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Review on vitamin D3 chewable tablet as antihypertensive agent

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Abstract :
The purpose of this review was to create vitamin D3 chewable tablets for hypertension using the wet granulation method and to evaluate the tablet properties. vitamin D3 is used as vitamin D. Tablets were put through a variety of tests (weight variation, thickness, hardness, disintegration, and assay of vitamin D3, among others), and the results were in compliance with the pharmacopoeial specification. All the physical properties studied show that all excipients are suitable for tablets. Take-away tablet Water is not necessary for administration since a substance is first broken down into particles in the oral cavity, which facilitates swallowing.

Keyword : Vitamin D3, wet granulation , chewable tablet, antihypertension.

Introduction :[1]
Tablets that must be broken and chewed in between the teeth before being swallowed. These tablets are designed to dissolve evenly and gradually in the mouth, either with or without chewing. A palatable chewable tablet is one that can be consumed with little to no water after being chewed. Wet granulation or direct compression are typically used in the production of chewable tablets. Since mannitol is non-hygroscopic and moisture-sensitive medications require it, it is frequently utilized as an excipient in chewable tablets. The gum core of a chewable tablet, which may or may not be coated, makes up its composition. Fillers, waxes, antioxidants, sweeteners, and flavoring ingredients make up the core, which is made of an insoluble gum basis. Based on the base utilized and its characteristics, the percentage of gum base varies from 30 to 60%. To make it more appetizing, a flavoring agent is added.

Physical Properties – Colour
Odour
Taste
Melting temperature
Polymorphism
Moisture content
Aqueous solubility
Active drug stability
Compressibility

Chemical Properties-
Chemical structure and chemical class
Major reactions
Major incompatible compounds
Drug dose

Need for the Development of Chewable Tablet -
Due to patient's low acceptance and compliance with current distribution regimens, the small market size for pharmaceutical companies and drug uses, along with the high cost of illness care, the demand for non-invasive delivery systems continues.

General Formulation Factors -
The demand for non-invasive delivery systems is still present because to patients' low acceptance and compliance with current distribution protocols, the small market size for pharmaceutical companies and drug uses, as well as the high cost of disease care.
Aroma-
Aromas are typically used to refer to pleasant odors. For instance, a properly designed chewable tablet with orange flavor should have the distinctive sweet-sour flavor and aroma of a real orange.

Physiology of Taste –[2,3,4,5]

When something is placed in the mouth in order to determine the entirety of a component, a person can communicate their taste impression as a feeling.

Generally, there are three basic components of taste:

1. Salty and sweet, mostly near the tongue's tip
2. On the side of the tongue, it's sour
3. On the rear of the tongue, it's bitter

Taste Masking –One of the major limiting factors in the formulation of oral dosage forms with unpleasant taste is sweeteners, which are necessary to complete the experience and produce a pleasant taste of the product. Flavour masking and processing approaches are two main methods to overcome this problem. **Techniques for Taste Masking**

Before formulation, there were certain typical issues like terrible mouthfeel and taste. The desired product should have a flavor and sweetener that are appropriate, a decent tongue feel, and good compressibility. It should also prevent or reduce stimulation of the taste buds. The methods utilized to resolve these issues are as follows:

1. Coating by Wet granulation
2. Microencapsulation
3. Solid dispersions
4. Adsorbate Formulation techniques (Solvent method)
5. Ion Exchange
6. Spray congealing and spray coating
7. Formation of different salts or derivatives
8. Use of amino acids and protein hydrolytes
9. Inclusion complexes
10. Molecular complexes

Sweetners[7,8]

Dextrose – The sugar produced when starch is completely hydrolyzed is dextrose. It is accessible in both anhydrous (but naturally hygroscopic) and monohydrated forms, with a sweetness level that is roughly 70% that of sucrose

Sorbitol- The isomer of sorbitol that is more hygroscopic and slightly sweeter than mannitol. It is marketed as Sorb-Tab and crystalline Tablet Type for direct compression.

