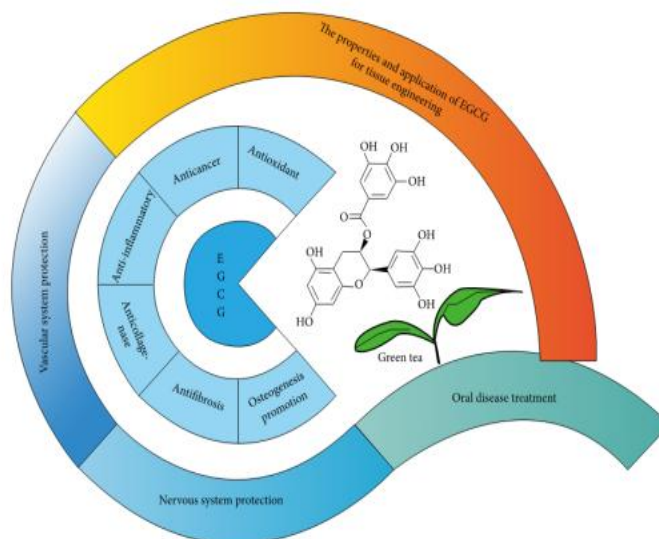
### Solubility of Epigallocatechin Gallate

EGCG is soluble in ethanol as well as in water but in water it is partially soluble. So according to Nguyen et al. in a study presents an efficient method which increases the solubility of EGCG in water [13]. In the study the use of herbal tea sweeteners such as steviosideglucosides (SG), rebaudioside A (RebA) and rubusoside (Ru), stevioside (Ste) enhances the water solubility of complex of EGCG [13].

System of the hydrophilic matrix in the pharmaceutical industries has been proven over decades. As tablets made using matrix-control release are compared to other systems is relatively easy and are more forgiving of the variations in the different ingredient production and their methods, and end-use conditions compared to the coated control released tablets [14].

Consumption of the tablets that can be administered orally is most used form of drug administration. Tablets are prepared generally as single or multiple compressions [15,16,17]. Powdered tablets are prepared for compression of the tablets from the already established mills, granulation and mixing units that can be dry or wet depending upon the production method [18,19]. The powdered tablets prepared conventionally require lots of man power to operate these different machines and cost of the operations are also high which finally resulting in increasing the cost of tablet. But in the present research, inclusion of 3D printing techniques vanish the drawbacks of the established processes.

All over the world the tablets are manufactured in a large scale industry having big plants for the manufacturing with stringent rules to follow to maintain the stability, proper dosage form of the drug in tablets [20]. Previous research works show the potential of the printed medicines. Inkjet printer can be used to deposit drugs like paracetamol, theophylline, and caffeine [21]. But very few micrograms of drug are seen to be deposited. Complex multiple step process of the 3 dimensional printing was imported which produce solid dosage forms [10,22]. For the overcoming, of all these high cost manufacturing process for the formulation of tablets and their manufacturing the use and the



**Fig. 3. A multi-schematic figure showing the applications as well as properties of EGCG [11]**

technique of a 3D printer (desktop based 3D printer) allows in achieving this goal. Also the use of 3D printer makes viable 3D printed tablets that are capable for immediate and sustained release.

### 3. METHODOLOGY

#### 3.1 Design of the experiment

##### 3.1.1. Experiment design follows below steps

##### 3.1.1.1 Hydroxypropyl methylcellulose (HPMC) gel formulation

Hydroxypropyl Methylcellulose or HPMC have different levels of the viscosity grades that are used in layer of immediate release [i.e. HPMC 2906 (1% w/v)] and in layer of sustained release [i.e. HPMC2208 (1% w/v)].

- **Preparation of HPMC 2906 (1% w/v) in gel form**

HPMC 2906 powder in a quantity of 1 gram was taken and added to hot water (approx. 30 ml near to boiling water level) and stirred rigorously for around half an hour. This stirring is done so that it is thoroughly mixed and forms a good dispersion. After that ice cubes weighing 69.5 grams are added into it and is stirred rigorously which increases the polymer solubility of the HPMC powder in water. Now this gel (gel-like) is put into refrigerator where it would be kept for around minimum 24 hours so

that a free from air bubbles, and a good consistency smooth homogenous gel is formed [23].

