Review Article

Advancing Vitamin D3 Therapy: The Emergence of Nano-Carrier Entrapped Vitamin D3-Oral Formulation

Abstract:

Vitamin D is essential for bone health and supports various non-skeletal functions, including immune response and metabolic regulation. Despite the importance of Vitamin D, Vitamin D deficiency has become a widespread, global issue, with approximately one billion people affected. In India, deficiency rates are alarmingly high, regardless of socio-economic status, age, or geographic location. Traditional Vitamin D supplements often have low bioavailability due to the fat-soluble nature of the vitamin, which limits its absorption in the gastrointestinal tract.

Nanotechnology-based Vitamin D formulations, particularly nanoemulsions, offer a solution to this challenge. Nanoemulsions have smaller droplet sizes (<200 nm) that increase the bioavailability and stability of hydrophobic nutrients. Nano-Carrier Entrapped Vitamin D3-Oral formulation, formulated using Aqueol® Nanotechnology, features a stable nanoparticle structure with a size of less than 150 nm. This advanced formulation enhances resistance to digestive enzymes and pH fluctuations, ensuring the efficient delivery of Vitamin D3 directly to the intestinal absorption sites for improved bioavailability. This formulation has shown superior efficacy in clinical trials, with higher and more consistent serum Vitamin D levels compared to traditional formulations.

Clinical studies on Nano-Carrier Entrapped Vitamin D3-Oral formulation demonstrate its effectiveness in addressing mechanical low back pain, improving vitamin D levels in children, and reducing inflammatory markers in COVID-19 patients. This formulation represents a promising

innovation for overcoming widespread Vitamin D deficiency and may lead to further advancements in nanotechnology-based delivery systems for improved nutrient absorption and bioavailability.

Introduction:

Vitamin D, a fat-soluble vitamin, plays a key role in regulating calcium levels and promoting bone health.[1] Beyond its well-known skeletal functions, it also supports various non-calcemic processes in the body, such as cardiovascular health, metabolism, immune response, and protection against conditions like type 2 diabetes and certain cancers.[2,3,4] The primary way humans obtain Vitamin D is through skin synthesis triggered by ultraviolet B (UVB) radiation.[5] However, due to factors like limited sun exposure, lifestyle changes, pollution, and dietary habits, many individuals rely on supplements to achieve adequate Vitamin D levels.[5,6] A deficiency in this vitamin can result in skeletal disorders, including rickets in children and osteomalacia or osteoporosis in adults, and may also negatively affect non-skeletal health.[6] Ensuring sufficient Vitamin D intake is vital for maintaining overall 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. In India, Vitamin D deficiency is widespread6, 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. However, the clinically diagnosed cases represent only the tip of the iceberg [18-20]. 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.

Vitamin D deficiency or insufficiency has reached pandemic proportions, remaining largely undiagnosed and untreated on a global scale. An estimated one billion people around the world are affected by Vitamin D deficiency.[7,8] In India, this issue is particularly prevalent,[6] with deficiency rates ranging between 40% and 99% across both urban and rural areas.[7,8] These rates persist regardless of socio-economic status, gender, age, geographic location, environmental factors, or occupation.[7,8] Clinically diagnosed cases account for only a fraction of the true scale of the problem. Given its wide-ranging health implications, Vitamin D deficiency presents a significant burden, with serious consequences for the nation's development. Addressing this widespread issue requires urgent attention and targeted action.[6]

Traditional Vitamin D3 Formulations:

Vitamin D generally has low bioavailability due to its hydrophobic nature, which limits its solubility in aqueous environments like the gastrointestinal tract (GIT). To enhance its bioaccessibility, Vitamin D is often delivered in oil-in-water emulsions that improve solubility and facilitate the formation of mixed micelles.[9] Additionally, many Vitamin D formulations available in the Indian market are traditional fat-soluble preparations, which suffer from poor bioavailability due to limited solubility in the GIT.[10]

Apart from this, a high degree of variability was seen in the cholecalciferol content of commercial preparations available in the Indian pharmaceutical market.[11]

Thus, to enhance oral Vitamin D bioavailability and minimize variability in its absorption, a more effective approach is needed beyond merely increasing supplement dosage. Developing better strategies to improve Vitamin D status is crucial for advancing public health outcomes.[12]

Introduction to Nanotechnology:

