Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 15 [10] September 2026. 23-29
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Online ISSN 2277-1808
Journal's URL: http://www.bepls.com
CODEN: BEPLAD



ORIGINAL ARTICLE **OPEN ACCESS**

Formulation and Evaluation of Herbal granules for hypocalcemia in women

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ABSTRACT
Women require calcium at various stages of life from birth to menopause. Even after menopause women require high amount of calcium to maintain calcium homeostasis. Bone density is more viable in women than in men. Women also require high amount of calcium during pregnancy and lactation. Large variety of allopathic calcium supplements are available, but constipation is major disadvantage. Herbal formulations containing calcium crude drug are rich in calcium and fibre can overcome such problem. The current study emphasis on use of herbal formulation for hypocalcaemia especially in women. The present study designed to formulate granules containing herbs rich in calcium like Fox nut (makhana), Sesame seeds, chia seeds and veld grape (hadjode). The formulation was evaluated for organoleptic and other screening test. Calcium content was determined by the EDTA method and atomic absorption spectroscopy. The formulation is rich in calcium (2.04%) and helps to improve calcium absorption.
Keywords: *Hypocalcemia, Fox nut, Sesame seeds, veld grape, herbal formulation, evaluation, EDTA titration, Atomic Absorption Spectroscopy.*

Received 26.06.2026 Revised 20.08.2026 Accepted 26.09.2026

INTRODUCTION

Calcium is necessary for healthy physiological function. The body's different hormones interact dynamically with one another and with other factors to maintain calcium homeostasis. Vitamin D, fibroblast growth factor 23 (FGF23), Calcitonin, and Para Thyroid hormone (PTH) are four crucial elements that control the blood's calcium level. [1]

The majority of the body's calcium, or around 45% of it, is bonded to albumin and other plasma proteins. 15% of the total is made up of small anions, mostly citrate and phosphate. About 40% of the total is contributed by the free or ionised state. [2]

The total blood calcium content is typically reported as 8.5 to 10.5 mg/dL (2.12 to 2.62 mmol/L) in most cases. A calcium level that is below this range is referred to as hypocalcemia. Before identifying hypocalcemia, total calcium must always be adjusted for albumin levels since albumin binds the majority of the body's calcium. For every 1 g/dL (10 g/L) fall in serum albumin content, the blood total calcium concentration drops by about 0.8 mg/dL (0.25 mmol/L). [3] Total blood calcium is normal in patients with a respiratory alkalosis (such as hyperventilation), but ionized calcium is low. Hypocalcemia clinical signs may occur as a result. [4] Etiology for hypocalcaemia is depicted in figure 1 and sign & symptoms in Figure 2.

