A SYSTEMMATIC REVIEW ON NANOCRYSTALS

Lakuminarayanan[1], Gayathri.H[2*], Damodharan.N[3]

Article History: **Received:** 19.05.2023 **Revised:** 11.05.2023 **Accepted:** 30.06.2023

Abstract

Nanotechnology is the modern formulation and it will rule the medicine and pharmacy fields. By using this technology an innovative formulation is prepared by reducing macromolecule to Nanomolecule for poor soluble drug: the drug nanocrystals. But the nanocrystal is not about the future the first product is already in the market. The technique that are used for the preparation in industries are reviewed. The pharmaceutical drug formulation, drug properties as well as drug procedure are discussed.

Keywords: Nanocrystals, Nanoparticle, Nanocarrier, Phospholipid

[1,2,3] SRM College of Pharmacy, SRMIST, Kattankulathur campus, Tamil Nadu, India,
Email: [2*]gayathrh@srmist.edu.in

DOI: 10.31838/ecb/2023.12.s3.578

1. INTRODUCTION

Most of the drugs that are currently marketed are poorly soluble drugs. 40 % of the drugs which are marketed are low solubility of drugs but high penetrable (1)is BCS class 2 and low solubility and low penetrable is BCS class 4(2)(3). The poorly soluble drug delivered by many formulations like prodrug, salt formation, cyclodextrins, , and using some carriers (e.g., o/w emulsion delivery) have been widely used but they have difficulty like instability, less drug loading, side effects, and toxic reactions(4). Liposomes successfully achieved formulated hardly soluble drug in the 1990s but they have poor chemical and physical stability and manufacturing cost is high. Micronization was the conventional approach for poorly soluble drugs. The drug compounds are made into micrometres range that give the advantages of greater surface area this, in accordance with the Noyes- Whitney equation, causes a rise in dissolution and improves the absorption in the gastrointestinal tract(3)(5). It fails to improve saturation stability and bioavailability of the drug for very poor solubility compounds so the technologies move towards micro to Nano sized drug delivery. A new drug solid nanoparticle came out in 1990 that is nanocrystal. Nanocrystals are the most suitable way of delivering hardly soluble drugs there the size of a nanometre ranges normally between 10 – 1000nm (6)and contains 100% drug particles without the carriers and a minimum quantity of surfactant or polymeric steric stabilizers helps for their stability and they further increase the dissolution velocity(7). They have the favourable of (Ⅰ) Delivering drug through a different method for drug delivery (like oral, Intervenes, intramuscular, ocular, etc.) (Ⅱ) better adhesion to membranes (Ⅲ) Dissolution rate is faster and High solubility(8).

In this review, we are going to see about the formulation and drugs treated to diseases

Preparation techniques of nanocrystals

Techniques to prepare for nanocrystals are categorized bottom-up, top-down, and combination technologies. The top-down method produces Nano sized particles by bigger particles into smaller particles by milling and homogenization. In the bottom-up method, the Nano-crystals are constructed by the precipitation method from the molecule. The combination technologies are formed by combining two technologies Contain milling, high-pressure homogenization, and precipitation method(9).

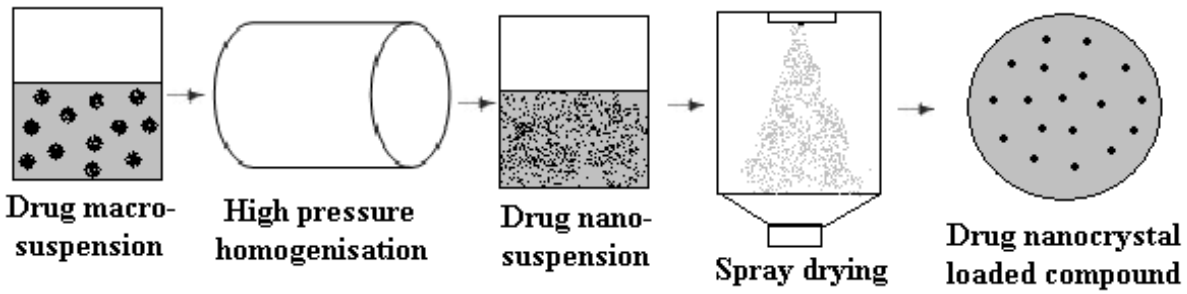

Figure: 1 Production of nanocrystals

Bottom-up processes

Bottom-up this method is also defined as the precipitation method(10). In this technic the compound in the homogeneous mixture the molecules grouped to create a crystallized or shapeless compound. In this method, the dissolver is used for drug particles to sever(11). When the dissolver solution is added to a non-solvent with the addition of a stabilizer such as a surfactant produces precipitation of the drug. The temperature, surfactants, and stirring rate help to avoid the increasing size to form a micrometer and produce a Nanometre range(10). They should have the property of