Lactose- When a byproduct of the cheese-making process, is the source of the monosaccharide lactose. Despite being largely acknowledged as the medicinal excipient that is utilized the most everywhere. Due to its incredibly low sweetness level (15% sucrose), its applicability to chewable pills is minimal at best.

Mannitol- Mannitol is a white, crystalline polyol approximately 50% as sweet as sucrose. It is freely soluble in water and, when chewed or dissolved in the mouth, imparts a mild cooling sensation due to its negative heat of solution.

Flavouring Agents-

From the perspective of consumer acceptance, taste is almost certainly the most important parameter of the evaluation of chewable tablets. Taste is a combination of the perceptions of mouth-feel, sweetness and flavour. Mouth-feel is affected by heat of solution of the soluble components, smoothness of the combination during chewing and hardness of the tablet. These factors are directly and almost entirely related to the active ingredient and major excipients. Sweetness, at an appropriate level, is a necessary background to any flavour. The primary contributors to sweetness in a chewable tablet are the drug, natural sweeteners and artificial sweetness enhance that may be incorporated in the formulation. Flavouring agents are available in a variety of physical forms from a large number of suppliers specializing in these materials. Virtually all offer technical support services, which will be addressed in the section on flavour formulation. Various forms available include water-miscible solutions, oil bases, emulsions, dry powders, spray-dried beadlets, and dry adsorbates. A typical flavour having the capability of producing several hundred combinations for a given application.

Colourants-

Colourants are used in the manufacture of chewable tablets for the following reasons

To increase aesthetic appeal to the consumer

To mask non uniform colour of raw materials

To complement and match the flavour used in the formulation

To aid in product identification and differentiation

Dyes-

When dissolved in a solvent, these chemical compounds reveal their tinctorial strength or coloring ability. They typically contain 80 to 93% pure colorant material (occasionally 94 to 99%). Dyes is soluble in glycerine and propylene glycol.

Vitamin D3 –[8-19]

The role of vitamin D3 in maintaining bone health is derived from 7-dehydrocholestrol.Scientists now understand that a lack of vitamin D3 directly contributes to conditions such as depression, back pain, cancer, insulin resistance, Hypetension, weakened immunity, and macular degeneration. Vitamin D3 (cholecalciferol) is referred to as vitamin D. Low levels of vitamin D3 have also been linked to other conditions like high blood pressure, diabetes, multiple sclerosis, and rheumatoid arthritis. As vitamin D, vitamin D3 was used. Osteomalacia, a painful bone disease, is brought on by vitamin D deficiency whereas vitamin D enhances bone health.

Muscle deterioration and fractures are also caused by vitamin D deficiency. Reducing BMD loss is associated to lowering the risk of bone fracture. Additionally, vitamin D might stop the loss of bone mineral. Low mood is psychiatric and neurologic condition caused by vitamin D3 insufficiency. Bone mineral Density (BMD)can be change by combination of calcium and vitamin D.

Vitamin D Defiency Cause :[20]

1. Bone Loss
2. Hair loss
3. Muscle pain
4. Depression
5. High Blood Pressure
6. Heart Attack
7. Breast Cancer

Vitamin D is important for Bone and Muscle Health, but it affects many other aspect of our health .

1. You are constantly sick
2. You are exhausted
3. Your bone Density is declined
4. You have a back pain
5. Your muscle are always sore
6. You are losing hairs

Hypertension and vitamin D deficiency are both quite common.This review will cover the connection between low vitamin D levels and blood pressure as well as the usage of calcium supplements as a preventative measure for lowering blood pressure.

