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ORIGINAL RESEARCH PAPER

Formulation Development and Evaluation of Cholecalciferol (Vitamin D3) Granules and Tablets

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Abstract
The aim of this investigation was to develop dispersible form of vitamin D3 in granular and tablet form. Vitamin D is a fat soluble vitamin and is practically insoluble in water. This leads to poor bioavailability of Vitamin D. Currently, Vitamin D3 is available in granules as well as tablet form. It has been recommended to take by dispersing in milk. Since vitamin D3 is insoluble in water it disperses poorly in milk which led to non-homogeneous delivery until contents were washed with additional amount of water. This also leads to poor patient compliance. Its hydrophobicity further limits its absorption and thus bioavailability. Thus if vitamin D3 is administered in a better dispersible form, it improves bioavailability. The objective of this work was to present Vitamin D3 in granular and tablet form with improved dispersability, to minimize the complexity of formulations and to make cost effective product.

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INTRODUCTION

Vitamin D, also known as the sunshine vitamin, can be produced in the body with mild sun exposure or consumed in food or supplements. Adequate vitamin D intake is important for the regulation of calcium and phosphorus absorption, maintenance of healthy bones and teeth, and is suggested to supply a protective effect against multiple diseases and conditions such as cancer, type1 diabetes and multiple sclerosis.[1,2]

In spite of the name, vitamin D is not actually considered a vitamin. Because the body can produce its own vitamin D, it is not necessarily an essential part of the diet and is considered a pro-hormone. It is estimated that sensible sun exposure on bare skin for 5-10 minutes 2-3 times per week allows the body the ability to produce sufficient vitamin D. Vitamin D3 is made in the skin when 7-dehydrocholestrol reacts with ultra violet light at 270-300nm wavelengths- peak vitamin D3 production occurs between 295-297nm. Vitamin D is important for the absorption of calcium from the stomach and for the functioning of calcium in the body.[1-3]

There are many reasons deficiency occurs. Darker skin pigments and sunscreen use can significantly decrease the body's ability to absorb the UVB rays required to produce vitamin D. Despite this, recent studies have suggested that up to 50% of adults and children worldwide are vitamin D deficient.[1]

Possible Health Benefits of Vitamin D

Healthy Bones

Vitamin D plays a substantial role in the regulation of calcium and maintenance of phosphorus levels in the blood, two factors that are extremely important for maintaining healthy bones. Vitamin D deficiency in children can cause rickets, a disease characterized by a severely bow-legged appearance triggered by impaired mineralization and softening of the bones.[1]

In adults, vitamin D deficiency manifests as osteomalacia or osteoporosis. Osteomalacia results in poor bone density, muscular weakness and often cause small pseudo fractures of the spine, femur and humerus. Osteoporosis is the most common bone disease among post-menopausal women and older men.[1-2]

Reduced Risk of Flu

Children given 1,200 IU of vitamin D per day for 4 months during the winter reduced their risk of influenza-A infection by over 40%.[4]

Reduced Risk of Diabetes

Several observational studies have shown an inverse relationship between blood concentrations of vitamin D in the body and risk of type 2 diabetes. In type 2 diabetics, insufficient vitamin D levels may have an adverse effect on insulin secretion and glucose tolerance. In one particular study, infants who received 2,000 IU/day of vitamin D had an 88% lower risk of developing type 1 diabetes by the age of 32.[3,4]

Healthy Infants

Children with normal blood pressure who were given 2,000 IU/day had significantly lower arterial wall stiffness after 16 weeks compared with children who were given only 400 IU/day.[4]

Healthy Pregnancy

Pregnant women who are deficient in vitamin D seem to be at greater risk of developing preeclampsia and needing a cesarean section. Poor vitamin D status is also associated with gestational diabetes mellitus and bacterial in pregnant women. It is also important to note that vitamin D levels that were too high during pregnancy were associated with an increase in food allergy of the child during the first two years of life.[4]

Cancer Prevention

Vitamin D is extremely important for regulating cell growth and for cell-to-cell communication. Some studies have suggested that calcitriol (the hormonally active form of vitamin D) can reduce cancer progression by slowing the growth and development of new blood vessels in cancerous tissue, increasing cancer cell death and by reducing cell proliferation and metastases. Vitamin D has an influence on more than 200 human genes, which can be impaired when D status is suboptimal.[4]

Vitamin D deficiency has also been associated with an increased risk of cardiovascular disease, hypertension, autism, Alzheimer's disease, rheumatoid arthritis, asthma severity and swine flu. However, more reliable studies are needed before these associations can be proven.