In recent decades, nanotechnology has advanced rapidly, and the use of nanoemulsions (droplet size < 200 nm) over traditional coarse emulsions (droplet size > 200 nm) has garnered significant attention

in the nutrition and food industry as delivery systems for lipophilic nutrients and bioactive compounds.[12] Nanoemulsions are an innovative colloidal delivery system capable of encapsulating, protecting, and transporting lipophilic bioactives. Compared to conventional systems, these emulsions have smaller droplets, typically ranging from 50 to 500 nm, which enhances bioavailability, stability against phase separation, and absorption of hydrophobic compounds.[13] Their physicochemical benefits include reduced aggregation and improved optical clarity. Additionally, due to their smaller size and larger surface area, lipid nanoparticles are digested more rapidly in the gastrointestinal tract. Research indicates that reducing the size of lipid nanoparticles can increase the bioaccessibility of hydrophobic substances, such as curcumin and carotenoids.[12,13]

It has been demonstrated that the cholecalciferol nanoemulsion formulation (D<200 nm) exhibits higher bioavailability and homogeneity when compared to the conventional coarse emulsion >200 nm.[13]

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 studied in animal models of Non-alcoholic Fatty Liver Disease (NAFLD).[13]

For the following reasons, the nanoemulsions are likely to be better than conventional Vitamin D preparations:[13]

- 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

Introduction to Nano-Carrier Entrapped Vitamin D3-Oral Solution:

Nano-Carrier Entrapped Vitamin D3-Oral Solution is prepared using patented Aqueol® Nano-technology. Aqueol® Nano-technology is a patented nano-technology – precision-engineered technology that offers a stable, uniform ultra-fine nanoparticle of average <150 nm particle size, which is evenly interspersed and thoroughly water-miscible, also featuring enzyme-resistant and pH-resistant barriers that shield the nanoparticles from the breakdown in the presence of enzymes and pH Variations during transit through the Gastro-intestinal Tract (GIT).[14] Finally, a stable hydrophilic surface that allows a smooth passage of the particle across the Unstirred Water layer of the intestine. Consequently, it delivers Vitamin D3 directly at the absorption site without relying on the lipid digestion process, as seen in conventional systems.[14]

Features of Nano-Carrier Entrapped Vitamin D3-Oral Solution:

1. The size of each particle of Nano-Carrier Entrapped Vitamin D3-Oral Solution is less than 150 Nanometres (<150nm).
2. pH-Resistant Barrier and Enzyme Resistant Barrier protect each particle of Nano-Lipid Carrier Entrapped Vitamin D3-Oral Solution from harsh GI environments at varying pH conditions and from different enzymes to reach the enterocytic surface for absorption.
3. The Outer Hydrophilic Layer facilitates the transportation of Nano-lipid Carrier Entrapped Vitamin D3-Oral Solution to pass through the unstirred aqueous layer of GIT.
4. Negative Zeta Potential to stabiliz individual particles in Nano-Carrier Entrapped-Oral Solution.

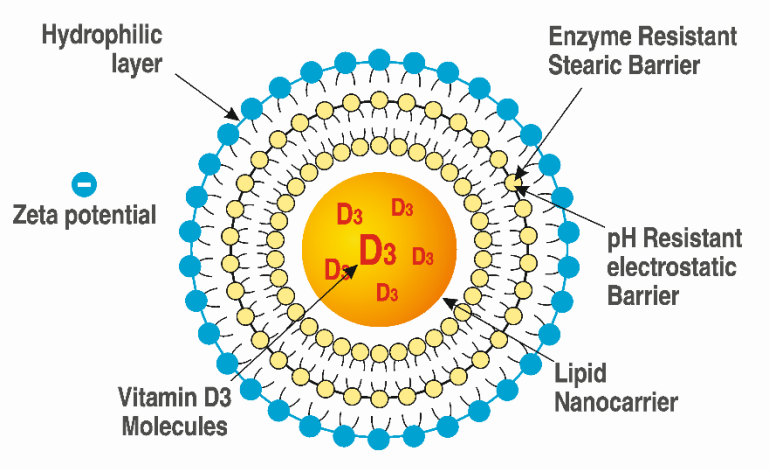

Figure1: Nano-carrier Entrapped Vitamin D3-Oral Solution

Table 1 : Clinical Highlights of Nano-Carrier Entrapped Vitamin D3-Oral Solution:

