A novel, nanoparticle based liquid oral formulation of Vitamin D_3 for managing Vitamin-D deficiency: A survey of doctor's preferences and practices in India

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ABSTRACT

Objective: **To understand the overall opinion of Orthopedicians on their perceptions, practices and preferences regarding a nano-droplet formulation of vitamin –D_3. (Arachitol-NANO™).**

Design & setting: Survey study conducted in 81 locations across India.

Methods: **This was a cross-sectional survey study conducted across India, in both rural and urban regions spanning 81 locations. A total of 205 practicing orthopedicians were included in this survey. Data was compiled and analyzed from the responses received for a 10 item survey questionnaire. The questionnaire was designed to capture the perceptions, practices and preferences of Orthopedicians, based on their clinical experience with at least 25 patients with vitamin D deficiency, managed with Arachitol Nano.**

Results: **77.77% doctors' responses suggested that Vitamin D Deficiency was present in more than 50% patients attending the clinics. From an orthopedician's clinical practice perspective, the most common age group affected by Vitamin D Deficiency was adults and elderly(87.91% responses). Approximately 60% responses received, favored a 'single-dose oral liquid formulation' of vitamin-D as the most convenient dosage format for the treatment of Vitamin D Deficiency. Responses from almost all the doctors (99.51%) suggested that the use of nanoparticles technology in vitamin D_3 formulations could improve absorption of vitamin-D. While 67.53% of the doctors' responses recommended the use of Nano formulation for all patients with Vitamin D deficiency, the rest of the responses suggested its use in specific patient profiles of vitamin D deficiency. Approximately 99% of the responses received, rated the clinical experience with the nano droplet formulation to be good to excellent, both in terms of efficacy and tolerability. The responses also suggested that the nano droplet formulation is both, a convenient and an accepted format by the patient, reflected by the fact that more than 99.5% of the doctors' responses suggested it to be beneficial in their patients.**

Conclusions: **The study results reflect that Arachitol Nano has the acceptance of both doctors and patients as well, which is reiterated in the overwhelming number of responses from orthopedicians suggesting that Arachitol Nano would be beneficial for their patients with Vitamin D deficiency.**

Key words: Nano-droplet, nanoparticles, nanotechnology, Vitamin-D Deficiency

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Introduction

Deficiency of vitamin-D has gained more interest in recent times and it has been found to be a global phenomenon.[1-3] Due to the association of vitamin-D deficiency with multiple medical conditions, vitamin-D is being investigated as a potential treatment of many pathologic conditions, including psoriasis, type 1 diabetes mellitus, rheumatoid arthritis, multiple sclerosis, Crohn's disease, hypertension, cardiovascular disease, and many common cancers.[4-7]

Vitamin-D deficiency is fast becoming a global and national health concern. According to an Indian data published in 2014, vitamin-D deficiency prevails in epidemic proportions all over the Indian subcontinent, with a prevalence of 70%–100% in the general population. Based on the data of vitamin-D supplementation studies in ostensibly healthy Indians, the authors (Ritu G. & Gupta A.) of this article also state that, although vitamin-D supplementation resulted in significant improvement in vitamin D status, but a large proportion of the population did not attain sufficiency, despite supplementation.[8,9]

Vitamin-D deficiency can be easily corrected by vitamin-D supplementation. However, it has been reported that the efficiency of absorption of vitamin D in oral route is approximately 50%.[10] Vitamin D is a fat soluble vitamin, which is absorbed in a bile fat complex. Hence, its absorption may be hindered when there are inadequate lipids in the intestine.[11] Additionally, formation of mixed micelles with a hydrophilic surface is an absolute prerequisite for the absorption of vitamin D.[12] Thus, in order to improve the absorption of vitamin D, it is important to enhance its water solubility.[11] In this context, various nanoparticle delivery technologies using functional lipids (Ex: Phytosterols and ω-3 fatty acids) have been studied for nutraceutical delivery.[11] Similarly, several researchers have explored the role of nanotechnology (nanoparticles) in the delivery of vitamin D.

