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Bioavailability of nanoemulsion formulations vs conventional fat soluble preparations of cholecalciferol (D3) – An overview

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ABSTRACT

Vitamin D deficiency is recognized as a pandemic affecting all ages and strata of population. The endogenous cutaneous synthesis of vitamin D is insufficient to maintain normal body requirement which necessitates the need for vitamin D supplementation or food-fortification. Conventional fat-soluble preparations of vitamin D have been traditionally used for prevention and therapeutic purposes. Recent advances in technology have enabled delivery of vitamin D through nanoemulsion formulations which ensure higher absorption and drug delivery. The following review briefly discusses the issues of bioavailability of nanoemulsion preparation of vitamin D vis-a-vis conventional fat soluble preparations.

1. Introduction

Vitamin D is a fat-soluble vitamin which is essential for maintaining blood levels of calcium and phosphate for mineralization of bones, muscle contraction, nerve conduction and general cellular functions. Optimal calcium and vitamin D nutrition for bone mineral health is important for prevention of rickets and osteomalacia and safeguarding against osteoporosis and fractures among elderly.

Vitamin D deficiency/insufficiency affects nearly one billion people worldwide and remains the most underdiagnosed and undertreated medical condition.[1] Despite India being a tropical country with adequate sunlight, vitamin D deficiency is prevalent in pandemic proportion across all strata, irrespective of socio-economic factors, age, gender, geographical region and environmental conditions.[2] The sunlight induced vitamin D synthesis is affected by personal host factors like clothing, lifestyle and environmental factors like atmospheric pollution, latitude and season.[3,4] The adverse effects of prolonged poor calcium and vitamin D nutrition on bone health of elderly Indians was clearly observed in several studies carried out in India. A large scale study on healthy Indians above 50yrs of age has revealed significantly lower bone mineral density (BMD) and higher prevalence of osteoporosis (35.1%, females 42.5%, males 24.8%) in comparison to US Caucasians (females 18%, males 6%), Europeans (females 21%, males 6%), Taiwanese (females 11.4%, males 1.6%) and Sri Lankans (5.8%) but similar to only Chinese (female 50.1%, males 22.5%).[5] Another study evaluating the prevalence of vertebral morphometric fractures in healthy Indians above 50 years showed a very high prevalence ranging from 14.7 to 22.4% in females to 17.2–21.6% in males.[6]

Since Indian diets provide negligible amount of vitamin D[7] and sun induced synthesis is inadequate, supplementation of vitamin D would play an important role in reducing the burden of vitamin D deficiency in the absence of Government's policy on universal food fortification with vitamin D.

1.1. Nano particle based delivery system

Majority of vitamin D formulations available in the market in the form of tablets, capsules or sachets are conventional fat-soluble preparations. Vitamin D being a non-polar lipid with poor bioavailability due to its low solubility in aqueous fluids of gastrointestinal tract, a robust drug delivery system in the form of nanoemulsion formulations of vitamin D3 has been recently introduced in the market for supplementation.

Nanoemulsions are new colloidal delivery system that

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encapsulate, protect, and deliver lipophilic bioactive substances and are being increasingly used in food and pharmaceutical industry.[8] These are liquid dispersions in which the size of the droplets is small ranging from (50–500 nm) compared to other conventional delivery system. These nanoemulsions show better stability against phase separation, better bioavailability and absorptive capacity of hydrophobic compounds.[8,9]

1.2. Nanoemulsion formulations – in-vitro/in-vivo studies

Nano-technology based nanoemulsion formulation of cholecalciferol (D < 200 nm)have been shown to be superior to the conventional coarse emulsion with diameter of particles > 200 nm in terms of bioavailability and homogeneity based on simulated gastrointestinal tract system (GIT) and in-vivo studies in mice.[10] Similarly, miscellized/nanoemulsion preparations of vitamin A and E have shown significantly greater absorption and higher plasma levels as against standard oil preparations following supplementation.[11,12]The bioaccessibility of vitamin D3 was found to be maximum in long chain triglycerides (corn oil or fish oil) as compared to medium chain triglycerides or mineral oil. These differences can be accounted for variability in release of bioactive compounds and solubilisation.[13] A fish oil based nanoemulsion of vitamin D3 was studied in a simulated GIT wherein the nanoemulsion achieved an increased bioavailability compared with the non-capsulated vitamin9. Another in-vivo study on rats showed superior intestinal absorption of vitamin D3-loaded nanostructured lipid carriers concluding it to be a promising approach for fortifying beverages.[14] Nanoemulsion vitamin D which has also been investigated for its anti-inflammatory and anti-oxidant properties in non-alcoholic fatty liver disease (NAFLD) in animal models was found to be more hepatoprotective when compared with conventional vitamin D supplements based on histopathological findings and improved biochemical profile in NAFLD.[15]

