Literature review

- **Black *et al.*, (2017),** reviewed that vitamin D has been recognized as an essential nutrient for bone health and its deficiency is a global concern. The insufficient exposure to UV-B radiation may lead to deficiency of this vitamin and therefore the dietary intake of this nutrient for the external sources become important.
- **Mithal *et al.*, (2009),** described vitamin D status in different part of the globe and in indian context it has been mentioned that in northern part of India, Vitamin D deficiency is widespread affecting neonates (96%), healthy hospital staff (78%), healthy school girls (91%), and pregnant women (84%), while in southern part of India, vitamin D deficiency was found in 40% of males and 70% of females.
- **Kennel *et al.*, (2010)**, reviewed that vitamin D is an essential micronutrient owing to its ability to maintain calcium and phosphorus concentrations at the required level by improving the efficacy of the small intestine to absorb these minerals from the diet. The deficiency of vitamin D leads to rickets, osteomalacia, hyperparathyroidism, and osteoporosis.
- **Gupta *et al.*, (2019),** reviewed that two main forms of vitamin D are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). These are poorly water soluble and are prone to degradation under the environmental conditions including temperature and light. Keeping these aspects into consideration, novel formulation strategies are required for the efficient delivery of vitamin D. They also mentioned that novel delivery systems like solid dispersion, self-emulsifying delivery system and nanoparticles/nanoemulsion could be potential delivery system for efficient delivery of vitamin D.

- **Li *et al.,* (2021),** mentioned that a majority of drug discovery molecules are in BCS II or IV class and for these molecules with poor aqueous solubility, drug solubilization approaches including solid dispersion could be of potential use. The investigators developed HPMCAS based solid dispersion and the in vitro dissolution of the developed solid dispersion formulations was conducted using two-stage dissolution.

- **Dadkhodazade *et al.,* (2018),** studied *Saccharomyces cerevisiae*-based delivery system for the delivery of cholecalciferol. The developed system was evaluated for the particle size and the formulation was characterized by the FTIR and the XRD. Also, release profile of cholecalciferol was investigated in the simulated gastric fluid and simulated intestinal fluid.

- **Menard *et al.,* (2012),** synthesized novel surfactant for the solubilization of poorly soluble compounds. Surfactants are commonly used in pharmaceutical formulations comprising a poorly aqueous soluble active agent. Surfactants could improve drug's solubility via micellar solubilization and play a vital role in the modulation of membrane permeability. They also possess the potential to inhibit p-glycoprotein, thereby improving the drug's bioavailability and intracellular drug concentration, which is having an implication in tackling drug resistance. However, surfactants are associated with the limitation of local irritation, membrane disruption, and cellular death. Hence, surfactant-based formulations should be investigated for their cytotoxic potential.

- **Nakamichi *et al.,* (2004)**, described development of enteric solid dispersion based on hydroxypropylmethylcellulose acetate succinate (HPMCAS). HPMCAs is an important enteric polymer and it is more stable than

hydroxypropylmethylcellulose phthalate (HPMCP), therefore possesses potential as carrier for drug delivery.

- **Mustafa *et al.*, (2022),** described the development of gefitinib solid dispersion by the spray drying method and evaluated its mucoadhesive and dissolution properties. The study showed that the polymer/surfactant used in the developed solid dispersion formulation had no cytotoxic effect on Caco-2 cells and seems to be nontoxic.

- **Vora *et al.*, (2017),** developed PLGA microspheres for the sustained release of cholecalciferol. The developed formulation was evaluated for the drug loading and drug release. DSC and XRD based studies indicated the amorphous form of the drug in the carrier and the SEM study indicated the surface morphology and characteristic of the microspheres. The developed polymeric formulation demonstrated good stability profile of cholecalciferol at different conditions of storage.

- **Asfour *et al.*, (2023),** developed cholecalciferol (VD3) nanoemulsion (NE) by high-speed homogenization method. NE showed high drug loading and namometer size. Formulation was evaluated for the size under the TEM and stability study was also conducted. The developed formulation showed good stability and improved bioavailability.

- **Marwaha *et al.*, (2022),** conducted randomized, crossover study to compare the relative bioavailability of vitamin D3 nanoemulsion in human volunteers and compared that with cholecalciferol. The findings showed that nano emulsion formulation showed higher bioavailability compared to cholecalciferol.