Nanotechnology (nanoparticles) may help in improving the oral bioavailability of nutrients that have poor water solubility.[11] The improvement in absorption could be because nanoparticles reduce the necessity of lipids in the absorption, provide protection against harsh environment of the gastrointestinal tract and possibly enhance trans-mucosal transport.[11-13]

Sun et al studied the advantages of employing nanoparticles of Vitamin D_3, both in in-vitro and in-vivo studies and suggested that a higher absorption of nanoparticle based formulation of vitamin D_3 on oral administration, as compared with conventional vitamin D_3.[11] Other researchers have also suggested that nanoparticles of Vitamin D_3 may also enhance important properties of vitamin D supplements, like therapeutic efficacy, photo-stability and biodegradation.[11,13,14]

Arachitol-Nano™ (Abbott India Ltd) is a nano-droplet formulation of vitamin-D_3 which contains 'Vitamin D_3 encapsulated in lipid nano-particles, with a hydrophilic surface'. The formulation has gained good acceptance amongst healthcare practitioners since its availability in 2014. Arachitol Nano delivers vitamin D with a better efficiency of absorption. Being a novel formulation, doctor's opinion and perceptions on the product are currently not available. Hence, this survey was undertaken to understand the overall opinion of a sample of orthopedicians on their perceptions, practices and preferences regarding the nano-droplet formulation of vitamin –D_3.

Methods

Design

This was a cross-sectional survey study conducted across India in both rural and urban regions spanning 81 locations.

Respondents

A total of 205 practicing orthopedicians were included in this survey. The doctors were expected fill the survey questionnaire, based on their clinical experience of Arachitol Nano with at least 25 patients with vitamin D deficiency.

Survey Questionnaire

A 10 item questionnaire was designed to capture data pertaining to the study objectives (table-1). The questions were designed to ascertain some general data like the status of Vitamin D deficiency in outpatient settings and the most common age groups affected by Vitamin D deficiency. The questionnaire also collected information regarding the perceptions, practices and preferences regarding the nano-droplet formulation of vitamin –D_3.

Statistical methods

Data entry was done in Microsoft Excel 2013 (version Office 365) in a study (questionnaire) specific excel spreadsheet validated for the 10 item study questionnaire. Validation was done using built-in validation tools in MS excel to minimize data entry errors. Data entered was verified for approximately 10% data points by the data manager using the matching method with physical paper copies of the filled questionnaires in random fashion. Cleaned and finalized datasheet was locked and subjected to data analysis. Data was imported in Stata 13.1 (IC), StataCorp LP, 4905 Lakeway Drive College Station, Texas 77845 USA (http://www.stata.com) and data was computed.

Data for responses to multiple choice questions are

Table 1: Study questionnaire

Sr.	Questions
1.	In your clinical practice, what percentage of the total patients you see, are Vitamin-D deficient?
2.	In your clinical practice, which is the most common age group which presents to you with Vitamin-D deficiency?
3.	In your clinical practice, in Vitamin-D deficiency management, which of the following dosage formats is the most convenient for your patient?
4.	In your opinion, do you think use of modern technology like nano - particles in Vitamin-D3 formulations could improve absorption?
5.	In your clinical practice, which patients would you recommend Arachitol NANO ™ (Vitamin-D3 oral solution 60,000 IU/5 ml Nano Droplet Form)?
6.	In your clinical practice, how is your experience in terms of efficacy, with Arachitol-NANO™ (Vitamin-D3 oral solution 60,000 IU/5ml Nano droplet Form)?
7.	In your clinical practice, how is your experience in terms of tolerability, with Arachitol-NANO™ (Vitamin-D3 oral solution 60,000 IU/5ml Nano droplet Form)?
8.	In your clinical practice, how is your experience in terms of patient convenience, with Arachitol-NANO™ (Vitamin-D3 oral solution 60,000 IU/5ml Nano droplet Form)?
9.	In your clinical practice, how is your experience in terms of patient acceptability, with Arachitol -NANO™ (Vitamin-D3 oral solution 60,000 IU/5ml Nano droplet Form)?
10.	Based on your experience and feedback, do you think that, Arachitol - NANO™ (Vitamin-D3 oral solution 60,000 IU/5ml Nano droplet Form), would be beneficial to your patients?

expressed as numbers with percentages (%) for each response. Since, there were multiple responses provided by some responders, the percentage values were calculated based on the total number of responses for each question independently. Total number of responses for the respective categories was used as the denominator used for calculating percentages. Being a survey questionnaire study, no statistical analysis tools were used for comparisons or analyses. Descriptive data for the responses for each questions are tabulated with numbers and percentages. Graphical presentation is done using multiple bar diagrams and pie charts, as appropriate.