1.3. Clinical studies in healthy subjects

Two recent clinical studies in children and adults evaluating efficacy of micellized vitamin D3 supplementation over conventional fat soluble D3 clearly demonstrated significantly greater increase in serum 25(OH)D following supplementation with nanoemulsion formulation as compared with conventional vitamin D3 preparation available in the market. Better bioavailability of nano preparation was further corroborated with significantly higher number of study subjects achieving serum 25(OH)D levels of >20 ng/ml in the group receiving nano preparation as compared to those who received conventional fat-soluble formulation of vitamin D3.[16,17] The results of both these studies comparing a liquid nano formulation of D3 with a fat soluble preparation clearly indicate the superiority of nano technology based preparations over conventional fat-soluble preparation in terms of bioavailability using serum 25(OH)D as a surrogate marker.

A recent open-labelled crossover unpublished study was undertaken to evaluate the bioavailability of nano preparation (test drug) with fat soluble formulation of cholecalciferol (reference) in healthy adults. The objective of the study was to compare the area under the concentration-time curve up to 120 h ($AUC_{0-120\,h}$) values of test medication vs reference medication under fasting conditions and to compare the maximum observed drug concentration (Cmax) and time to observe max drug concentration of a single oral dose of 60,000 IU in healthy participants. The results showed that relative bioavailability in terms of serum levels of cholecalciferol following supplementation with nano preparation of vitamin D3 was significantly higher than fat soluble D3 by 36%(P = 0.001) based on $AUC_{0\text{-}120}$. Also, the Cmax value of serum cholecalciferol following supplementation with nano preparation of D3 was higher by 43% (P = 0.001) [unpublished data]. A study by Nandgaye et al., showed higher area under the curve ($AUC_{0-28days}$) and Cmax with vitamin solution formulated with nanotechnolgy when compared with conventional vitamin D3 tablets/capsules which however, did not achieve statistical significance in terms of bioavailability with bioequivalence acceptance limit of 80–125%.[18]

1.4. Advantages of nanoemulsion formulations of vitamin D3

The nanoemulsions are considered superior to conventional vitamin D preparations for the following reasons: **a)** It has greater therapeutic role in patients with malabsorption syndromes due to inflammatory bowel disease, celiac disease, short bowel syndrome, hepatobiliary disorders, pancreatic insufficiency and bariatric surgery who suffer from deficiency of essential fatty acids and fat soluble vitamins including vitamin D, **b)**Better compliance as it can be taken directly or with water/juice etc. **c)** Vitamin D nanoemulsions may also have also greater hepato-protective effect against high fat diet induced liver injury as observed in rats compared to conventional oral vitamin D preparations.

2. Conclusion

With emergence of nanotechnology, utilization of nanoemulsions over conventional coarse emulsions as delivery vehicles for lipophilic nutrients and bioactives has got substantial thrust in nutrition and food industry in the recent past. In-vitro and In-vivo bioavailability studies of vitamin D in simulated GIT system, animal and human subjects have clearly shown that bioavailability of nanoformulations of D3 was significantly greater than conventional fat soluble oral preparations. The development of nanoemulsions of vitamin D with different carriers, applicability in food industry and clinical efficacy are still being explored and may hold promise in the future.

Declaration of interest

We declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Author contribution details

RKM: conception and design of manuscript, led the development of the manuscript and have primary responsibility for the final content. AD: manuscript preparation and final draft of manuscript. All authors read and approved the final manuscript.