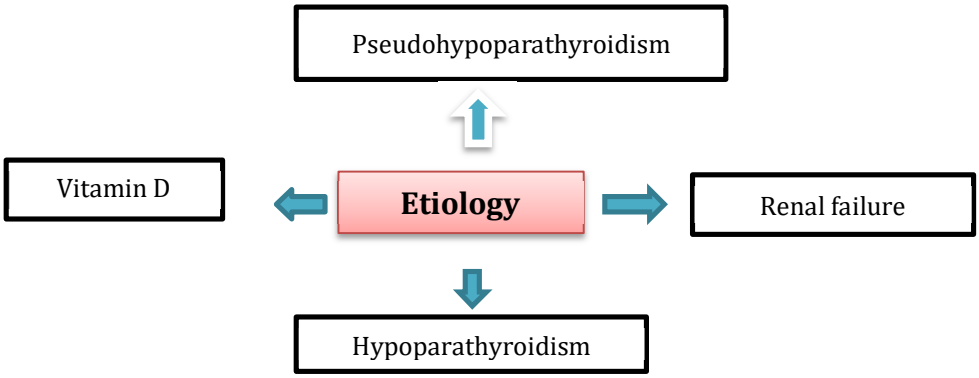


Fig1. Etiology of hypothyroidism

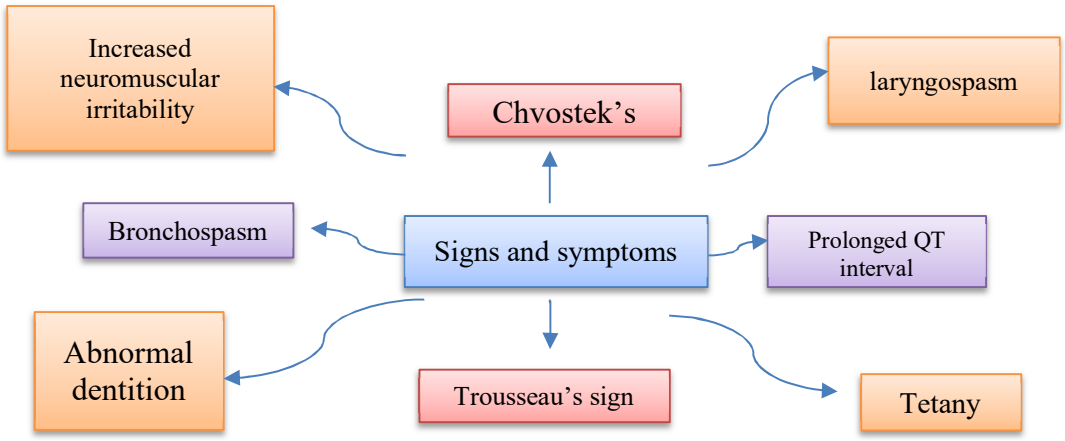


Fig2. Sign and Symptoms of hypothyroidism

Daily required dose of calcium:
The recommended dietary allowance (RDA) is a national system of nutrition recommendations. In 2020, the U.S. Department of agriculture (USDA) and the U.S department of health and human services (HHS) jointly released updated dietary guidelines for American which set the following RDAs for calcium given in Table 1. [5, 6, 7]

Table. 1: Daily required dose of calcium [8]

Category	Age	Daily dose
Children	Age 2- 3 year Age 4- 8 year	700 mg 1000 mg
Women	Age 9- 18 year Age 19- 50 year Above 51 year	1300 mg 1000 mg 1200 mg
Pregnant women	Under age 19 year Age 19 and above	1300 mg 1000 mg
Lactating women	Under age 19 year Age 19 and above	1300 mg 1000 mg
Men	Age 9- 18 year Age 19- 70 year Above 71 year	1300 mg 1000 mg 1200 mg

MATERIAL AND METHODS

Materials:

Fox nut, sesame seeds, chia seeds were brought from the local market. While veld grape were brought freshly from the garden and other additives like saccharin and sodium starch glycolate has been used from the college laboratories.

Methods:

Preparation of raw material:

Raw material- Fox nut (makhana), Sesame seeds, chia seeds and veld grape (hadjode) were taken as raw ingredients. [9, 10, 11] Veld grape was brought into raw form and dried in sun for complete 10 days due to its wet composition. Fox nut, sesame seeds, chia seeds and veld grape were grounded in a mixer grinder to get respective flours.[12] These flours were then cleaned to sift out minute impurities. Fox nut were roasted using a microwave oven for 8-10 minutes. The cleaned and roasted nuts were ground using a plate mill to obtain whole flour and then whole flour was sieved to collect fine powder.[13]

Formulation of herbal granules:

The formula and role of each ingredient was given in Table 2. All ingredients are weighed using digital balance as per formula. The powders were passed through the 22 number mesh for collecting the fine powder of every ingredient. Fine powder of each ingredient was mixed together in the mortar pastel, leave it aside for few minutes. The saccharin granules were grind to obtain powder and mixed with sodium starch glycolate. Few ml of distilled water added to above mixture to form a thick paste. The raw component powder was blended with this paste to create a dough-like mixture. The formed dough was allowed to pass through the mess number 18 so that the granules were produced. The granules were dried in the hot air oven with the temperature of 50-60°C for about 45 minutes. The granules were allowed to cool and leave it aside for 3 to 4 minutes so that it won't catch moisture after packaging. [13-15]

Table. 2: Formula of herbal granules and Role of each ingredient

Sr. No.	Ingredients	Quantity taken	Role
1	Fox nut	12 gm	Rich in Calcium content, even used as antidiabetic.
2	Sesame seeds	6 gm	Rich in calcium, protein, fatty acid and act as flavonoids.
3	Chia seeds	6 gm	Act as antioxidant and rich in calcium, fibre. Helps in weight loss.
4	Veld grape	2 gm	Act as analgesic and anti-inflammatory. Rich in calcium, sitosterol, amyrin and amyrone.
5	Sodium starch Glycolate	6 gm	Binder
6	Saccharin	1.5 gm	sweeter

Evaluation of Herbal Granules:

Pharmacognostical evaluation of herbs powders

Pharmacognostical analysis of herbal powders consists of preliminary phytochemical screening. [16]

Evaluation of granules:

Herbal granules were evaluated for organoleptic characters [i.e., color, odor, taste, and texture, was recorded].