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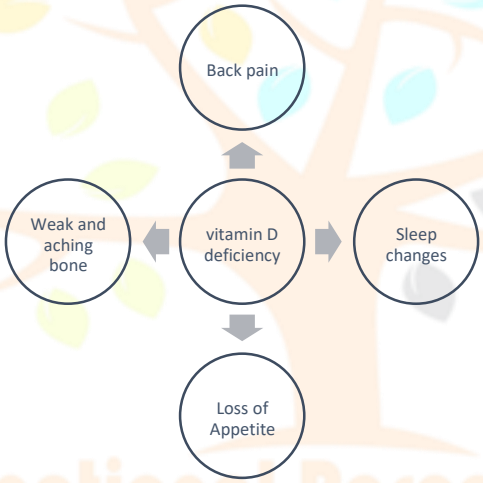


Fig -01 Deficiency of Vitamin D3

- **Back pain :**

Lack of vitamin D3 is strongly linked to lumbar disc degeneration (LDD).Lack of vitamin D3 can worsen or cause neck and back discomfort.

Fig-02 Back pain

- **Sleep Changes :**

Vitamin D in our Blood with higher risk of poorer sleep quality .on the other hand, high Doses of vitamin D consumption may be related to reducing Melatonin[4] level, the hormone that control your sleep cycle

Fig-03 Sleep changes

- **Loss of appetite :**

Loss of appetite is one of the early signs of vitamin D3 insufficiency, which can also lead to additional symptoms like nausea, fatigue, weakness, depression, and sweating.People who are vitamin D3 deficient may experience appetite loss.

Fig-04 Loss of Appetite

- **Weak and Aching Bone :**

Bone pain is more likely to occur when vitamin D levels are insufficient and the body is unable to adequately absorb calcium and phosphorus. Clinical manifestations of low vitamin D3 levels can include chemical class and structure, major reactions, major incompatible substances, and drug dose.

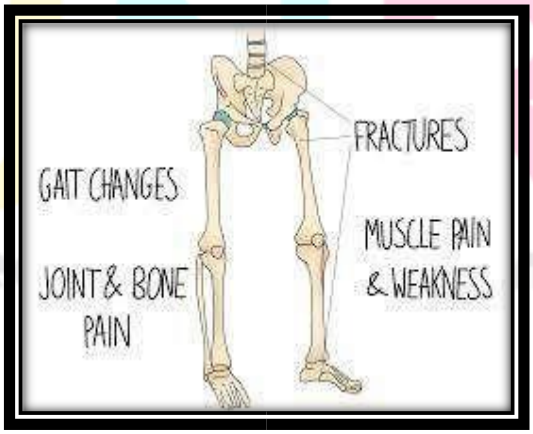


Fig -05 Weak and aching Bone

Vitamin D Advantages :

1. Help the body absorb and retain Calcium and Phosphorus 2. Reduce cancer cell growth
3. Control infection.
4. Reduce indflamation
5. Help protect older adults from Osteoporosis

6. Prevent cramps ans spasma in the muscle
7. Vitamin D may fight Disease
8. Supporting immune health

Vitamin D3 Disadvantages :

1. Bone pain
2. Kidney problems
3. Calcium Stones
4. Hyperglycemia
5. Nausea
6. Vommiting
7. Weakness
8. Confusion
9. Agitation

HYPERTENSION :

Consistently elevated blood pressure is a symptom of the hypertension disease. Values for blood pressure are represented by two numbers. The highest reading, the systolic blood pressure, represents the pressure generated by each heartbeat. The bottom figure, known as diastolic blood pressure, represents the blood pressure in the vessels while the heart is at rest. High blood pressure levels over an extended period of time may produce abnormal cardiac changes.

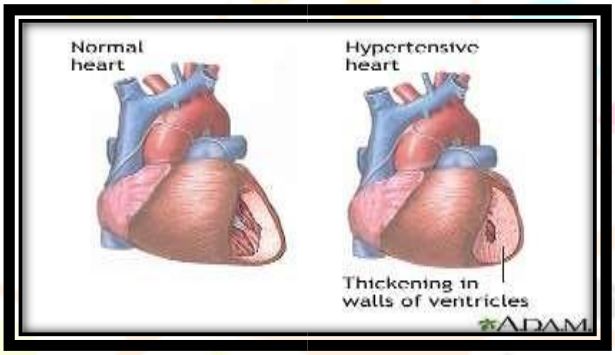
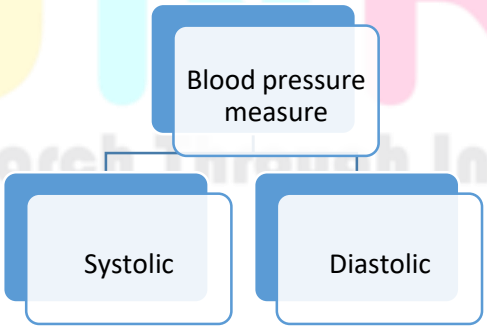