- **Preparation of HPMC2208 (1% w/v) in gel form**

HPMC2208 powder in a quantity of 1 gram was taken and added to hot water (approx. 30 ml near to boiling water level) and stirred rigorously for around half an hour. This stirring is done so that it is thoroughly mixed and forms a good dispersion. After that ice cubes weighing 69.5 grams are added into it and is stirred rigorously which increases the polymer solubility of the HPMC powder in water. Now this gel (gel-like) is preserved at 4 degree Celsius maintaining the shelf-life for 24 hours to prevent air bubbles [23].

##### 3.1.1.2 Preparation of Epigallocatechin gallate paste

- **For the immediate release layer:**

The Epigallocatechin gallate powder with the required excipients for the immediate release layer which are used here are sodium starch glycolate (SSG) and the microcrystalline cellulose (MCC) are mixed rigorously for minimum 30 minutes. In the powder blend, HPMC 2906 (1% w/v) used here as a binder. Now HPMC 2906 gel (pre-adjusted volume) is mixed till the paste becomes homogenous and no aggregates and separation should be observed.

- **For sustained release layer**

The Epigallocatechin gallate powder with the required excipients for the sustained release layer used herein are HPMC2208 (with different percentages) and Poly Acrylic Acid (PAA) that are mixed rigorously for minimum 30 minutes. Whereas for the Epigallocatechin gallate powder, HPMC2208 (in 1%w/v) is utilized as binder that binds total ingredients collectively and forming a paste.

Now the paste that is prepared is loaded separately into the 3D printer's different syringe tool and Epigallocatechin gallate bi-layer tablets are extruded from 1.2 mm nozzles using software (FabStudio) based 3D printer.

### 3.2 Sample materials:

- Epigallocatechin Gallate (Appearance: White powder) acts as the active component. (from Enzo Life Sciences)
- Hydroxypropyl Methylcellulose (HPMC)
- HPMC 2906 (Hypromellose, Sigma-Aldrich)
- HPMC2208 (Methocel K100M Premium, Colorcon)
- Micro-crystalline cellulose (MCC is derived from Pharmacel 102)
- Sodium Carboxymethyl Cellulose (SCC) (Sigma-Aldrich)
- Poly Acrylic Acid (PAA is carbopol with no. 974P NF, Surfachem Group)
- Trisodium Phosphate Dodecahydrate (Sigma-Aldrich)

### 3.3 Instrument:

- 3D Printer (Desk-top) having a tray having movement in x-y axis used to obtain the 3D printed tablets and two nozzles in z-axis movement used to extrude Epigallocatechin gallate bi-layer tablets.
- The United States Pharmacopeial (USP) Convention Type-I apparatus for in-vitro release (Dissolution-Erweka Dt600 Dissolution Tester) used to create an acidic medium which represents the human stomach.
- Hardness tester with no. C50, from I Holland Ltd.
- Friability tester E-1851, Erweka.

### 3.4 Data Collection

**Table 1. Different constituent's composition for immediate release**

Constituent's composition	(Percentage w/w) per Immediate Release layer
Epigallocatechin gallate	78
MCC PH 102 (disintegrant)	11
SSG type A (disintegrant)	8
HPMC 2906 (binder)	3

**Table 2. Different constituent's composition for sustained release**

Constituent's composition	Amount of constituents (Percentage W/W)			
Epigallocatechin gallate	88.4	86.4	84.4	80.4
HPMC2208 (hydrophilic matrix)	6	8	10	14
Poly Acrylic Acid (hydrophilic matrix)	2.8	2.8	2.8	2.8
HPMC2208 (binder)	2.8	2.8	2.8	2.8

### 3.5 Data Analysis

Different disintegrants were used to study the functionality of immediate release. The disintegrants used are microcrystalline cellulose (MCC) and sodium starch glycolate (SSG), based on Tables 1 & 2. The functionality of sustained release investigated with the help of a hydrophilic matrix; HPMC2208 and poly acrylic acid (or PAA) on various percentages of HPMC2208 [(6% w/w), (8% w/w), (10% w/w), (14% w/w)].

For potential analysis, a desktop based 3D printer is used for extruding Epigallocatechin gallate bi-layer tablets (using FabStudio software). For Epigallocatechin gallate bi-layer tablets containing Epigallocatechin gallate as an active drug a 3D printer is used which formulates various sustained release tablets.

