Drug Corner

Advancements in Vitamin D3 Formulations : A Review of UNS D3 Ultra Nano 60 Thousand

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Vitamin D plays a crucial role in maintaining calcium balance, bone health and various non-calcemic processes in the body. However, factors like reduced sun exposure and dietary habits lead to widespread deficiencies, impacting skeletal and non-skeletal health. Traditional fat-soluble Vitamin D formulations have poor bioavailability, necessitating high supplemental levels that may pose risks. Nanotechnology offers a solution with nanoemulsions improving bioavailability and stability. The UNS D3 Ultra Nano 60 Thousand utilizes En-Infi™ nanotechnology, delivering stable, uniform ultra-fine nanoparticles for enhanced absorption. Clinical studies show its superior efficacy and safety compared to conventional formulations. The formulation's innovative use of C3 CURA™ adds further benefits, improving immunity and metabolic wellness. Future advancements may focus on targeted delivery and innovative nanoparticle formulations to further enhance Vitamin D3's bioavailability and effectiveness. Overall, UNS D3 presents a promising solution to combat Vitamin D deficiencies, offering a reliable and effective supplementation method.

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Key words **: Vitamin D Deficiency / drug therapy, Biological Availability, Cholecalciferol, Healthy Volunteers, Administration, Oral.**

Vitamin D, a fat-soluble vitamin, is crucial for maintaining calcium balance and bone health[1]. It also influences various non-calcemic processes in different body tissues, including the cardiovascular system, metabolism, type 2 diabetes, multiple cancers and immune function[2-4]. The primary source of Vitamin D for humans is through the skin's synthesis upon exposure to ultraviolet B radiation (Fig 1) provides an overview of the Vitamin D metabolism. However, due to factors such as reduced sun exposure, lifestyle changes, pollution, dietary habits and specific dietary components, many people require Vitamin D supplements to meet their needs[5,6]. Vitamin D deficiency can lead to skeletal issues like rickets in children and osteomalacia and osteoporosis in adults, as well as impact non-skeletal health. Addressing these factors and ensuring adequate Vitamin D intake is essential for overall health and well-being[6].

Vitamin D deficiency/insufficiency has become a pandemic and a widely untreated and underdiagnosed issue Worldwide. Approximately one billion individuals worldwide experience a deficiency in Vitamin D[7,8]. In India, Vitamin D deficiency is widespread[6], with deficiency rates ranging from 40% to 99% across both urban and rural areas, irrespective of Socio-economic factors, gender, age, geographical regions, environmental conditions or profession[7,8]. However, the clinically diagnosed cases represent only the tip of

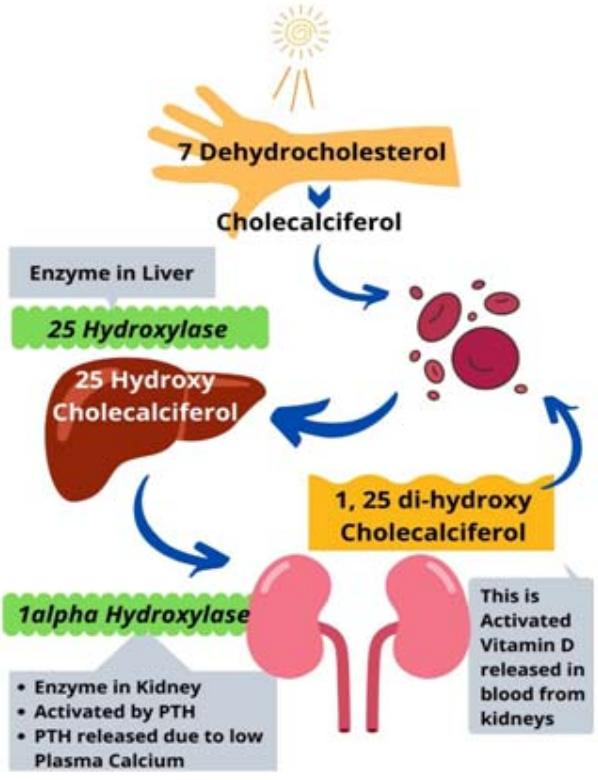

Fig 1 — Process of Vitamin D metabolism

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the iceberg. Considering the numerous implications it may cause, the burden posed by this silent epidemic on the country's development is substantial. Therefore, addressing Vitamin D deficiency demands significant attention and decisive action[6].