Fig-06 Hypertensive Heart

Chronically high blood pressure causes a variety of abnormalities in the left ventricle and left atrium that are referred to as hypertensive heart disease. Unhealthy lifestyle decisions, such as not receiving enough regular exercise, are to blame.Diuretics, beta-blockers, ACE inhibitors, calcium channel blockers, angiotensin receptor blockers, and vasodilators are just a few of the medications that doctors use to treat it.

According to the poll, just 37% of the 188.3 million Indians who are believed to have the condition have a diagnosis. Additionally, a lot of people delay starting their treatment even after being diagnosed. Only 30% of people who are diagnosed with hypertension start treatment, and only 15% are able to keep their blood pressure levels stable.



1.Systolic Blood Pressure- Measure the pressure in arteries when Heart beats

2. Diastolic Blood Pressure- Measure the pressure in arteries when Heart Rest between beats.

Systolic and Diastolic Blood pressure ratio – **120/80 mm Hg**

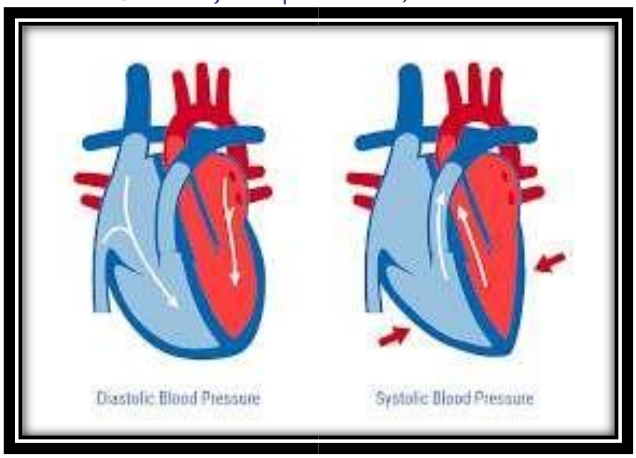


Fig – 07 Systolic and diastolic Blood Pressure range

Table -01 Blood Pressure Readings

Blood Pressure Category	Systolic mm Hg (upper)		Diastolic mm Hg (lower)
Normal	Less than 120	And	Less than 80
Prehypertension	120-139	Or	80-89
High Blood Pressure Stage I	140-159	Or	90-99
High Blood Pressure Stage II	160 or higher	Or	100 or higher
Hypertension Crisis	Higher than 180	Or	Higher than 110

Risk of getting High Blood pressure :
Weight problem
Consume insufficient amounts of fruit and vegetables and too much salt Do not exercise enough.
Consume excessive amounts of wine, coffee, or other caffeinated beverages, or smoke.
A great deal of stress and older.
Having a blood pressure problem in a family member.
Making healthy lifestyle adjustments can sometimes help lower your blood pressure if it's already high and help lessen your risk of developing high blood pressure.

Signs of Hypertension –
Mostly people with high Blood pressure have no symptoms,even if blood pressure readings reach dangerously high levels.
Nosebleeds Fatigue
- Headache
- Shortness of Breadth
- Nausea
- Vomiting
- Blurry or double vision
- Chest pain
- Dizziness

Diagnosis – [21]

a measurement of blood pressure The top number, known as the systolic pressure, represents the pressure in the arteries during a heartbeat, while the bottom number, the diastolic pressure, represents the pressure between heartbeats. An inflatable cuff is typically wrapped around the arm to take blood pressure. The reading of blood pressure is recorded by a machine. An automatic blood pressure reading is what this is. Millimeters of mercury, or mmHg, are used to measure blood pressure. Based on how high it is, high blood pressure is divided into categories. Staging describes this. Staging aids in treatment planning.