1. The medication must dissolve in at least single dissolver(12).
2. The dissolver should be miscible with a non-soluble(12).
3. The dissolver used in this process should be eradicated to an appropriate level in the final outcome(12).

Top-down processes

Many pharmaceutical company uses this technique for the preparation of nanocrystal. They use milling technologies and high pressure homogenization to reduce the particle size for preparation of nanocrystal. They are used prepare for anticancer nanocrystal according to report(13) .With this methodology many drugs are marketed.

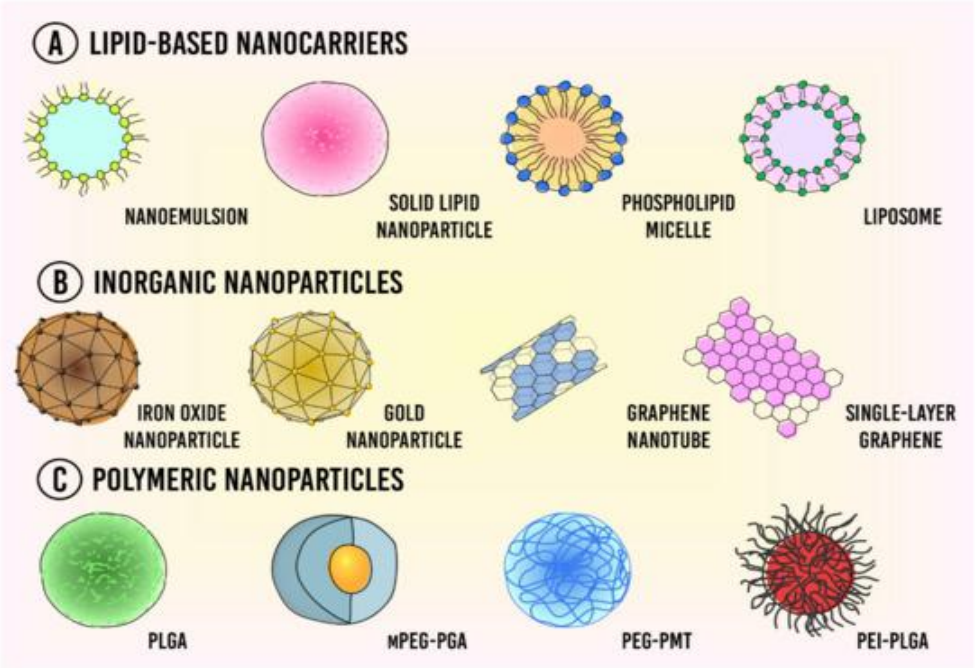

Figure: 2 Types of nanocrystals

Bo Ram So, Hyeon Jin Yeo, Jeong Jae Lee , Young Hoon Jung, Sung Keun Jung discussed that Gelidium amansii nanocrystal was prepare resulting to reduce inflammation in keratinocyte and no cell poison in HaCaT, Beas -2B, or in mouse cell Raw 264.7 cell line. They produce ultraviolet which prevent activation of protein, cyclooxygenase and protein expression produced from HaCat cell even translocation of c-Jun is blocked by the UVB from TGa CNC, it block from the cytosol to nucleus. Furthermore, they prevented UVB-induced phosphorylation of the Akt, c-Jun N-terminal kinase (JNK)1/2/MKK4/7, ERK1/2/MEK/2/B-Raf, and epidermal growth factor receptor (EGFR) in HaCaT cells.In mice the nanocrystal with Gelidium amansii is applied on skin dorsal which results in reduction of acute UVB-induced epidermal thickness growth and COX-2 expression. After analysing the TGa CNC blocks the aberrant COX-2 production as well as the signalling pathway of mitogen-activated protein kinases (MAPKs) which results in anti-inflammatory(14). Tsung-Ju Li, Chih-Chia Huang, Pin-Wei Ruan, Kuei-Yi Chuang, Kuang-Jing Huang d, Dar-Bin Shieh, and Chen-Sheng Yeh Presented the medication is unleash by hyperthermia activity and temperature-responsive. 5-fluorouracil (5-FU) are entrapped in a magnetic nanocrystal which is used as a core, as well as anti-human epidermal growth factor receptor 2 (anti-HER2) antibody is also entrapped they can specifically targets the cancer cell. The radiofrequency energy for hyperthermia to tumor is conveyed via the targeted nanocrystal it is administered by externally. Oligonucleotide medication get released which is present in carrier it is triggered by locoregional heat that give negative impact to tumour cells. This shows great effective than hyperthermia or chemotherapy only, this were resulted by determining cell viability assays and pathological. They were injected by intravenous shows the signs and symptoms of your cancer are reduced they were analysed in In-vivo by accomplishing radiofrequency synchronisation of hyperthermia and treatment(15).

