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COMPARATIVE OPEN-LABEL BIOEQUIVALENCE TRIAL OF VITAMIN D3 60 K FORMULATIONS: ULTRA NANO VS. NANO SOLUTION AND CONVENTIONAL FORMULATION

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ABSTRACT

Background: Vitamin D supplementation plays a significant role in addressing vitamin D deficiency/ insufficiency. Various conventional and nanoformulations of 60k Vitamin D3 are available in the market to cater to this requirement. The ultra nano oral solution formulated with patented En-Infi™ nanotechnology comes with ultra nano vitamin D3 particles. The main objective of this study was to determine the bioequivalence of ultra nano oral solution (test formulation) with nano solution and conventional capsule (reference formulation - R1, R2, respectively). **Method:** This was an open-label, balanced, randomized, single-dose, three-treatment, single-period, parallel bioequivalence study of test formulation with reference formulations R1 and R2. Subjects (n=30) were supplemented with a single dose of one of these formulations. Their blood sample was assessed for the maximum observed drug concentration (C_{max}), the area under the concentration-time curve up to 144 h ($AUC_{0–144h}$), and the time to reach maximum drug concentration (T_{max}) for the metabolite 25-HydroxyvitaminD3 [25(OH)D3]. **Result:** Among the 30 participants, the C_{max} of serum 25(OH) D from the test formulation was higher than that of R2 by 14.94%. The area under the concentration-time curve up to 144 h (AUC_{0-144h}) of serum 25(OH)D3 from the test formulation was higher than that of R2 by 20.52%. The C_{max} and AUC_{0-144h} of serum 25(OH)D3 levels from the test formulation were comparable to that of R1. Thus, the test formulation is bioequivalent to R1 and shows a trend of superiority over R2. T_{max} of 25(OH)D3 was found to be 8.3602 hr, 6.4674 hr, and 7.3419 hr for test formulation, R1, and R2 respectively. The test formulation was safe and well tolerated, as no adverse events were reported. **Conclusion:** The test formulation, formulated with En-Infi™ nanotechnology, exhibited higher C_{max} and AUC_{0-144h} compared to the R2, and showed bioequivalence to the R1, and was well tolerated. These elevated metabolite levels (serum 25(OH)D) are likely attributed to the superior rate and extent of absorption of vitamin D3 from the test compared to R2. The comparable data confirms the advantages of En-Infi™ nanotechnology and underscores the benefits of ultra-nanoparticles utilized in the test formulation.

KEYWORDS: Cholecalciferol; vitamins; vitamin D deficiency; Administration, Oral; Area Under Curve; Healthy Volunteers.

INTRODUCTION

Vitamin D deficiency/insufficiency has become a pandemic and a widely untreated and underdiagnosed issue worldwide. About 1 billion people globally are vitamin D deficient. India, despite its sunny climate, faces significant deficiency rates ranging from 40% to 99% across both urban and rural areas, irrespective of socioeconomic factors, gender, age, geographical regions, environmental conditions, or profession.[1,2]

The primary function of vitamin D is widely recognized to involve maintaining calcium homeostasis, which is crucial for bone mineralization.[3] Numerous published studies substantiate that beyond its established role in calcium-phosphate regulation, vitamin D exerts various non-calcemic effects across multiple tissues and systems, such as cardiovascular events, obesity, metabolic syndrome, type 2 diabetes, various cancers, immune disorders, and adverse pregnancy outcomes.[4–6]

Vitamin D is a secosteroid hormone that is made in the skin upon exposure of the skin to UV-B radiation.[7] Serum 25(OH)D is the barometer for vitamin D status as it is the only vitamin D metabolite in routine clinical

practice that is used to determine whether a patient is vitamin D deficient, sufficient, or intoxicated.[8]