Results & Discussion

The analysis of the responses received for each of the questions is as follows:

1) Of the 198 responses received for ascertaining the percentage of patients in clinical practice with vitamin D deficiency, maximum number of responses (25.25%) suggested 71%-80% patients to be vitamin D deficient, closely followed by 20.71% & 16.16% responses which suggested 61% - 70% and 81%-90% patients to be vitamin D deficient respectively. Cumulative responses for this data are represented in (figure-1). The results are in line with recent data suggesting that the prevalence of vitamin D deficiency is more than 70% in India.

2) Of the 273 responses received for ascertaining the most common age group affected by vitamin D deficiency, maximum number of responses (50.55%) suggested 'Elderly' as the most common age group to be vitamin D deficient, followed by 37.36% responses which suggested 'Adults' to be the most common age group with vitamin D deficiency. Cumulative responses for this data are represented in (figure-2). While published literature suggests that vitamin D deficiency is seen across all age groups, these results may be more indicative of the more common age group of patients treated by the orthopedicians.

3) Of the 259 responses received for the question on the most convenient dosage format for patients in vitamin-D supplementation, 60.23% responses suggested 'a single dose, oral liquid formulation' to be most convenient for patients. Cumulative responses for this data are represented in (figure-3). Clearly, majority of the doctors consider Arachitol Nano as a very convenient format of oral vitamin D delivery, given that it is in a 'ready to use' format, unlike the conventional formats like granules and capsules which need to be administered with water or milk.

4) Almost all the doctors opined that the use of

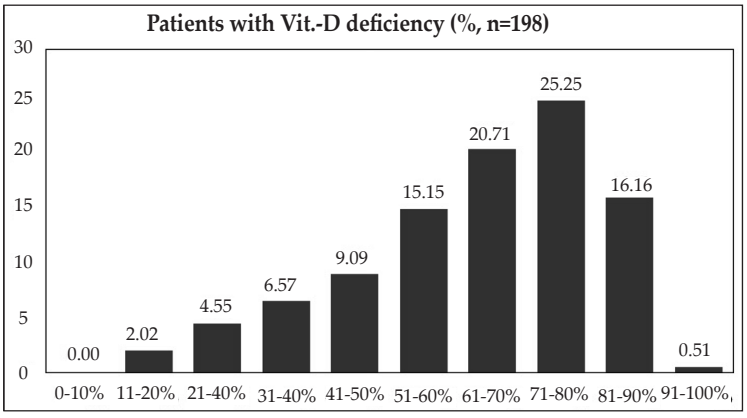

Figure 1: Doctor responses for percentage of total patients with Vitamin-D deficiency (expressed as % of total responses. Total responses received n=198)

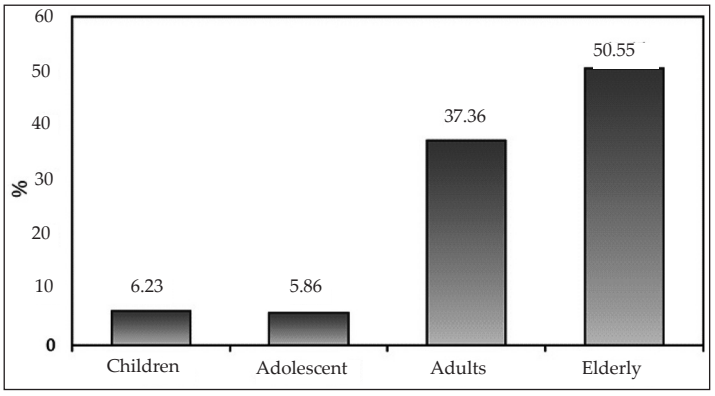

Figure 2: Doctor responses for the most common Vitamin-D deficient age-group (expressed as % of total responses. Total responses received n=273)