- Stage I Hypertension –

The top figure ranges from 130 to 139 mm Hg, whereas the bottom ranges from 80 to 89 mm Hg.

- Stage II Hypertension –

The top number is at least 140 mm Hg, while the lowest number is at least 90 mm Hg.
Sometimes the top blood pressure reading is high but the bottom value is normal (less than 80 mmHg). Isolated systolic hypertension is what is known as this. It is a typical kind of elevated blood pressure in adults over 65.

Fig-08 Sphygmomanometer

Treatment of Hypertension –[22]

Types of Medicine use to treat Hypertension depend on overall health and high Blood pressure .
Medicine use to treat high Blood Pressure include- 1.Water pills (Diuretics)-

These drugs remove Sodium and water from body.There are different classes of diuretics ,including thiazide , loop Diuretics, potassium sparing .
Diuretics used to treat Blood pressure , including chlorothalidone, Hydrochlorothizide and other.
A common side effect of diuretics is increase Urination.Urination can reduse potassium levels. A good balance of potassium is necessary to help the Heart beat correct

2.ACE inhibitor –

These drugs help relax Blood vessels. They block the formation of natural chemical that narrows blood vessels . Angiotensin II receptor Blocker include Losartan and other.

3.Angiotensin II receptor blocker (ARBs) –

Additionally, these medications help to relax blood vessels by blocking an enzyme that naturally constricts blood vessels. Examples of angiotensin II receptor blockers (ARBs) include candesartan and other.

4.Calcium Channel Blocker –

These medications aid in blood vessel muscle relaxation. Amlodipine, Diltiazem, and others are among them.

Homeopathic Treatment[22]

It takes a lifetime of medication to treat this chronic illness. However, homeopathy treats hypertension holistically and addresses the underlying symptoms in addition to momentarily lowering blood pressure.

Nux Vomica

effective in treating hypertension brought on by alterations in lifestyle Patient
is typically short-tempered, energetic, tense, and skinny.

Increased propensity to eat alcohol, caffeine, and fried and spicy foods.
Aggressive and extremely ambitious men The patient can be constipated.
It is typical for a person to feel worse in the morning and better over the day.

Rauwolfia
One of the top homeopathic treatments for hypertension There is severe irritation of the neurological system.
Pregnant ladies should not use this.
Decreases mortality over time

Natrum Mur
Useful for individuals who consume excessive salt or who are accustomed to seasoning every food item with salt The patient like foods that are fried, salty, spicy, and sour.
An increase in thirst and a dry tongue
There is a high prevalence of abdominal and foot swelling. Puffy or swollen face
Tongue with an uneven coating, anemia, and palpitations
Events from the person's past that may have sparked rage but that has been suppressed

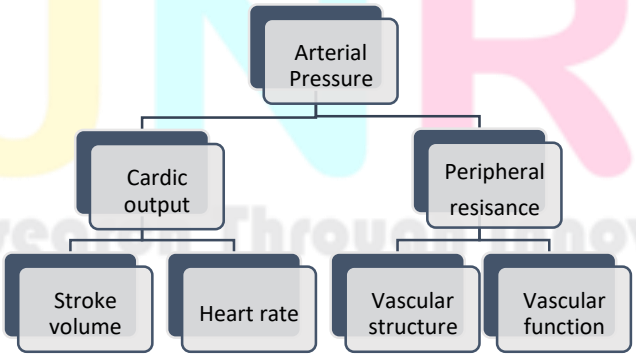
Glonine
The washing of one's face increased blood flow causing congestion in the head and face, along with a throbbing headache You are unable to lay your head down on a pillow because of how heavy your head feels.
The head feels swollen and enormous.
There can be a connection between the sun and the issue, where exposure to the light makes things worse. Patient lacks motivation, is irritable, and is overly enthusiastic about everything.