Weekly supplementation of 60,000 IU of vitamin D3 increases serum 25(OH) D to optimal values (>30 ng/mL) and is more patient-friendly in terms of compliance. The Endocrine Society Clinical Practice Guideline on evaluation, treatment and prevention of vitamin D deficiency defines vitamin D deficiency as 25(OH)D level below 20ng/ml (50 nmol/l), vitamin D insufficiency as 25(OH)D level at 21-29ng/ml and sufficiency if the 25(OH)D level is above 30ng/ml.[1]

Various factors contribute to vitamin D deficiency, including air pollution, altitude, skin pigmentation, sunscreen use, obesity, and indoor or nighttime work patterns. Additionally, the limited availability of vitamin D in Indian diets exacerbates the problem.[6,9,10] Relying solely on sun exposure and dietary intake may not effectively prevent deficiency in the majority of the population. Considering these challenges and the absence of widespread vitamin D fortification in food, supplementation becomes crucial in addressing deficiency.[9,10]

The guideline recommendations for the treatment of vitamin D deficiency as per the Endocrine Society Clinical Practice Guidelines recommend treatment of vitamin D deficiency with varying daily/weekly vitamin D supplementation. Weekly 60,000 IU of vitamin D supplementation is preferred by patients based on a compliance point of view. However, most available formulations in the Indian market are traditional fat-soluble preparations, which have poor bioavailability due to their low solubility in the gastrointestinal tract (GIT).[9]

This necessitates the development of a reliable and efficient drug delivery system to enhance vitamin D absorption in the Indian population.[11] Nanoparticle formulations of vitamin D3, utilizing nanotechnology, offer improved bioavailability by dispersing fatty molecules into aqueous micellar spheres, thus enhancing absorption.[11–13] The internationally patented En-Infi™ nanotechnology – precision engineered used in the test formulation offers a stable, uniform ultra-fine nanoparticle of average 26.01 nm particle size, which is evenly interspersed and completely water miscible. This formulation contains a natural colorant, C3 Cura™, which enhances immunity and enables metabolic wellness. The objective of this study was to determine the bioequivalence of test product formulated with En-Infi™ nanotechnology with reference formulation R1 (an oral formulation), and R2 (a conventional capsule) in healthy participants.

Methods

This was an open-label, balanced, randomized, single-dose, three-treatment, single-period, parallel, oral bioequivalence study of the test formulation, 60000 IU Vitamin D3 Oral Solution of Universal NutriScience Pvt. Ltd., India (manufactured by Stabicon Life Science Pvt. Ltd., India), with reference products, DePURA, 60000 IU Vitamin D3 Oral Solution of Sanofi India Limited and Uprise®- D3 60K Cholecalciferol Capsule USP of Alkem Laboratories, India (manufactured by Indchemie Health Specialties Pvt. Ltd., India). Each group comprised 10 healthy adult human subjects under fasting conditions. A total of 30 healthy adult human subjects under fasting conditions were enrolled.

The study was conducted by Synergen Bio Pvt. Ltd., in accordance with the Royal Pune Independent Ethics Committee (RPIEC) approved protocol (Version no.: 01 dated 15th Sep 2023), Informed Consent Documents (ICD's), (English and Marathi versions) and Case Record Form (CRF). The study complied with the ICMR Ethical Guidelines for Biomedical Research on Human Subjects (2017), ICH-GCP Guidelines, Declaration of Helsinki (Fortaleza, Brazil, October 2013), G.S.R. 227(E) New Drugs and Clinical Trials Rules, 2019 and Guidelines for Bioavailability and Bioequivalence Studies, Central Drugs Standard Control Organization, March 2005.

Inclusion criteria

Healthy, non-smoking, non-alcoholic male human subjects aged between 18 and 45 years; subjects with a BMI between 18.50 - 30.00 kg/m^2 and body weight not less than 50.00 kg; subjects in normal health as determined by personal medical history, clinical examination including vital signs and clinically acceptable results of laboratory examinations (including serological tests); subjects having a normal or clinically not significant 12-lead electrocardiogram (ECG) recording; subjects having a normal or clinically not significant chest X-Ray (P/A view); subjects with negative alcohol breath test and negative urine screen result for drugs of abuse (including amphetamines, barbiturates, benzodiazepines, marijuana, cocaine, and morphine) and subjects willing to adhere to the protocol requirements and to provide written informed consent.