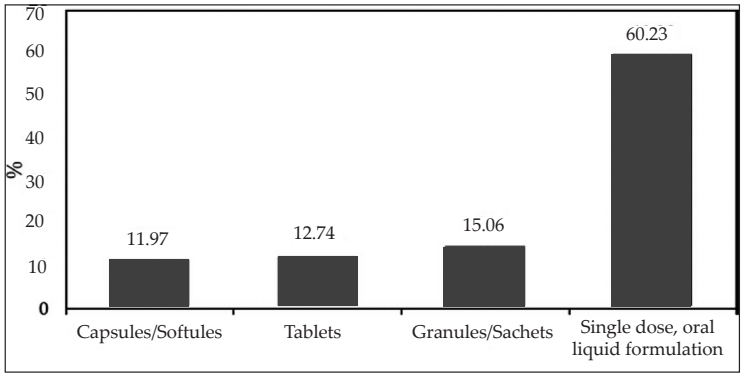

Figure 3: Doctor responses for the most convenient dosage format for Vitamin-D deficient patients (expressed as % of total responses. Total responses received n=259)

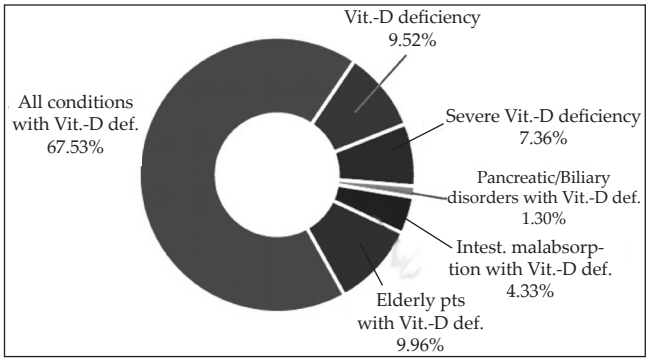

Figure 5: Doctor responses for the patient group where they would recommend Arachitol Nano (expressed as % of total responses. Total responses received n=231)

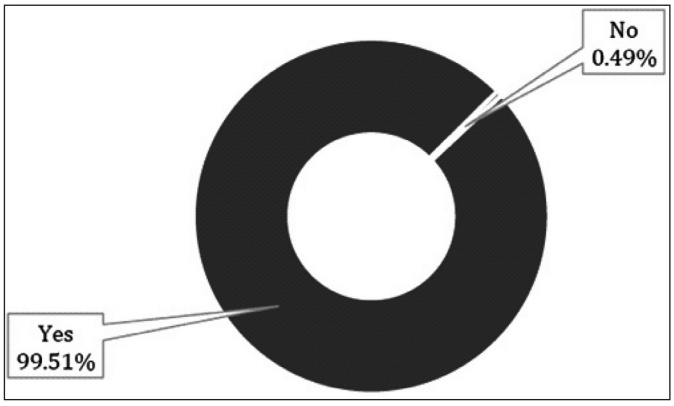

Figure 4: Doctor responses for their opinion on whether nanoparticles could improve absorption of vitamin D (expressed as % of total responses. Total responses received n=203)

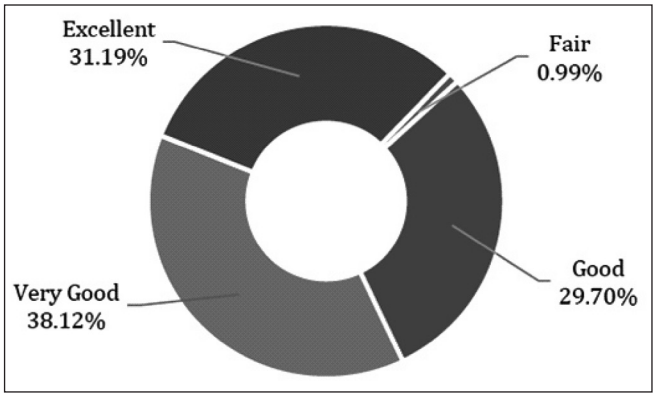

Figure 6: Doctor responses for rating efficacy of Arachitol Nano based on their clinical experience (expressed as % of total responses. Total responses received n=202)

nanoparticles technology in vitamin D_3 formulations could improve the efficiency absorption of vitamin-D. 99.51% of the total 203 responses received, were in favor of nanoparticles' ability to improve absorption. Cumulative responses for this data are represented in (figure-4). Thus, in line with the previously reported findings of Sun et al, who suggested that vitamin D nanoparticles have an improved efficiency of absorption.