Belladonna
Hemorrhaging is linked to blood pressure.
Pupils are dilated, and the face seems flushed.
The temporal arteries are throbbing and the pulse rate has increased.

Aconitum
Useful in cases where blood pressure spikes unexpectedly in persons with healthy baseline readings Person is extremely worried and has a dread of dying.
Elevated agitation and palpitations

During these instances, the patient may experience throbbing headaches. Cigarette smoking makes blood pressure readings worse.

Physiology of Hypertension –



Manufacturing –[23,24,25]

Manufacturing for chewable tablets include achieving the right level of tablet hardness, maintaining the right moisture content, and properly incorporating the coloring ingredient. Once the parameters have been defined throughout development, the manufacturer in the department is routinely responsible for all of these. To ensure the creation of appropriate specifications, it is important to thoroughly investigate the process development and scale-up factors. The blending process involves adding colored powder to white

granules if the color is added as a lake for direct compression mix. As a result, the colored powder will cover the white granules uniformly.

Methods of Manufacturing-
The Chewable tablets were prepared by using the following method -

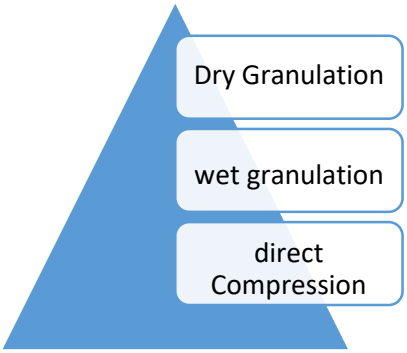


Fig – 09 Types of Granulation

Granulation-
Granules are formed when smaller, single-particle entities known as primary powder particles are forced to stick together during the granulation process. Granules used in pharmaceuticals range in size from 0.2 to 4.0 mm. Powder flow and compressibility can be improved with granulation, and the segregation of the blend's component parts can be avoided. Two techniques are mainly used in granulation.

Dry granulation-
It is a brand-new technique for producing granules in a semi-automatic fashion. Any pharmaceutical medication with a solid dose form can be used with this strategy. Existing solid dosage form development and manufacturing technologies are replaced by the dry granulation method, which allows for quicker development and better quality. The powder combination is compacted using this method without the aid of heat or solvent. There are two approaches to dry granulation. Slugging, which involves recompressing the powder and milling the resultant tablet to produce the granules, is the more popular method.

Direct Compression-
The most popular option is direct compression because it offers the quickest, most efficient, and simple method of creating tablets. When a number of substances may be blended, this technique is typically used. Since it does not require soaking or drying, it is better suited for APIs that are sensitive to heat and moisture. It also increases the stability of the active ingredient by minimizing negative (bad) effects. This procedure involves mixing API with excipients and lubricant before compressing the mixture to make the product simple to produce.

Wet granulation-
The most popular granulation technique is wet granulation. Wet massing of a powder mixture with a granulating liquid, wet sizing, and drying are the steps in this procedure. The granulating liquid comprises a solvent that must be non-toxic and volatile so that it may be eliminated by drying. Water, ethanol, and isopropyl alcohol are common liquids.
The wet mass is driven through a screen in the conventional wet granulation process to create wet granules that are then dried.

Wet Granulation Method :

Marketed Product –

Table -02 Marketed Product of Hypertension

Sr.no	Brand Name	Active Ingredients
1.	Altace	Ramipril
2.	Tenormin	Atnelol
3.	Bystolic	Nebivolol
4.	Norvasc	Amlodipine besylate
5.	Verela	Verapamil
6.	Minipress	Prazosin
7.	Diovan	Valsartan

Evalution Parameter –[28,29]

Chewable Compressed Tablet Evaluation:
Pharmacopoeial and non-pharmacopoeial tests were used to assess the tablet's qualities.