- **Wang *et al.,* (2022),** investigated solubilization of cholecalciferol using hydroxypropyl-β-cyclodextrin (HPBCD) mediated complex formation. A DSC analysis was employed to confirm complexation between HPBCD and Vit D3 by disappearance of vit D3 peak in the complex, which could be attributed to the amorphous form of vitamin D3 by lodgings in hydrophobic cavity of HPBCD. This was also supported by FTIR and XRD based investigation of the complex. Computational investigation showed better understanding of molecular level interaction in the investigated complex.

- **Pantić *et al.,* (2016),** explored supercritical fluid for the encapsulation for fat soluble vitamin including vitamin D and vitamin K. The developed aerogels were characterized using FTIR, XRD and DSC. The XRD study showed that the characteristics peaks of vitamin D were not present in the formulation. The reason could be the change in the crystalline characteristics of molecule to amorphous nature. Further, the dissolution behaviour was investigated using in vitro dissolution testing.

- **Yue *et al.,* (2020),** developed lipid carrier using solid lipid and liquid lipid. The developed formulation was evaluated for hardness, uniformity of content and dissolution behaviour followed by stability study. The developed formulation exhibited better content uniformity and stability profile.

- **Chaves *et al.,* (2023),** studied enrichment of cornstach with two important nutrients. Curcumin and cholecalciferol are biomolecules with great potential in food industry, hut their limited stability is a concern for their incorporation into powdered food products and therefore investigation was conducted for enrichment of cornstarch with curcumin and cholecalciferol. The biomolecules

were loaded in lipid-based formulation (liposomes) and subsequently lyophilized. The freeze-dried product was mixed with cornstarch using maltodextrin as binder. Freeze-dried liposomes exhibited good loading of curcumin and cholecalciferol. In summary, the lyophilized liposomes enhanced the stability in curcumin and cholecalciferol in corn-starch.

- **Żurek *et al.,* (2023),** proposed a mathematical modeling-based method to overcome limitation linked with pharmacokinetics evaluation of vitamin D3. The method investigated the comparison of pharmacokinetics of liposome and oil-based product of cholecalciferol. The results showed that cholecalciferol liposomes were of more potential in increasing calcidiol level blood.

- **Lhamo *et al.,* (2017),** reviewed the world-wide epidemic situation of vitamin D deficiency and reported the physiological importance of vitamin D in various disease state and normal daily intake.

- **Tripkovic *et al.,* (2012),** reported the higher effectiveness of vitamin D3 over vitamin D2. Considering pharmacological and stability issues related to both vitamins, they stressed on replacing administration of vitamin D2 by vitamin D3.

- **Mostafa and Hegazy, (2015),** depicted the development of new analogues of vitamin D which are under clinical trial for its efficiency in the treatment of psoriasis. Such activity actually relies on its immuno-modulatory action of inhibiting cellular proliferation and differentiation.

- **Hollick *et al.,* (2013),** have reviewed the required dose of vitamin D and depicted that 34 ng/mL and 38 ng/mL of 25(OH)D is required for calcium absorption from the intestine and for performing the neuromuscular function.

They also reviewed that 40ng/ml was the concentration which could prevent hyperparathyroidism.

- **Sun *et al.,* (2013),** patented the solid dispersion (SD) formation of dronedarone by dispersing a drug onto a solid carrier. As per surface morphology analysis by SEM, final formulation appeared in the form of amorphous structure which clearly depicted the presence of polymer over the crystalline structure of drug.
- **Mahmoud and Ebeed, (2012),** patented the homogeneous preparation of vitamin D containing adherent as polyethylene glycol (molecular weight in the range of 1500 to 8000) by dissolving them in an organic solvent (*e.g.* ethanol) having low toxicity. The dispersion also composed of antioxidant and a chelating agent as metal extractor for chemical stability. Finally, spray dryer was used to spray vitamin D dispersion over calcium salt and granules were produced which were observed to increase the stability of vitamin D.
- **Valleri and Tosetti, (2006),** performed a study in which a stabilized formulation of calcium and vitamin D was developed which leads to a high level of bio-availability using propylene glycol or polyethylene glycol (weight range of 300-1500), liquid paraffin or silicone oil. The even and diffused distribution of glycols within the granulating mixture played a binding effect which in turn allowed even distribution of vitamin D and also improved the flow properties of calcium.
- **Yuji and Yoshiki, (1993),** patented a technology in which a solid pharmaceutical preparation of active form of vitamin D3 was formed by developing two layers. Development of layers depends upon solubility of polymers in organic solvent as highly soluble polymers were composed of

external layer while slightly soluble composed of inner layer. The inner layer also composed of basic substance which was added in concern of its stability in acidic medium. Different additives as basic substances were examined for neutralization capability and among them one with more basicity and low water content was selected. While conducting stability studies, it was observed that a new excipient with low water content and maximum absorption capability present as inner layer would limit the degradation of vitamin D3.