Traditional Vitamin D3 Formulations :

The bioavailability of Vitamin D is typically relatively low because its strong hydrophobicity leads to a low solubility in aqueous fluids, such as those in the Gastrointestinal Tract (GIT). Therefore, Vitamin D is often delivered in an oil-in-water emulsion that is specifically designed to enhance its bioaccessibility by improving its solubility and the formation of mixed micelles. Several fat-soluble nutrients and dietary bioactive components exhibit a "U" shaped pattern, with potential risks associated with both low and high levels of intake. Therefore, to improve Vitamin D status, we cannot unlimitedly increase the supplemental level. Otherwise, it may put a subgroup of the population at risk of exposure to high levels of Vitamin D. Indeed, it has been estimated that around 1% of the population in the US may be at a possibly harmful level (>125 nmol/L)[9]. Also, 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)[10]. Thus, to improve oral Vitamin D bioavailability and to reduce the variation of Vitamin D absorption, rather than simply increasing the supplemental level, there should be a better strategy to improve Vitamin D status for public health[9].

Nanotechnology has witnessed rapid growth in recent decades and along with the emergence of nanotechnology, the utilization of nanoemulsion (d< 200 nm) over conventional coarse emulsion (d >200 nm) as delivery vehicles for lipophilic nutrients and bioactives has received substantial attention in nutrition and food industry[9]. These nanoemulsions are a novel type of colloidal delivery system that may encapsulate, safeguard, and transport lipophilic bioactive compounds. Compared to conventional delivery systems, the droplets in these liquid dispersions are more minor, ranging in size from 50 to 500 nm. The nanoemulsions exhibit improved bioavailability, stability against phase separation and hydrophobic chemical absorption capacity[11]. Physiochemical advantages include lesser aggregation and higher optical clarity. Additionally, lipid nanoparticles tend to undergo quicker digestion within the Gastro-intestinal tract due to their smaller size and extensive surface area. Studies have shown that reducing lipid nanoparticle size increases the bioaccessibility of hydrophobic components, eg, curcumin and carotenoid[9].

It has been demonstrated that the cholecalciferol nanoemulsion formulation (D<200/ nm) exhibits higher bioavailability and homogeneity when compared to the conventional coarse emulsion with particle diameters >200/ nm[11].

Based on histopathological findings and improved biochemical profile, it was found that Vitamin D nanoemulsion is more hepatoprotective compared to conventional Vitamin D supplements when anti-inflammatory and anti-oxidant properties of Vitamin D nanoemulsion were studiedin animal models of Non-alcoholic Fatty Liver Disease (NAFLD)[11].

For the following reasons, the nanoemulsions are likely to be better than conventional Vitamin D preparations:

- It has a better compliance rate.
- It has a better therapeutic role in patients with malabsorption syndromes caused by inflammatory bowel disease, celiac disease, short bowel syndrome, hepatobiliary disorders, pancreatic insufficiency and bariatric surgery who suffer from deficiencies of essential fatty acids and fat-soluble vitamins, including Vitamin D.
- Improved hepatoprotective effect than conventional formulation[11]

Introduction to UNS D3 Ultra Nano 60 Thousand :

UNS D3™ Oral Solution is prepared using patented nanotechnology. This internationally patented En-Infi™ nanotechnology – precision engineered used in the formulation offers a stable, uniform ultra-fine nanoparticle of average 26.01 nm particle size, which is evenly interspersed and thoroughly water miscible. This formulation contains a natural colorant, C3 Cura™, which enhances immunity and enables metabolic wellness. Free from sugar; safe for diabetic and Cardiovascular (CVD) patients.

The UNS D3 Nano 60 thousand formulations, 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 Gastro-intestinal Tract (GIT). Consequently, it delivers Vitamin D3 directly at the absorption site without relying on the lipid digestion process, as seen in conventional systems.

Also, this novel formulation uniquely utilizes another proprietary technology comprising C3 CURA™. Curcuma drops (Curcumin) are a natural colorant at adequate concentration levels. As opposed to other colorants used by different brands, for instance, Tartrazine. It is highly bioavailable (500 times more

bioavailable) and has faster and easier absorption of curcumin in the body. C3 Cura™ is comprised of active constituents of curcumin and helps reduce dosage to 1/100th of marketed products (Fig 2). Apart from being a natural colorant, C3 CURA™ adds value to the formulation as a stabilizing agent and provides practical clinical outcomes by supplementing the Immunity profile of Vitamin D3 and enabling metabolic wellness.