Angle of repose, bulk density, tapped density, Carr's Index, and Hausner ratio were calculated according to Aulton and Kelvin.[17]

Particle size:

Particle size is determined by "Sieve Analysis method" where granules are passed through the different numbering sieves from larger mesh of 25mm to fine mesh of 1.00 mm [15]

Granules density: [18]

Bulk density:

Bulk density is determined by the formula:

$$\rho = \frac{m}{v}$$

Whereas,

ρ: bulk density of particle

m: mass of particle(5gm)
v: volume of particle(13 gm)

$$\rho = 0.38$$

Therefore, the bulk density of the granules is 0.38 gm

Flow property of granules-

Angle of Repose: The angle of repose is a parameter commonly used for the evaluation of interparticle force. The simplest method for the determination of the angle of repose is the "poured" angle. A funnel with a wide outlet is affixed at a distance of 10 cm above the bench, where a piece of paper is placed directly beneath the funnel. Powder is added while the funnel is closed. The relationship between flow properties and angle of repose has been established. When the angle of repose is less than 25 degrees, the flow is said to be excellent; on the other hand, if the angle of repose is more than 40 degrees, the flow is considered to be poor.

Angle of repose is calculated as follow-

$$\theta = \tan^{-1}(\frac{h}{r})$$

Where,
h= height of pile
r= radius of circle

a. **Carr Index:** Carr Index of any solid is calculated for compressibility of a powder which is based on true density (ρT) and bulk density (ρB).
CI=100[(ρT−ρB)/ρB]
A Carr index greater than 25 is considered to be an indication of poor flowability, and below 15, of good flowability.

b. **Hausner's ratio:** The Hausner ratio is a number that is correlated to the flowability of a powder or granule material . A Hausner ratio greater than 1.25 - 1.4. Is considered to be an indication of poor flowability.
The Hausner ratio (H) is related to the carr's index (C), another indication of flowability for granules
Hausner ratio is given by formula:

$$Hausner\ ratio = \frac{\text{tapped density}}{\text{bulk or poured density}}$$

A. Calcium determination

a. By EDTA: The calcium content is calculated by the procedure given in Indian Pharmacopoeia using 0.5 gm of granules. [19,20]

b. By AAS: 0.5 gm granules were used to determine calcium content of herbal granules by using atomic absorption spectroscopy. [21,22]

RESULT AND DISCUSSION

Hypocalcemia in women has been one of the major diseases due to adverse effect of various drugs as well as some conditions especially, Denosumab drug which have been reported by the case study performed in women. It has shown that 2%- 20% of women witch post-menopausal osteoporosis and 10%- 50% of bone metastasis women has taken a single 120 mg dose has been affected by hypocalcemia later. Furthermore, in phase 3 trials of single 120 mg dose, upto 33% of patient were women who experienced severe hypocalcemia had recurrent events despite intake of oral supplement of calcium and vitamin D. So, in present study we have focused on giving natural remedy in the form of natural herbs which will avoid the further side effects.

Preliminary Phytochemical Screening:

The preliminary phytochemical screening test was carried out to determine the active constituents present in selected herb. The Table 3 shows the result obtained for phytochemical screening.

The selected herbs were done after looking forward to the efficacy that the maximum calcium should be present. According to synthetic drugs of calcium supplement the calcium is absorbed in large amount after the intake it passes through various phases of absorption, metabolism and excretion, so as a result the taken herbs already has higher amount of calcium which can even be retained in body after passing through various phases. All the herbs are rich in fiber which helps in resisting increasing weight caused due to calcium supplement treatment, they also provide the properties like Anti-inflammatory, Anti-oxidant, Anti-rheumatic and Anti-diabetic property with maintaining the metabolism. Besides these flavonoids and essential fatty acids are also provided by these herbs in large quantity.