5) Of the 231 responses received for the doctors' willingness to recommend Arachitol Nano™ (Vitamin-D_3 oral solution 60,000 IU/5 ml Nano Droplet Form),67.53% responses suggested willingness to recommend in cases of vitamin D deficiency in various patient profiles. Cumulative responses for this data are represented in (figure-5).

6) Of the 202 responses received for the doctors' clinical experience based rating of 'efficacy' of Arachitol Nano NANOTM (Vitamin-D3 oral solution 60,000 IU/5 ml Nano Droplet Form),69.31% responses rated the efficacy as 'Very good to excellent' followed by 29.70% of responses which rated the efficacy as 'Good'. Thus, almost all (99.01%) doctor responses indicated that Arachitol-NANOTM is efficacious. Cumulative responses for this data are represented in (figure-6).

7) Of the 204 responses received for the doctors' clinical experience based rating in terms of 'tolerability' of Arachitol Nano NANO™ (Vitamin-D_3 oral solution 60,000 IU/5 ml Nano Droplet Form),78.92% responses rated the tolerability as 'Very good to excellent' followed by 20.59% of responses which rated the tolerability as 'Good'. Thus, almost all (99.51%) doctors indicated that Arachitol-NANO™ is well tolerated. Cumulative responses for this data are represented in (figure-7).

8) Of the 204 responses received for rating the doctors' clinical experience in terms of 'patient convenience' for using Arachitol Nano NANO™ (Vitamin-D_3 oral solution 60,000 IU/5 ml Nano Droplet Form), 28.43% responses rated Arachitol Nano as 'Excellent', 47.06% as 'Very good', 22.55% as 'Good', and only 1.47% and 0.49% as 'Fair' and 'Poor' respectively. Cumulative re-

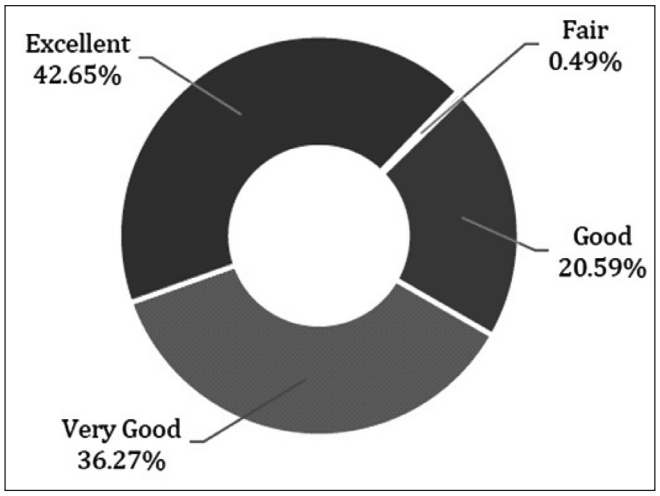

Figure 7: Doctor responses for rating tolerability of Arachitol Nano based on their clinical experience (expressed as % of total responses. Total responses received n=204)

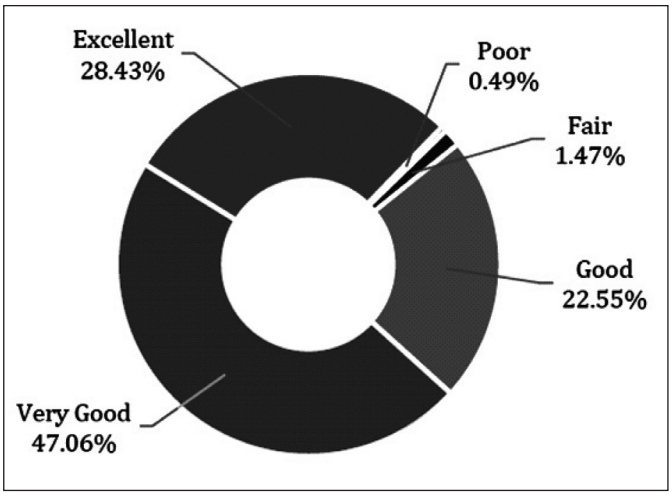

Figure 8: Doctor responses for rating patient convenience with Arachitol Nano based on their clinical experience (expressed as % of total responses. Total responses received n=204)