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References

1. Hollick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357:266–281.
2. Marwaha RK, Goswami R. Vitamin D deficiency and its health consequences in India. In: Hollick MF, ed. *Vitamin D Physiology, Molecular Biology and Clinical Applications, 2nd ed*. New York: Human press; 2010:529–542.
3. Marwaha RK, Yenamandra VK, Sreenivas V, et al. Regional and seasonal variations in ultraviolet B irradiation and vitamin D synthesis in India. *Osteoporos Int*. 2016;27:1611–1617.
4. Mithal A, Lau E. The Asian audit: epidemiology, cost and burden of osteoporosis in Asia 2009. In: *International Osteoporosis Foundation*; 2009. Available at:

https://www.iofbonehealth.org/sites/default/files/PDFs/Audit%20Asia/Asian_regional_audit_2009.pdf. Accessed on 12 April 2019.
5. Marwaha RK, Tandon N, Garg MK, et al. Bone health in healthy Indian population aged 50 years and above. *Osteoporos Int*. 2011;22:2829–2836.
6. Marwaha RK, Tandon N, Gupta Y, et al. The prevalence of and risk factors for radiographic vertebral fractures in older Indian women and men: Delhi Vertebral Osteoporosis Study (DeVOS). *Arch Osteoporos*. 2012;7:201–207.
7. Puri S, Marwaha RK, Agarwal N, et al. Vitamin D status of apparently healthy schoolgirls from two different socioeconomic strata in Delhi: relation to nutrition and lifestyle. *Br J Nutr*. 2008;99:876–882.
8. Walia N, Dasgupta N, Ranjan S, Chen L, Ramalingam C. Fish oil based vitamin D nanocapsulation by ultrasonication and bioaccessibility analysis in simulated gastro-intestinal tract. *Ultrason Sonochem*. 2017;171:623–635.
9. Gupta R, Behera C, Paudwal G, Rawat N, Baldi A, Gupta PN. Recent advances in formulation strategies for efficient delivery of vitamin D. *AAPS PharmSciTech*. 2019;20:11.
10. Kadappan AS, Guo C, Gumus CE, et al. Efficacy of nanoemulsion- based delivery to improve vitamin D absorption: comparison in-vitro and iv-vivo studies. *Mol Nutr Food Res*. 2018;62(4).
11. Lewis JM, Bodansky O, Birmingham J, Cohlan SQ. Comparative absorption, excretion and storage of oily and aqueous preparations of vitamin A. *J Pediatr*. 1947;31:496–508.
12. Jacquemin E, Hermeziu B, Kibleur Y, et al. Bioavailability of oral vitamin e formulations in adult volunteers and children with chronic cholestasis or cystic fibrosis. *J Clin Pharm Ther*. 2009;34:515–522.
13. Ozturk B, Argin S, Ozilgen M, McClements DJ. Nanoemulsion delivery systems for oil-soluble vitamins: influence of carrier oil type on lipid digestion and vitamin D3 bioaccessibility. *Food Chem*. 2015;187:499–506.
14. Mohammadi M, Pezeshki A, Mesgari Abbasi M, Ghanbarzadeh B, Hamishehkar H. Vitamin D_3-loaded nanostructured lipid carriers as a potential approach for fortifying food beverages; *in vitro* and *in vivo* evaluation. *Adv Pharmaceut Bull*. 2017;7:61–71.
15. El-Sherbiny M, Eldosoky M, El-Shafey M, et al. Vitamin Dnanoemulsionenhances hepatoprotective effect of conventional vitamin D in rats fed with a high-fat diet. *Chem Biol Interact*. 2018;288:65–75.
16. Marwaha RK, Dev T, Mittal A, et al. A randomised controlled trial comparing the efficacy of micellised and fat-soluble vitamin D3 supplementation in healthy adults. *Br J Nutr*. 2019;121:859–865.
17. Marwaha RK, Yenamandra VK, Ganie MA, et al. Efficacy of micellized vs. fat-soluble vitamin D3 supplementation in healthy school children from Northern India. *J Pediatr Endocrinol Metab*. 2016;29:1373–1377.
18. Nandgaye KM, Samant RS, Kadam SB, Palkar PJ. Relative oral bioavailability of three formulations of vitamin D3: an open label, three treatment study. *Int J Basic Clin Pharmacol*. 2019;8:138–142.