Exclusion criteria

Known hypersensitivity to vitamin D or any of its analogues and derivatives; use of any prescribed medication (including herbal remedies) during two weeks before the start of the study or OTC medicinal products during the week prior to study initiation; subject who has received active vitamin D3 compounds or a high dose of vitamin D3 (>5000IU) within 30 days before study entry; subject outside the normal ranges for Vitamin D test.; subjects with major illness during the 90 days before screening and subjects with abnormal diet patterns (for any reason) during the four weeks preceding the study; including fasting, high protein diets etc.; subjects who consumed tobacco/tobacco-containing products, pan or pan masala, gutkha, masala (containing beetle nut and tobacco) and caffeine and /or xanthine-containing foods or beverages (i.e., coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.),

grapefruit juice and poppy-containing foods for at least 48.00 hours prior to initiation of the study; unwilling to follow throughout the study and following the last dose of the study medication; subjects incapable of understanding the informed consent information.

The subjects who were eligible, when assessed against the inclusion and exclusion criteria for the study, were randomly assigned to the products. Randomization was carried out using the PROC PLAN procedure of SAS® (SAS Institute Inc., U.S.A.) version 9.4 in blocks such that the design was balanced.

Study drug

After an overnight fast of at least 10.00 hours, the study drug single dose of 5mL of 60000 IU test formulation or reference formulation 1 (allocated as per the randomization schedule) was administered to the subject's mouth via oral syringe in a sitting position. One capsule of reference formulation 2 (allocated as per the randomization schedule) was administered to subjects orally; they were instructed not to chew, crush, or open the capsule but to swallow it whole. Subjects on oral solution were instructed to swallow it with about 50 mL of water from approximately 240 mL. Part of the water (3 x 5 mL approximately) from the same was used to carefully rinse the syringe thrice. The remaining part of the 240mL water was then given to swallow, thus ensuring complete administration of the dispensed investigational product. The primary endpoints were C_{max}, $AUC_{0\text{-}144h}$, and the secondary endpoint was T_{max}.

Statistical analysis

Descriptive statistics (geometric mean, arithmetic mean, median, standard deviation, coefficient of variation, minimum and maximum) were computed and reported for primary and secondary pharmacokinetic parameters for 25(OH)D3. Statistical analysis was performed using SAS® version 9.4. Statistical analysis was performed on data obtained from 30 subjects who completed the study. Bioequivalence was evaluated by means of statistical analysis of variance (ANOVA) with 90% confidence intervals (CI) of the test/reference ratio with logarithm-transformed data.

RESULTS

Overall demographic characteristics of all subjects are given in Table 1.

Table 1: Overall Demographic Profile of all subjects (N = 30).

Variable	Profile			Percentage
Race	Asian			100.00 %
	Others			0.00 %
Gender	Male			100.00 %
	Female			0.00 %
Diet	Non-Vegetarian			93.33 %
	Vegetarian			6.67 %
Smoking status	Non-smokers			100.00 %
	Smokers			0.00 %
Alcohol Consumption	Non-alcoholics			100.00 %
	Alcoholics			0.00 %
	Mean	**SD**	**Min**	**Max**
Age (Yrs)	31.6	6.59	21	43
Height (cm)	167.9	7.17	151	184
Weight (kg)	70.247	11.0855	52.60	89.70
BMI (kg/m^2)	24.900	3.5442	19.4	29.76

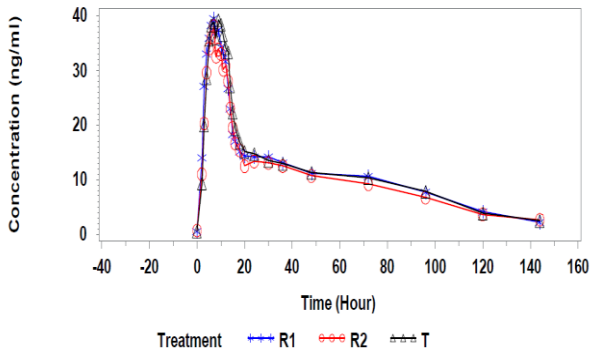

Figure 1: Linear plot of mean serum concentration of baseline corrected 25-hydroxy vitamin D3 vs. time for test product (T), reference product 1 (R1), and reference product 2 (R2) (N=30).