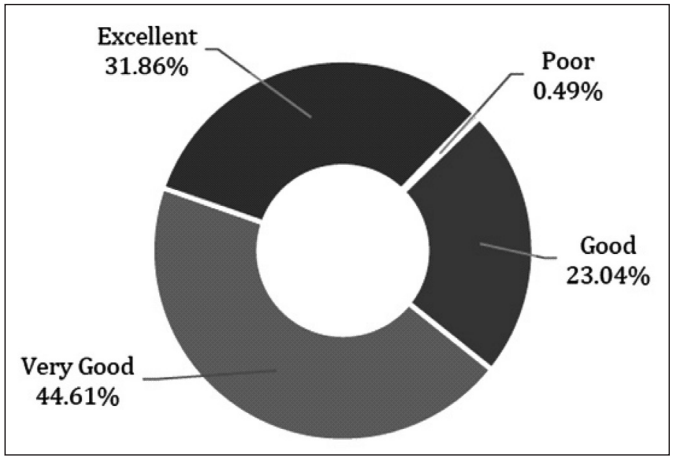

Figure 9: Doctor responses for rating patient acceptability with Arachitol Nano based on their clinical experience (expressed as % of total responses. Total responses received n=204)

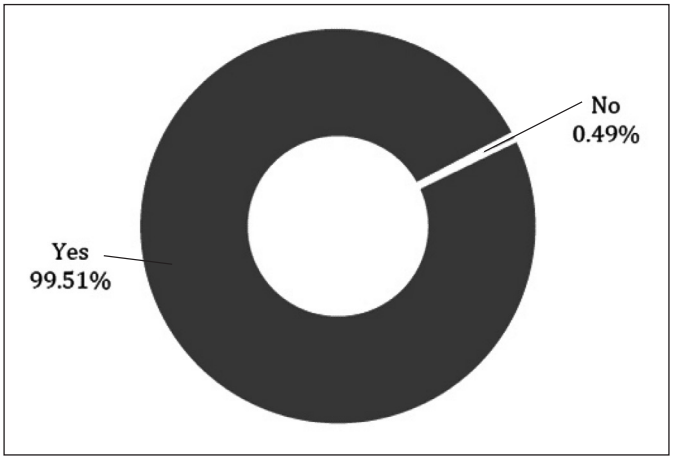

Figure 10: Doctor responses for 'willingness to recommend' Arachitol Nano to their patients based on their clinical experience (expressed as % of total responses. Total responses received n=205)

sponses for this data are represented in (figure-8).

9) Of the 204 responses received for rating the doctors' clinical experiences in terms of the 'patient acceptability' for using Arachitol Nano™ (Vitamin-D_3 oral solution 60,000 IU/5 ml Nano Droplet Form), 31.86% responses rated Arachitol Nano as 'Excellent', 44.61% as 'Very good', 23.04% as 'Good', and only 0.49% as 'Poor' respectively. Cumulative responses for this data are represented in (figure-9).

10) Of the 205 responses received for rating the doctors' acceptance of Arachitol Nano™ (Vitamin-D_3 oral solution 60,000 IU/5 ml Nano Droplet Form), 99.51% responses indicated that Arachitol Nano would be 'Beneficial' to their patients. Cumulative responses for this data are represented in (figure-10).