#### 3.5.1 In-vitro analysis of released drug

For the released in-vitro drug a type-I apparatus of the U.S. Pharmacopeial (USP) Convention with the 3D printed tablets are used at 50rpm in acidic medium ((representative of the stomach)) for 2 hours. After that trisodium phosphate

dodecahydrate solution with 0.2 M concentration is added to increase the pH level to about 6.8 which will represent the gastrointestinal fluid. Now five 3D printed tablets are taken and added to the acidic medium 675ml of 0.1M HCl. Afterwards 5 ml samples are taken out from the acidic solution at 0.25, 0.5, 01, and 02 hours of intervals [24]. Now quickly trisodium phosphate dodecahydrate solution of 0.2M solution added to it after two hours has been completed to increase the pH of the solution to 6.8 [24]. If the pH has increase more than the desired value, then it can be adjusted by adding few drops of HCl solution of 0.2M concentration. Subsequently, 5ml sample at two, four, six, eight, and ten and twelve hours of intervals are taken out. Now UV-Visible spectrophotometer is used to analyze 1ml solution taken from each of the 5 ml sample solution after diluting it with a suitable dissolution medium (taken 9ml in quantity and at a temperature of  $98.6^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$  of temperature).

### 3.5.2 Physical characterization of 3D printed tablets

Weight: Percent of variations in weight of 20 individual tablets were calculated and compared with their average [25,26].

Friability: 15-20 3D printed tablets are randomly taken and then it was put on for sieving where loose coating was brushed out utilizing soft bristle brush. Afterwards the weight of each tablet was taken and placed on the friability tester where they were rotated for sometime at steady rotational speed (25rpm) (5 minutes). Now again the tablets were placed on a sieve and dusted using a brush and then weighed again to calculate the loss percentage [25,26,27].

Hardness: The tablets printed should be soft and should be easily disintegrate and release the drug and on the other hand it should be hard enough so that it cannot be easily breakdown during its transportation and storage. Five three-dimensionally printed tablets were selected and then tested over a hardness tester machine. (C50, hardness tester by I Holland) [25,26,28].

## 4. RESULTS AND DISCUSSION

### 4.1 Dissolution of 3D printed tablets

The initial burst release of the active drug occurred (less than 20% in 0.5 hours) by the immediate release layer of the tablet designed. Due to the disintegrants added in the formulation of the tablets,

the release of the immediate release layer was considered good as the large quantity of the active drug is released. In two hours of time interval, the initial release of the active drug with HPMC2208 in the 6% w/w(dry weight) and the 8% w/w(dry weight) found to be higher (>70%) as compared to it from the 10% w/w(dry weight) and the 14% w/w(dry weight) (around 55% or more). This happened due to some small channels which are found on the surface side of the 3D printed tablets. The drug released by the active drug with 14% w/w HPMC2208 was found to be consistent and when the amount of HPMC2208 increased than the active drug's release decreases. HPMC increase leads to increased water uptake, better wettability and greater swelling of the gel barrier formulation and the hydrophilic matrix which are consistent to the reduction which is observed in the drug release rate with greater amount of HPMC2208 [27].