Values of pharmacokinetic parameters (Table 2) for C_{max} (46.4529 ng/ml vs 45.2277 ng/ml) and AUC_{0-144h} (1557.593ng.hr/ml vs 1567.735 ng.hr/ml) of 25(OH) D3 in Test and R1 were noted respectively which indicates that the values of C_{max} and AUC_{0-144h} were higher in case of Test formulation compared to R1. Similarly, values of pharmacokinetic parameters for C_{max} (46.4529 ng/ml vs. 40.4148 ng/ml) and AUC_{0-144h} (1557.593 ng.hr/ml vs 1292.363 ng.hr/ml) of 25(OH) D3 in Test and R2 were noted, respectively which indicated that the values of C_{max} and AUC_{0-144h} were higher in case of Test product compared to R2.

Pharmacokinetic parameter for T_{max} of 25(OH) D3 was found to be 8.3602 hr, 6.4674 hr, and 7.3419 hr for Test, R1, and R2, respectively. A linear plot of the mean serum concentration of baseline corrected 25-hydroxy vitamin D3 Vs. time for test product (T), reference product 1 (R1), and Reference product 2 (R2) is given in Figure 1.

Table 2: Descriptive statistics of formulation means for 25-hydroxy vitamin D3 obtained by a non-compartmental model (N = 30).

Pharmacokinetic Parameters (Units)	Test product [T]	Reference product [R1]	Reference product [R2]
C_{max} (ng/mL)	46.4529	45.2277	40.4148
AUC_{0-144h} (ng.hr/mL)	1557.593	1567.735	1292.363
T_{max} (hr)	8.3602	6.4674	7.3419

The logarithmic transformed data of pharmacokinetic parameters were analyzed for 90% Confidence intervals (CI) using ANOVA. The mean (90% CI) values for Test and R1 of C_{max} were 102.60 (87.16-120.78) and of AUC_{0-144h} were 98.89 (82.90-117.96) given in Table 3. The mean (90%CI) values for T and R2 of C_{max} were 114.94 (87.26-151.41), and of AUC_{0-144h} were 120.52 (83.76-173.43) indicated in Table 4.

Table 3: Geometric least squares means, ratios, 90% Confidence Intervals, and p-values for pharmacokinetic parameters (C_{max} and AUC_{0-144h}) of baseline corrected 25-hydroxy vitamin D3 (N = 20) (T vs R1).

Pharmacokinetic parameters (Units)	Geometric mean ratio test/reference (%)	P value	90% Confidence interval (parametric)	
			Lower	Upper
C_{max} (ng/mL)	102.60	0.7879	87.16	120.78
AUC_{0-144h} (ng.hr/mL)	98.89	0.9135	82.90	117.96

As seen in Table 3 and Table 4, the 90% confidence intervals of the differences of least squares means for the Ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-144h} of test formulation is within the bioequivalence acceptance limits of 80.00 - 125.00% when compared with vitamin D3 oral solution and capsule. The C_{max} of 25(OH)D3 from the test was higher than that of R2 by 14.94%. The (AUC_{0-144h}) of 25(OH)D3 from the test was better than that of R2 by 20.52%.

Table 4: Geometric least squares means, ratios, 90% Confidence Intervals, and p-values for pharmacokinetic parameters (C_{max} and AUC_{0-144h}) of baseline corrected 25-hydroxy vitamin D (N = 20) (T vs R2).