Vitamin D is a fat soluble vitamin and is practically insoluble in water. This leads to poor bioavailability of Vitamin D.[5] Currently, Vitamin D3 is available in granules as well as tablet form. It has been recommended to take by dispersing in milk. Since vitamin D3 is insoluble in water it disperses poorly in milk which led to non-homogeneous delivery until contents were washed with additional amount of water. This also leads to poor patient compliance. Its hydrophobicity further limits its absorption and thus bioavailability. Thus if vitamin D3 is administered in a better dispersible form, it improves bioavailability.[4,5] Hence, in the present study, an attempt was made to develop Vitamin D3 granules and tablets for better solubility and dissolution, which may lead to better absorption and bioavailability.

MATERIALS AND METHODS

Vitamin D3 was obtained from Supreme Pharmaceuticals, Mysore (India). Lactose, magnesium stearate and poly vinyl pyrrolidone (PVP) were of AR grade and were purchased from SD Fine Chem, Mumbai (India). All other reagents and chemicals used in the study were of AR grade and were obtained from SD Fine Chem, Mumbai (India) or CDH, Mumbai (India).

Identification of Vitamin D3

Identification of the Vitamin D3 was carried out by FTIR spectroscopy.

Drug-Excipient Compatibility

A successful formulation of a stable and effective solid dosage form depends on careful selection of excipients that are added to facilitate administration, promote the consistent release and bioavailability of drug and protect it from degradation. If the excipients are new and not been used in formulation containing the active substance, the compatibility studies are paramount importance. Compatibility of Vitamin D3 with excipients was established by infrared absorption spectral analysis (FTIR). Any changes in chemical composition after combining with the excipients were investigated with IR spectral analysis.

Formulation of Vitamin D3 Granules and Tablets

The formulae for the preparation of Vitamin D3 granules and tablets are given in Table 1.

Table 1. Formula used for Vitamin D3 granules and tablets

Ingredients	Quantity (mg)	
	Granules	Tablets (quantity per tablet)
Vitamin D3	120	120
Lactose (anhydrous)	800	800
Polyvinyl pyrrolidone (PVP)	5	5
Purified water	Qs	Qs
Magnesium stearate	---	0.5%

Preparation of Granules

The required quantities of Vitamin D3, Lactose, PVP and magnesium stearate were weighed separately. Vitamin D3 and lactose were passed through British Standard sieve (BSS) 40# and magnesium stearate was passed through BSS 100#. For wet granulation, the binder solution was prepared by dissolving PVP in water and the solution was added slowly to the powder mass and mixed to get a coherent mass, which was passed through BSS #16 and dried at 50°C. Then, the dried granules were passed through BSS # 20 to get required granule size. The prepared granules were stored in air-tight light resistant containers till further use.

Preparation of Tablets

The dried granules were blended with magnesium stearate as lubricant and the tablets were compressed using a rotary tablet press using suitable punch set.

Evaluation of Vitamin D3 Granules

The prepared Vitamin D3 granules were evaluated for bulk density, tapped density, Carr's index, Hausner ratio, size distribution, dispersibility in water, along with stress test using standard procedures.[6] The stress test was done by storing the prepared granules and tablets at 50°C for 7 days and evaluating the above parameters at the end of test period.

Evaluation of Vitamin D3 Tablets

The prepared tablets of vitamin D3 were evaluated for thickness, hardness, friability and dispersibility using reported procedures.[7]

RESULTS AND DISCUSSION

The identification of Vitamin D3 was done by comparing the FTIR spectrum of the drug (Fig. 1) with standard FTIR spectrum.[8] The spectrum was similar to the standard FTIR spectrum, indicating that the API was Vitamin D3.