### 4.2 3D Printed Tablets with Mechanical Characteristics

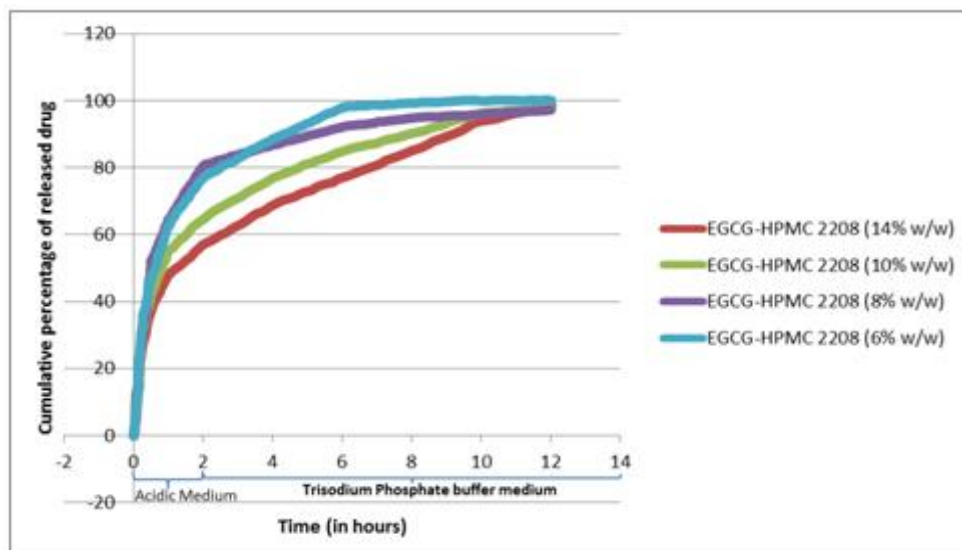
The mechanical properties regarding 3D printed tablets were assessed for the following factors-hardness, friability, and the weight variation accordingly complied with USP specifications [28]. During formulation, the absolute weight may vary slightly and all the printed tablets weights from 650 mg-750 mg which is range for many commercial bi-layer tablets as shown in Table 3. The active drug with HPMC2208 6% w/w 3-D printed tablet can be found to be of highest variation compared with among other concentrations. This can be checked by modifying the formulation. The 3-D printed tablets found to be stored and handled with no loss on its building structure. The factor friability has variation due to the lowered percent of binder and lowered viscosity grade of the HPMC2900 1% w/w (dry weight) present for immediate release layer and is also binder or binding-agent [29] whereas the friability of the active drug with HPMC2800 14% w/w was found to be up to mark.

### 4.3 Printed-Drug Release Mechanism

Drug release formulations release in the first two hours i.e. at acidic conditions and buffer conditions i.e. 2 hours to 12 hours, both the conditions has been shown in the experiment [27,30,31]. For all the formulation concentrations the experiment model remains same. The method adapted in the present research creates EGCG tablets which are hard enough that it cannot be broken into pieces

**Table 3. Different constituent's composition for immediate release**

EGCG-HPMC 2208 (Percentage w/w)	Weight Variation (in mg)	Thickness (in mm)	Hardness (kg cm <sup>-2</sup> )	Friability (%)
6	698-716 ( $\pm 5-10$ )	6.2-6.8 ( $\pm 0.5$ )	7.4-9.6 ( $\pm 0.5$ )	0.91-0.95 ( $\pm 0.05$ )
8	692-701 ( $\pm 5-10$ )	6.4-6.9 ( $\pm 0.5$ )	8.2-10.4 ( $\pm 0.5$ )	0.84-0.92 ( $\pm 0.05$ )
10	675-696 ( $\pm 5-10$ )	6.2-6.7 ( $\pm 0.5$ )	9.8-10.1 ( $\pm 0.5$ )	0.69-0.76 ( $\pm 0.05$ )
14	705-725 ( $\pm 5-10$ )	6.5-6.7 ( $\pm 0.5$ )	10.97-12.77 ( $\pm 0.5$ )	0.43-0.49 ( $\pm 0.05$ )

**Fig. 4. Epigallocatechin gallate with HPMC2208 [(6% w/w), (8% w/w), (10% w/w), (14% w/w)] and their dissolution profiles is shown in the graph**

during its storage and transportation and are soft enough such that it easily disintegrates when consumed. As shown in Fig. 4, the drug release kinetics can be seen which shows the initial release is obtained between 0-2 hours of time intervals and the sustained release of the drug can be obtained within 2-14 hours of time intervals. Also the technique of 3D printing adapted, makes the tablet cost efficient.

## 5. CONCLUSION

The complex formulation of Epigallocatechin Gallate bi-layer tablets were extruded using 3D printer which is a very cost efficient way of doing the same. The 3D printing technologies are evolving rapidly and in the field of pharmaceutical sciences it can make the complex process to be done in a very cost effective and time efficient way which ultimately will generate the production rates and also the cost of the tablets will become economical. The aim of the experiment focuses

on the getting an alternate and low cost method from that which is already used in the industries has been obtained. 3D printer can be used to create new drugs with bi-layer or multi-layer formulations and new design of printed tablets. 3D printing extruded tablets will in somehow contribute in a healthy nation.

The generated bi-layered tablets have developed using various analyses and method so that the set properties of the tablets did not get affected. The initial release and the sustained release methods were studied separately. The ultimate stage of the research completes when the 3D printed tablets with set time intervals for the initial and sustained release without changing the set mechanical properties of the tablet are obtained. The method provides completely natural tablet so it will be helpful for those people who are vegans and also as such it will not show any side-effects so it could be taken as supplement.

## DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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