Organoleptic properties of Tablet –
By looking at, chewing, and swelling the tablets, the color, flavor, and texture of the pills were manually assessed.

Weight variation test –
The weight variation test was to be run on 20 tablets. 20 tablets were individually weighed on a digital scale to determine their average weight. The weight of each person was compared to the average.

Length , width , and Thickness –
Each tablet's length, width, and thickness, which are measured in millimeters (mm), were determined using a micrometer screw gauge.

Hardness –
Using a hardness tester, the strength of the tablet crushing was measured.

Disintegration test –
Six tablets were placed in a basket rack to track the rate of disintegration. In 900 ml of distilled water at 37°C, six disks were employed to keep the tablets from floating.

Friability –
The friability of tablets was evaluated using the Friabilator, which has a chamber that rotates at 25 rpm..

Assay for vitamin D3 –

Mobile phase – Acetonitrile : Methanol = 91.09 Chromatographic system :
Flow rate : 1.5 ml/min
Column : Octadecylsilyl silica gel for liquid chromatography (C18) (Size – 4.6mm×250mm×5µm)
Detector : 265 nm,UV
Injection volume : 20µl
Tempreture : 40℃
Standard preparation :
100 milligrams of cholecalciferol were properly measured in a 100 ml volumetric flask. 30 ml of methanol were added, and then they were taken away. To bring the volume up to 100 ml, methanol was employed, and everything was well mixed. This solution was diluted from around 2 ml to 50 ml using methanol.

Sample preparation :
Taking 20 Tablet, crushed into a fine powder, in a 50 ml volumetric flask. 30 cc of methanol was added and dissolved. Up to 50ml of methanol were used to finish the contents.

Procedure :
0.2 l of the ready sample was injected into the chromatograph to perform the filtering. Chromatographs were created, and the major peak's reactions were recorded. The amount of cholecalciferol was calculated using the calculation below.

Calculation :
Content of cholecalciferol (IU)
AT / AS ×WS / 100×2/50×50/WT×PS/100×W mg /tablet
Where ,
AT = Area of sample Preparation ,
AS = Area of standard preparation
WT = weight of sample in mg se
WS = Weight of standard Cholecalciferol (Vitamin D3) in mg
Ps = Potency of vitamin D3 standard (100000 IU /gm)
W = Avarage weight of tablet
100000 IU/gm
1 mg = 100 IU
2 mg =200 IU
One tablet contain 200 IU vitamin D3 **Conclusion:**

The chewable vitamin D3 tablets produced in the current work satisfactorily meet all pharmacopoeial requirements. This kind of research can be carried out on additional medications in addition to this combo.Chewable tablets are a flexible dosage form that

combine the advantages of solid products in terms of stability and manufacturability with favorable administration and organoleptic effects.Opportunities for the use of chewable tablets in particular populations, such as with specialized pharmaceutical goods and in other healthcare sectors, such as nutrition, nutraceuticals, and veterinary medicine.