Author & Year	**Indication**	**Patients Profile & Population**	**Study duration**	**Intervention & Groups**	**Results**	**Conclusion**
Lakkireddy M et.al. (2019)[14]	Mechanical Low back ache	Adult with Mechanical low backache N=102	9 months	Group I : Vitamin D Granule (1g)/day Group II : Nano Carrier entrapped Vitamin D3 (60,000 IU)/day Group III : Soft gel capsule/day For consecutive 10 days	The highest increase in serum 25(OH) Vitamin D levels was seen in the Nano-carrier entrapped vitamin D group of 80ng/ml compared to 53ng/ml in granules and 51ng/ml in Soft gel capsules. Significant improvement in Mechanical low backache was seen after Vitamin D supplementation.	Hypovitaminosis D can be a potential causative factor for mLBA in addition to the other Known causes. The results with nano syrup formulation were significantly better compared to others. Formulation based Dosage adjustments assume significance in view of these results.

					The greatest improvement was seen in Nano-carrier entrapped vitamin D3 Group compared to Granules and Soft gel groups.	
Dr. Gabhale Y. et.al. (2018)[15]	Vitamin D deficiency	Children Age (8-15 years old) N: 79	12 Weeks	Group A : Cholecalciferol 60,000 IU/week (In Nano droplet form) Group B : Cholecalciferol 60,000 IU/week (In Nano-carrier Entrapped Vitamin D3) For 10 Consecutive Weeks	Significant improvement in both the groups starting from 6 weeks onwards. Vitamin D serum levels: 81% Improvement in Group-B at 6 weeks compared to 64% improvement in Group-A	Nano-carrier entrapped Vitamin D3 has shown to produce consistently higher rise in 25(OH) D levels
					75% Improvement in Group-B at 12 weeks compared to 65% improvement in Group-A	
Rastogi A et.al. (2022)[16]	Asymptomatic or mildly symptomatic SARS-CoV-2 RNA-positive vitamin D deficiency	Adults N: 40	21 Days	Group A : Nano Carrier Entrapped Vitamin D3 60,000IU/day Group B : Placebo For 7 consecutive days followed up by another 7 days for Participants	62% participants could achieve 25(OH) D>50 ng/ml by day-7. 75% participants could achieve 25(OH) D>50 ng/ml by day-14.	Greater proportion of vitamin D-deficient individuals with SARS-CoV-2 infection turned SARS-CoV-2 RNA negative with a significant decrease in fibrinogen on high-dose cholecalciferol supplementation

				who with 25(OH)D <50 ng/ml.	After 21 days, 62.5% of participants in the intervention group and 20.8%participants in the control arm became SARS-CoV-2 RNA negative. Significant reduction in fibrinogen levels in Vitamin D3 group compared to placebo group (P=0.007)	
Lakkireddy M et.al. (2021)[17]	COVID-19 patients with Hypovitaminosis D	Adults N: 130	11 Days	Group VD : Nano Carrier Entrapped Vitamin D3 60,000IU/day+ Standard therapy Group NVD : Standard therapy For 8 days with a BMI of 18-25 10 days with BMI >25	Significant Increase of 25(OH)D levels from 16ng/ml to 89ng/ml ($p<0.01$) in VD group Significant reduction in CRP, LDH, IL-6, Ferritin, and N/L ratio in VD group post treatment ($p<0.01$)	Improvement of serum vit.D level to 80–100 ng/ml has significantly reduced the inflammatory markers without any side effects. Adjunctive Vitamin D therapy for 8-10 days can be added safely to the existing treatment protocols of COVID-19.

Clinical Features of Nano-Carrier Entrapped Vitamin D3-Oral Solution:[14,15,16,17]

- Clinical trial data of more than 300 Indian Patients across different indications.
- Greater Bioavailability compared to Granules, Soft-Gelatin Capsules, and Micellar Syrup.
- Consistent and Predictable rise across Age, Gender and BMI.
- No risk of Hypervitaminosis/hypertoxicity was seen across all the clinical trials

Conclusion and Future Directions:

Nano-Carrier Entrapped Vitamin D3-Oral Solution presents a promising and innovative solution utilizing Aqueol® Nanotechnology, offering improved bioavailability, stability and potential health benefits. It 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 marketed formulations. Potential future advancements in Vitamin D3 formulations may involve ongoing exploration of nanotechnology-based delivery systems, similar to the Aqueol® Nanotechnology utilized in Nano-Carrier Entrapped Vitamin D3-Oral Solution. Such endeavours 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.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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