Table 3: Preliminary phytochemical screening

Test	Fox nut	Chia seeds	Sesame seeds	Veld grape
Test for organic constituents				
A.For carbohydrates Fehling's test – 1ml Fehling's A+ 1ml Fehling's B+ test solution. Boil (for 1min)	Reddish (Present)	Blue (Absent)	Reddish (Present)	Blue (Absent)
Benedicts test- 1ml test solution+ 1ml benedicts reagent. Boil (for 5min).	Greenish yellow (present)	Blue (absent)	Brick red (present)	Blue (absent)
B. For proteins 1. Ninhydrin test 3ml drug solution+ 5ml million's reagent. Water bath (for 5min).	Purple (present)	Purple black (present)	Purple red (present)	Purple (present)
Test for inorganic constituents The ash of drug material was prepared by burning the sample. 50% HCl was added to ash. Keep for 1hr. filter with filtrate perform following test.				
Test for calcium- 1. 10ml filtrate add 1 drop of dil. Ammonium hydroxide and saturated ammonium oxalate solution precipitate. Precipitate soluble in HCl.	Yellow (present)	Yellowish brown (present)	Yellow (present)	Yellow (present)
2. Filtrate + ammonium carbonate. ppt insoluble in ammonium chloride solution	white ppt (present)	white ppt (present)	white ppt (present)	white ppt (present)

Evaluation of Granules:

Formulated granules supplement is rich in calcium in required amount for the body, this supplement can be easily formulated even at home due to its easy availability of herbs and can be taken by every age group because of its masked taste which will be suitable for everyone from pediatric to geriatric.

Particle size –

The granules prepared are made to pass through the standard sieve size of 22.6 mm which states that the size of granules are 0.875 inches or 22600 microns.

Granules density-

Bulk density of the granules is 0.38 gm

Table 4 indicates various physical characteristics of formulated granules like angle of respose, carr's index and Hausner Ratio etc.

Table 4 : Physical Characteristics of the formulated granules

Sr. No.	Characteristic	Values
1	Angle of Repose	23.797
2	Bulk Density	0.38
3	Carr's Index	18.42
4	Hausner Ratio	0.894

The granules have also passed all the evaluation test such as flowability, density and size determination test. The flow properties of formulated granules is excellent as per reference values given in table 5.

Table 5 : The standard measures for flowability of powder or granule

Angle of repose	**Hausner's ratio**	**Flow properties**
25-30	1.00-1.11	Excellent
31-35	1.12-1.18	Good
36-40	1.19-1.25	Fair
41-45	1.26-1.34	Passable
46-55	1.35-1.45	Poor
55-65	1.46-1.59	Very poor
>66	>1.60	Very poor

Calcium determination:
After the formulation the amount of calcium present in the sample granules has also been determined by various methods of determination like EDTA and atomic absorption which provide the total amount of calcium present in the sample. It is found to be 1.95% by EDTA method and 2.04% by AAS. This indicate that the formulation is rich in calcium and can be used in hypocalcemia to provide sufficient amount of calcium.

CONCLUSION

The herbal granules calcium supplement for hypocalcemia was prepared after reviewing the available information about hypocalcemia. The appropriate herbs were selected with the help of a literature study. The amounts of binder, sweeter, chia seeds, Sesame seeds, fox nut and Veld grape were optimized and prepared the supplement simply by wet granulation and evaluating. Results from the angle of repose, Carr's index and Hausner's ratio showed that the granules possess excellent flow properties. The amount of calcium content in the prepared supplement was determined by two methods. Firstly, by titration using EDTA and by atomic absorption spectroscopy. It was found to be 2.4%, which is sufficient to fulfil daily need of calcium. The formulated herbal calcium granules supplement not only contains a rich amount of calcium but also has other additive properties such as anti-inflammatory and high fibre content that minimizes the suspected adverse effects like constipation. It can be taken with ordinary water or milk, which enhances calcium absorption.

DECLARTION OF COMPITING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

FUNDING

This work was supported by BUCD, Savitribai Phule Pune University (SPPU) under ASPIRE Research Project.

ACKNOLEDEGEMENT

The authors and very grateful to BUCD, Savitribai Phule Pune University (SPPU) for providing funds to carry out the work under ASPIRE research Mentorship. The authors are also thankful to Management, Principal and faculty of college Sir Dr. M. S. Gosavi College of Pharmaceutical Education and Research, Nashik, providing all the necessary facilities.

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CITATION OF THIS ARTICLE

Mali Dhanashri R., Pranali S, Sunil V. A. Formulation and Evaluation of Herbal granules for hypocalcemia in women. Bull. Env. Pharmacol. Life Sci., Vol 15 [10] September 2026. 23-29