Conclusion

Vitamin D deficiency is very common all over the Indian subcontinent, with a prevalence of above 70%.[9] This could be possibly attributed to the Indian social, religious and cultural practices which do not facilitate adequate sun exposure. The widely consumed food items such as dairy products are not fortified with vitamin D, and therefore subclinical Vitamin D deficiency is highly prevalent in both urban and rural settings, and across all socioeconomic and geographic strata. Vitamin-D deficiency can be corrected by vitamin-D supplementation. However, it has been reported that the efficiency of absorption of vitamin D in oral route is approximately 50%.[10] Nanotechnology (nanoparticles) may help in improving the oral bioavailability of nutrients that have poor water solubility. This was confirmed by Sun et al in

the study evaluating the oral bioavailability of Vitamin D nanoparticle based formulation.[11]

Arachitol-Nano™ (Abbott India Ltd) is an NDDS (Novel Drug Delivery System) formulation of vitamin-D3 which contains 'Vitamin D3 encapsulated in lipid nanoparticles, with a hydrophilic surface'. Arachitol Nano delivers vitamin D with a better efficiency of absorption.

This survey evaluated the clinical experience of 205 Orthopedicians across India, in their practice with Arachitol-Nano™. Vitamin-D deficiency was reported to be present in more than 50% patients attending the clinics by 77.77% doctors. Thus, a very high proportion of Indian individuals seem to have Vitamin D deficiency, in line with published literature. In terms of the preferred delivery format for vitamin-D formulation, an overwhelmingly high proportion of doctors voted for their preference for a single dose, oral liquid formulation of vitamin-D for management of Vitamin D deficiency. Most of the doctors believed that nano-technology can improve oral absorption of vitamin-D, and over one-third doctors recommended the use of nano-formulation for all patients with Vitamin D deficiency. In terms of the efficacy, tolerability and patient convenience, nano-particle formulation was the preferred formulation by most of the doctors over other conventional formulations. The nano-formulation was also reported to be convenient and widely accepted by the patients as well. In conclusion, the study results reflect that Arachitol Nano has the acceptance of both doctors and patients as well, which is reiterated in the overwhelming number of responses (204, 99.51%) suggesting that Arachitol Nano would be beneficial for patients with Vitamin D deficiency.

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References

1] Wolf G. The discovery of vitamin D: the contribution of Adolf Windaus. J Nutr. 2004;134:1299–1302.

2] Calvo M, Whiting S, Barton C. VD intake: A global perspective of current status. J Nutr. 2005;135:310–316.

3] Hollick M. High prevalence of VD inadequacy and implications for health. Mayo Clin Proc. 2006;81:353–375.

4] Vaishya, Vijay V, Agarwal A, Jahangir J. Resurgence of vitamin D: Old wine in new bottle. J Clin Orthop Trauma. 2015;6(3): 173-183, 2015.

5] Grant W, Hollick M. Benefits and requirements of VD for optimal health: a review. Altern Med Rev. 2005;10:94-111.

6] M. Hollick M. Sunlight and VD for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr. 2004;80(6) (Suppl 1):1678S–1688S.

7] Harris S.VD and type 1 diabetes [letter]," Am J Clin Nutr. 2004;79:889–890.

8] Ritu G, Gupta A. Vitamin D Deficiency in India:Prevalence, Causalities and Interventions. Nutrients. 2014;6(2):729- 775.

9] Van-der I M, Middlekoop B, Boeke A, Lips P. Prevalence of vitamin D deficiency among Turkish, Moroccan, Indian and sub-Sahara African populations in Europe and their countries of origin: An overview. Osteoporos Int. 2011;22:1009–1021.

10] Basu TK. Intestinal absorption in health and disease:micronutrients. Best Practice & Research Clinical Gastroenterology. 2003;17(6):957-979.

11] Fusheng S. Nanoparticles Based on Hydrophobic Alginate Derivative as Nutraceutical Delivery Vehicle: Vitamin D3 Loading. Artificial Cells, Blood Substitutes, and Biotechnology. 2012;40:113-119.

12] Rautureau M, Rambaud JC. Aqueous solubilization of vitamin D3 in normal man. Gut. 1981;22:393-397.

13] Bruno S. Oral insulin delivery by means of solid lipid nanoparticles. International Journal of Nanomedicine. 2007;2 (4):743- 749.

14] Luo Y. Development of zein nanoparticles coated with carboxymethyl chitosan for encapsulation and controlled release of vitamin D3. J Agric Food Chem. 2012;60(3):836-843.