References –

1. Lachmann L. Liebermann H.A. and Kiang J.L. 1998 . The Theory and Practice of Industrial Pharmacy, third edition, Varghese Publishing House, Bombay.
2. Smith DV Margolskee RF 2001. Making sense of tasteScientific America. 284(3): 36.
3. Nanda AR, Garg KS. 2002. An update on taste masking technologies for Oral pharmaceuticals. Indian journal Pharma sci. 64(1).
4. Roche Roto1993. Granulations and taste masking coatings for preparation of chewable pharmaceutical tablets. US Patent.
5. Khar RK Sohi H, 2004. Taste masking technologies in oral pharmaceuticals: Recent development and approaches. Drug Dev. Ind. Pharma 30-429.
6. Patel H. Shah V. Upadhyay U, 2011. New pharmaceutical excipients in solid dosage forms, International Journal of pharmacy and life sciences, 2(8):
7. Orally Disintegrating Tablet and film technologies. Second edition, 2004, 177.
8. Vieth R, Ladak Y, Walfish PG. J, 2003. Clin Endocrinol Metab. 88(1): 185-91.
9. Perez-Lopez FR, 2007. Vitamin D and its implications for musculoskeltal health in women: an update Maturitas. Jun 28.
10. Lappe J. Travers-Gustafson D. Davies K. Recker R. Heaney R, 2007. American Journal of Clinical Nutrition.85(6) :1586-1591.
11. Bodnar LM. Catov JM, Simhan HN, Holick MF, Powers RW. Roberts JM. J Clin Endocrinol Metab. 2007.
12. Maghbooli Z, Hossein-Nezhad A, Karimi F, Shafaci AR, Larijani B,2007. Diabetes Metab Res Rev.
13. Wilkins CH, Sheline YI, Roe CM, Birge SJ, Morris JC. Am J Geriatr Psychiatry, 2006.14(12):1032-40.
14. Perez-Lopez FR. 2007. Vitamin D and its implications for musculoskeltal health in women: an update Maturitas.
15. Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies on a request from Abtei Pharma Vertriebs GmbH on the scientific substantiation of a health claim related to Calcium plus Vitamin D3 chewing tablets and reduction of the risk of osteoporotic fractures by reducing bone loss. 2009. The EFSA Journal, 1180: 1-13.
16. Avenell A, Gillespie WJ, Gillespie LD, O Connell DL. 2005. The Cochrane Database of Systemic Reviews 3.
17. Boonen S, Lips P. Bouillon R, Bischoff-Ferrari HA, Vanderschueren D. Haentjens P. 2007. The Journal of Clinical Endocrinilogy and Metabolism, 92(4):1415-1423.
18. Homik J, Suarez- Almajor ME,Shea B. Cranney A, Wells G. Tugwell P. 1998. The Cochrane Database of Systemic Reviews 2.
19. Tang BMP, Eslick GD, Nowson C. Bensoussan A. Lancet 2007; 370(9588): 657-666.
20. https://www.nebraskamed.com/primary-care/9-vitamin-d-deficiency-symptoms-and-11-high-vitamin-dfoods#:~:text=%22Most%20patients%20with%20vitamin%20D,Not%20sleeping%20well.
21. https://www.mayoclinic.org/diseases-conditions/high-blood-pressure/diagnosis-treatment/drc-20373417#treatment.
22. https://www.lybrate.com/topic/homeopathic-remedies-for-high-blood-pressureb436/ebaa8f3c2e100ace6a712121f18c4bd2.
23. Solanki HK Bosuri T Thakkar JH. Patel 2010. CA Recent Advances in granulation technology International Journal of Pharmaceutical Sciences Review and Research. 5(3):48-49.
24. Surbhi G, Seema S, Singh G, Rana AC. 2012. Industrial Process Validation of Tablet Dosage Form: An Overview. International Research Journal of Pharmacy. 3(3):49-51
25. Ray C Arora V. Sharma V. Fast dissolving tablets-A Novel drug delivery system for pediatric and geriatric patient. International bulletin of drug research. 1(2), 55- 70.
26. https://www.rxlist.com/high_blood_pressure_hypertension_medications/drugscondition.htm#:~:text=Mild%20hypertension%20can%20sometimes%20be,Chlorthalidone%20(Hygroton)
27. https://www.rxlist.com/high_blood_pressure_hypertension_medications/drugscondition.htm#:~:text=Mild%20hypertension%20can%20sometimes%20be,Chlorthalidone%20(Hygroton).
28. Lachmann L., Liebermann H.A. and Kiang J.L, 1998.The Theory and Practice of Industrial Pharmacy, third edition, Varghese Publishing House, Bombay.
29. Cooper J. Gun C, 1986.Powder Flow and Compaction, Tutorial Pharmacy, New Delhi, CBS Publishers and Distributors.211-233.Indian Pharmacopoeia; Vol.II, Calcium and Vitamin D3 Tablets, 4466-4467.