The combination of C3 Cura™ and Vitamin D3 in UNS D3 Nano Formulation offers:

- Protection from lipase enzymes
- Protects against enzymatic degradation
- Enhanced stability
- Prevents agglomeration
- Maintains structural integrity

Efficacy and Safety of UNS D3 Ultra Nano 60 Thousand :

An open-label, balanced, randomized, single-dose, three-treatment, single-period, parallel-design bioequivalence study was conducted to compare the efficacy of UNS D3 to other marketed formulations in a group of healthy adult subjects under fasting conditions. The test formulation, 60000 IU Vitamin D3 Oral Solution of Universal NutriSciencePvt. Ltd., India, was compared with reference products: DePURA, 60000 IU Vitamin D3 Oral Solution of Sanofi India Limited (R1) and Uprise®- D3 60K Cholecalciferol Capsule USP of Alkem Laboratories, India (R2). Each group consisted of 10 subjects.

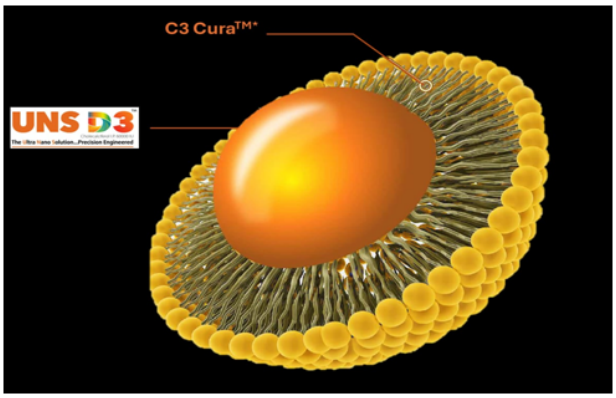

Fig 2 — Micelle structure of UNS D3 Ultra Nano 60 Thousand

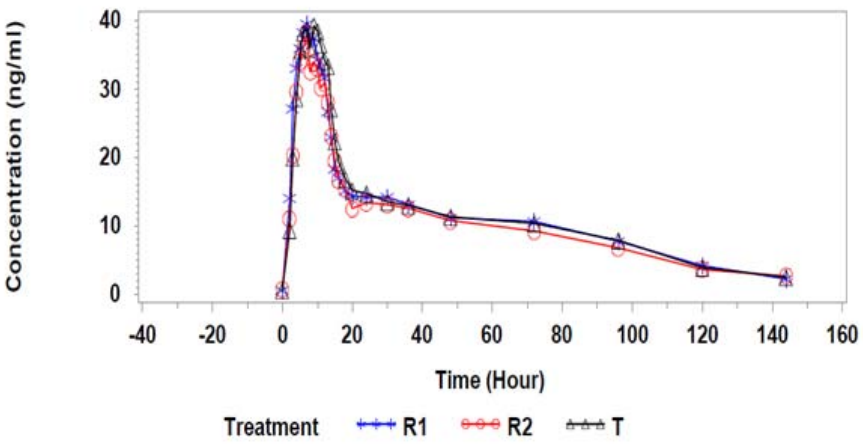

Fig 3 — Linear plot of mean serum concentration of baseline corrected 25-hydroxy Vitamin D3 *versus* time for test product (T), reference product 1 (R1), and reference product 2 (R2) (N=30)

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% (Fig 3). 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 (Table 1). The test formulation was safe and well tolerated, as no adverse events were reported.

The test formulation, formulated with En-Infi™ nanotechnology, exhibited higher C_{max} and AUC_{0-144h} compared to the R2, 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.

Table 1 — *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 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. It also offers improved compliance as it does not necessitate the consumption of milk or clarified butter for absorption[12].

Conclusion and Future Directions :

Thus, the UNS D3™ presents a promising and innovative solution utilizing advanced nanotechnology, offering improved bioavailability, stability and potential health benefits. This product is a viable option to combat the widespread deficiency of Vitamin D3, catering to a range of health-conscious consumers seeking a reliable and effective supplementation method. This will help the patient reach a sufficiency level from a deficiency or insufficiency level faster than other nano-marketed formulations.

Potential future advancements in Vitamin D3 formulations may involve ongoing exploration of nanotechnology-based delivery systems, similar to the En-Infi™ nanotechnology utilized in UNS D3 Ultra Nano 60 Thousand. Such endeavors could result in enhanced bioavailability and effectiveness of Vitamin D3 formulations. This may involve refining current nanoemulsion-based platforms or investigating innovative nanoparticle formulations. Furthermore, foundational research into targeted delivery using nanoemulsions presents promising prospects in enabling lower doses of Vitamin D3 to achieve therapeutic effects, reducing the risk of toxicity.

Declaration : Article is not published / submitted in any other journal.

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Conflict of Interest : No

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