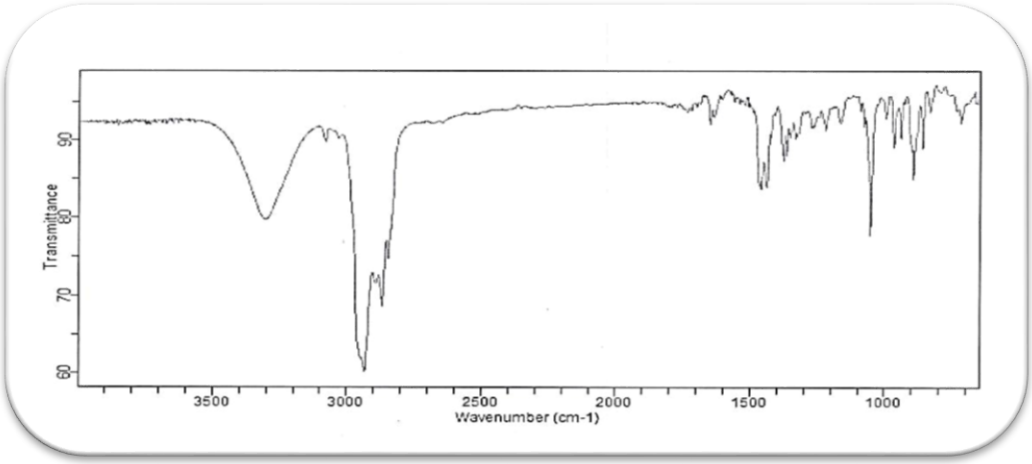

Fig 1. FTIR spectrum of Vitamin D3

The drug excipient compatibility was studied through comparison of FTIR spectra of drug and drug-excipient mixtures. There were no changes in the existing peaks and there were no appearance or disappearance of peaks, indicating that the excipients used were compatible with the drug (spectra not shown).

The results of evaluation of granules are shown in Table 2. The physical properties of granules were found to be good. The granules had very narrow particle size range. All the 100% granules were in the size range of BSS #16-20 mesh (Table 3). The granules had good flow property and good dispersibility. The dispersibility of granules was found to be better than tablets.

The results of evaluation of tablets are shown in Table 4. The average thickness of tablets was 4 mm and the hardness and friability were within acceptable range.[7,8]

The dispersibility of granules was found to be better than the tablets. The granules, due to their particle size, have higher surface area, leading to good solvent action, which might be responsible for better dispersibility.

The FTIR spectra of the formulations were recorded before and after the stress test (Fig 2). The spectra were identical indicating that the formulations were stable.

Table 2. Physical properties of vitamin D3 granules

Physical property	Result
Bulk density (g/cc)	0.45
Tapped density (g/cc)	0.55
Carr's index (%)	15
Hausner's ratio	1.15
Flow property	Good

Table 3. Particle size distribution of vitamin D3 granules

Mesh size (BSS)	Percentage retained
# 12	---
# 16	30
# 20	70
# 30	--
# 40	--

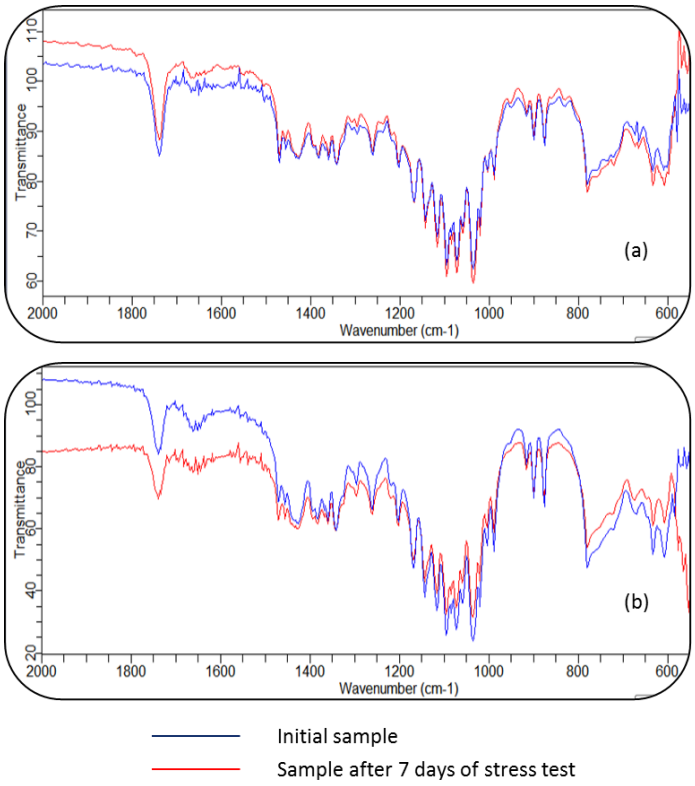

Fig 2. FTIR spectra before and after stress test of Vitamin D3 granules and tablets

Table 4. Physical properties of Vitamin D3 tablets

Physical property	Result
Thickness (mm)	4
Hardness (N/sq m)	20
Friability (%)	0.3

CONCLUSION

Dispersible Vitamin D3 granules were prepared with the intention that immediate release required for rapid onset of action and also for better patient compliance. Drug-excipient compatibility study has shown that there was no interaction between drug and excipients and therefore the formulations of vitamin D3 were stable.

From the observed results, the following conclusions could be drawn:

1. All the formulations were prepared with ease.
2. Granules had very good flow property.
3. The composition was kept very simple.
4. Formulations were found stable during stress study.
5. Dispersibility of granules was found to be very good.

Also, granule formulation showed better dispersability than the tablet formulation and can be considered as better composition than tablets. Hence dispersible granule composition is considered to be better for vitamin D3.

DECLARATION OF INTEREST

It is hereby declared that this paper does not have any conflict of interest.

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