- **Woo *et al.*, (2008),** prepared the solid dispersion of vitamin D and bisphosphonate using cyclodextrin as amorphous polymer along with stabilizing agent or pharmaceutically acceptable additives. The optimized formulation was obtained by preparing different formulations in the range of vitamin D and cyclodextrin weight ratio of 1:100 to 1:1600 respectively. The vitamin D was employed in an amount ranging 0.01 to 10% by weight while bisphosphonate in 1 to 30% weight range. The stabilizing agents were added to prevent oxidation and pharmaceutical additives including binding agent, lubricant, disintegrant, diluents, filler, compressing aid, buffer, suspending agent, emulsifying agent, surfactant and coloring agent were also added. The stability testing of this formulation showed that there was no significant change in the content of vitamin D3 till 4 weeks.

- **Luo *et al.*, (2012),** developed carboxymethyl chitosan coated zein nanocarrier for the encapsulation of cholecalciferol. The low-energy phase separation technique was used for the fabrication of nanocarrier and carboxymethyl chitosan was coated. Subsequently, calcium was used as cross-linker for carboxymethyl chitosan. The coated nanocarrier exhibited particle size in nanometer range and showed good drug encapsulation. The nanocarriers were

also characterized using FTIR and DSC. Nanocarrier showed controlled release of cholecalciferol in simulated body fluids with improved photostability of cholecalciferol.

- **Teng *et al.*, (2013),** prepared cholecalciferol loaded complex nanocarrier using carboxymethyl chitosan and soy protein isolate. The influence of calcium concentration, pH and the excipient ratio on the nanocarrier development was studied. The developed nanocarrier complex showed particle size in nanometer range with a negative zeta potential. The developed noncarrier had improved encapsulation efficiency for cholecalciferol with the desired release behavior in the simulated body fluids. The developed polymeric system represents a promising carrier for the improved delivery of cholecalciferol and other hydrophobic nutrients.
- **Guttoff *et al.*, (2015),** studied the effect of formulation composition and fabrication condition on cholecalciferol nanoemulsion size and stability. The effect of oil phase composition, oil-surfactant ratio, type of surfactant and stirring speed on nanoemulsion size was investigated. This study also showed the use of sodium dodecyl sulphate as co-surfactant to modify thermal stability of the susceptible bioactives.
- **Park *et al.*, (2017),** explored high pressure assisted homogenization method for the development of cholecalciferol loaded lipid carrier. The developed lipid carrier was characterized extensively and its release profile in simulated body fluids were also determined. The developed carrier showed optimum particle size, zeta potential, drug encapsulation and stability of bioactive. The release study showed the potential of developed carrier in protective the drug in gastric condition and required release in intestinal milieu.

- **Tipchuwong *et al.*, (2017),** performed emulsification of cholecalciferol by milk protein and product was developed as cholecalciferol enriched ice-cream. The stability of cholecalciferol with various emulsifiers was studied and storage stability of this micronutrient at −20 °C was determined. The findings demonstrated the potential of this product type in maintaining the stability of cholecalciferol.
- **Seo *et al.*, (2019),** mentioned that the cholecalciferol is an important micronutrient, but its stability and bioavailability is main limitation from delivery viewpoint. They attempted nanostructured lipid nanocarrier for improved delivery of cholecalciferol. A variety of carrier oils and emulsifiers were investigated. The stability of the developed nanocarrier was studied under different stress conditions including ionic concentration, pH, freezing-thawing, temperatures variation. Keeping the observations into considerations, an improved product of cholecalciferol was developed and the study pave the ways for further development in this area.
- **Ramachandra and Sudheer, (2023)** reviewed the potential of the intestinal lymphatics pathways for facilitating the absorption of a variety of substances lipids, vitamins, micronutrients and various others hydrophobic bioactive. This pathway is associated with various advantages including escape of first pass effect and augmented bioavailability of the biomolecules. There are various substances with poor hydrophilicity and lipid-based delivery systems can be explored to improve their bioavailability. Among, the lipid-based delivery systems, self-emulsifying drug delivery system exhibited tremendous potential in augmenting the bioavailability of biotherapeutics. The presence of various marketed product based on self-emulsifying drug delivery system demonstrate the potential of this technology.