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A Review on Development of Nano-Carrier Entrapped Vitamin D3-Oral Formulation: A Step Forward in Vitamin D3 Therapy

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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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.

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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.

Keywords: Cholecalciferol; Vitamin D deficiency; nano-carrier entrapped Vitamin D; bioavailability; Vitamin D supplementation.

1. INTRODUCTION

Vitamin D, a fat-soluble vitamin, plays a key role in regulating calcium levels and promoting bone health (Habib et al. 2020). 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 (Adams & Hewison 2010, Rosen 2011, Bener et al., 2013). The primary way humans obtain Vitamin D is through skin synthesis triggered by ultraviolet B (UVB) radiation (Silva & Furlanetto 2017). 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 (Silva & Furlanetto 2017, Aparna et al. 2018). 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 (Aparna et al. 2018).

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 (Shah et al., 2013, Kuchay & Mithal2018). In India, this issue is particularly prevalent (Aparna et al. 2018) with deficiency rates ranging between 40% and 99% across both urban and rural areas (Shah et al., 2013, Kuchay & Mithal2018). These rates persist regardless of socio-economic status, gender, age, geographic location, environmental factors, or occupation (Shah et al., 2013, Kuchay & Mithal2018). 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 (Aparna et al. 2018).

2. 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 (Reddy et al., 2024). 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 (Chugh et al., 2016).

Apart from this, a high degree of variability was seen in the cholecalciferol content of commercial preparations available in the Indian pharmaceutical market (Khadgawat et al. 2013).

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 (Kadappan et al., 2018).

3. 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 (Kadappan et al., 2018). 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 (Marwaha & Dabas 2019). 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 (Kadappan et al., 2018, Marwaha & Dabas 2019).

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 (Marwaha & Dabas 2019).

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) (Marwaha & Dabas 2019).

For the following reasons, the nanoemulsions are likely to be better than conventional Vitamin D preparations (Marwaha & Dabas 2019):

1. It has a better compliance rate.
2. 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.
3. Improved hepatoprotective effect than conventional formulation

4. 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) (Lakkireddy et al., 2019). 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 (Lakkireddy et al., 2019).

5. CLINICAL FEATURES OF NANO-CARRIER ENTRAPPED VITAMIN D3-ORAL SOLUTION (LAKKIREDDY ET AL. 2019, GABHALE ET AL., 2018, RASTOGI ET AL., 2022, LAKKIREDDY ET AL., 2021, MARWAHA ET AL., 2022, MANEK ET AL., 2017, IQBAL ET AL., 2023, BAI ET AL., 2023)

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

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)	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. The greatest improvement was seen in Nano-carrier entrapped vitamin D3 Group compared to Granules and Soft gel groups.	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.
Dr. Gabhale Y. et.al. (2018)	Vitamin D deficiency	Children Age (8-15 years old) N: 79	12 Weeks	Group A: Cholecalciferol 60,000 IU/week (In Nano droplet form)	Significant improvement in both the groups starting from 6 weeks onwards.	Nano-carrier entrapped Vitamin D3 has shown to produce consistently higher rise in 25(OH) D levels

Author & Year	Indication	Patients Profile & Population	Study duration	Intervention & Groups	Results	Conclusion
				Group B: Cholecalciferol 60,000 IU/week (In Nano-carrier Entrapped Vitamin D3) For 10 Consecutive Weeks	Vitamin D serum levels: 81% Improvement in Group-B at 6 weeks compared to 64% improvement in Group-A	
					75% Improvement in Group-B at 12 weeks compared to 65% improvement in Group-A	
Rastogi A et.al. (2022)	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 who with 25(OH)D <50 ng/ml.	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. 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	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

Author & Year	Indication	Patients Profile & Population	Study duration	Intervention & Groups	Results	Conclusion
					in fibrinogen levels in Vitamin D3 group compared to placebo group (P=0.007)	
Lakkireddy M et.al. (2021)	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.

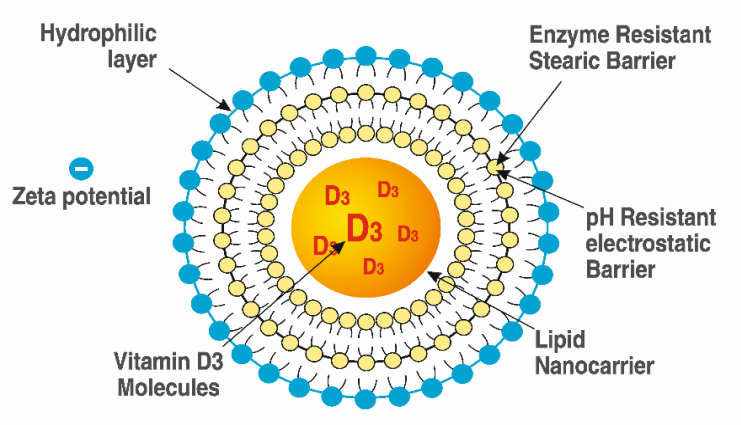

Fig. 1. Nano-carrier entrapped Vitamin D3-oral solution

5.1 Safety of Nano-Carrier Entrapped Vitamin D3-Oral Solution (Lakkireddy et al. 2019, Gabhale et al., 2018, Rastogi et al., 2022, Lakkireddy et al., 2021)

No cases of Toxicity related to Nano-Carrier Entrapped Vitamin D3-Oral Solution were reported in any trials of the nano-carrier-entrapped Vitamin D3 oral solution.

5.2 Long-term Safety of Nano-Carrier Entrapped Vitamin D3-Oral Solution

The study conducted by Lakkireddy et al. (2019) showed that follow-up at 9 months did not reveal any adverse effects associated with the nano-carrier-entrapped Vitamin D3 oral solution.

5.3 Limitation of Clinical Trials of Nano-Carrier Entrapped Vitamin D3-Oral Solution (Lakkireddy et al. 2019, Gabhale et al., 2018, Rastogi et al., 2022, Lakkireddy et al., 2021, Manek et al., 2017, Iqbal et al., 2023, Bai et al., 2023)

The biggest limitations are that the trials have been open-label and single-centre studies. These trials can be considered pilot studies for larger, randomised, blinded, multi-centre trials.

6. 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.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that No generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

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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