Pharmacokinetic parameters (Units)	Geometric mean ratio test/reference (%)	P value	90% Confidence interval (parametric)	
			Lower	Upper
C_{max} (ng/mL)	114.94	0.3924	87.26	151.41
AUC_{0-144h} (ng.hr/mL)	120.52	0.3855	83.76	173.43

DISCUSSION

Initially classified as a vitamin, vitamin D is now understood as a prohormone that serves as a precursor to calcitriol, a biologically active seco-steroid hormone.[14,15] Addressing vitamin D deficiency often involves supplementation, with recommendations in India typically involving a weekly oral dose of 60,000 IU for eight weeks.[16] 25(OH)D is the only vitamin D metabolite that is used to determine whether a patient is vitamin D deficient, sufficient or intoxicated. 25(OH)D is the major circulating form of vitamin D that has a half-life of approximately 2-3 weeks. 25(OH)D is a summation of both vitamin D supplementation and vitamin D that is produced from sun exposure.[8]

Studies have shown that utilizing nanoparticles of vitamin D can enhance its pharmacokinetic properties. For instance, a study explored the use of oleoyl alginate ester (OAE) nanoparticles as carriers for oral vitamin D3, demonstrating improved absorption compared to conventional formulations.[17] When considering oral dosage forms, absorption rates vary, with oral solutions exhibiting the highest absorption rates, followed by suspensions, powder-filled capsules, compressed tablets, and coated tablets.[18]

In the present study, authors have determined the bioequivalence of test product formulated with En-Infi™ nanotechnology with R1 formulated with WEE dispersion technology and R2 a capsule. The test formulation developed with En-Infi™ nanotechnology is an effective nano-drug delivery system for Vitamin D3 in humans. This patented nanotechnology has ensured that there is a good rate and extent of absorption of Vitamin D (a non-polar lipid with poor bioavailability).

The $AUC_{0–144h}$ and C_{max} values of 25(OH) D3 were higher for the test than for the reference R2 formulation. This indicates a trend of superiority over R2 under fasting conditions in healthy human participants. The rate and extent of absorption of 25(OH) D3 from the test formulation mirrors or equals that of R1, showing that the test formulation is bioequivalent to R1 in providing high and fast vitamin D3 absorption.

The investigational product was well tolerated and safe, as no adverse events were reported. The current study's results are consistent with previous reports, which demonstrated the superior bioavailability of nanoemulsion-based delivery systems for vitamin D compared to coarse emulsions and non-encapsulated forms, respectively.[19,20] In conventional oral formulations, vitamin D3 is absorbed through the pathway of lipid digestion and absorption. When orally consumed, vitamin D3 undergoes conversion into nanosized micelles through the action of bile from the liver and lipases/colipases from the pancreas.

These nanoparticles, as in test formulation, being water-soluble, cross the unstirred water layer covering the enterocytes, facilitating the absorption of vitamin D3.[13] Similarly, the test formulation, designed using En-Infi™ nanotechnology, encapsulates solubilized vitamin D3 within a nano-lipid system. This system features a stable hydrophilic surface that shields the nanoparticles from breakdown in the presence of high concentrations of bile and lipases during transit through the gastrointestinal tract (GIT). Consequently, it delivers vitamin D3 directly at the absorption site without relying on the lipid digestion process, as seen in conventional systems.

Nano formulation offers improved compliance as it does not necessitate the consumption of milk or clarified butter for absorption.[21] The nanoformulation process facilitates smooth paracellular, transcellular, and persorption pathways of vitamin D through the intestinal mucus layer, ensuring higher bioavailability compared to conventional formulations, regardless of the fat content in the gut.

CONCLUSION

The test formulation, incorporating En-Infi™ nanotechnology, exhibited increased C_{max} and AUC_{0-144h} compared to the R2 and demonstrated bioequivalence with R1. These heightened levels of metabolites (serum 25(OH)D3) likely stem from the superior absorption rate and extent of vitamin D3 in the test formulation in contrast to the R2. The consistent findings with R1 validate the advantages of En-Infi™ nanotechnology and underscore the merits of ultra-nanoparticles employed in the test formulation.

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Conflict of interest

The authors declare no conflict of interest.

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