Fatemeh Ghaffari1, Akbar Hajizadeh Moghaddam1, Mahboobeh Zare discussed that Free radicals are also causes Parkinson disease by inducing neurodegeneration. Quercetin has a natural polyphenol which preventing the harm that is created by free radical to neurodegenerative. It is poorly water soluble so nanocrystal technique has been used by oral medication. Quercetin nanocrystal coated on 6-hydroxydopamine which induces Parkinson-like model. It is performed by Evaporative Precipitation of Nanosuspension method. Which results in improves antioxidant enzyme activates and glutathione, and minimizes Malondialdehyde level in the hippocampal area. Quercetin nanocrystal shows bigger different in bioavailability compared to quercetin alone.(16) Zhu Xiali, Yingjie Zhang, Heqing Huang, Huijuan Zhang, Lin Hou & Zhenzhong Zhang discussed that photothermal therapy is performed with copper sulphide nanocrystal which as ability of high permeation level of near-infrared radiation. They have

presented simultaneous loading of docetaxel and functionalized CuS NCs onto chitosan-entrapped and folic acid with a modified nanoparticles they show anti-tumour efficacy when combined to NIR laser. The MCF-7 cancer cell is can be directly targeted by photothermal agent CuS Nanocrystal and DTX and it constructively transferred tumor tissue of a mice with S180 cancer cell line. Thereby, these concentrated targeting NPs could have a significant potential for tumour synergistic treatment as a distant and noninvasive tumour therapeutic technique(17). Eden Morales-Narváez, Helena Montón, Anna Fomicheva, and Arben MerkoçI discussed that the efficacy of fluorescent dye Alexa 647 and cadmium-selenide/zinc-sulfide (CdSe@ZnS) quantum dots (QDs) as reporters an experiment intended to expose apolipoprotein E (ApoE) has been correlated. Using visible light to excite sandwich immunocomplex microarrays, the study is carried out. Sandwich immunocomplex microarray which is used as analysis, it activated by excitation of visible light. ApoE biomarker is suited for Alzheimer's disease. The two variety microarrays (QD or Alexa 647) were evaluated below the identical test circumstances and then contrasted with an ApoE-targeting standard enzyme-linked immunosorbent assay (ELISA). Although their performance significantly varied depending on the excitation wavelength, the quantum dots proved to be extremely effectual result in the microarrays. Quantum dot microarray have a limit of detection of 247pg mL-1 at the 633nm, although at 532 nm, the excitation wavelength, it delivered a limit of detection of 62 pg mL-1, which shows sensitive than the Alexa microarray and ELISA. In the end, a human blood sample was utilised to evaluate repeated dilutions with great sensitivity and respectable precision and accuracy(18).

Naina Soni, Kiran Jyoti, Upendra Kumar Jain, Anju Katyalb, Ramesh Chandra, Jitender Madan discussed that the noscapinoids entrapped in silver nanocrystal results in apoptosis as well as improvement drug delivery. It is analysed by B16F1 cell of a mouse which has melanoma cancer cells. The noscapine is used on cancer and it prevents cellular proliferation even reduced brominated of noscapine has same property they can be performed by either alone or in combination with other chemotherapeutic drug. They have weak physicochemical qualities so they show effective only at large and repeated dosages. They help to improve cellular uptake and cytotoxicity of cancer cell. Precipitation technique were performed for the preparation which as the mean particle size 27.43 ± 4.51 nm of Red-Br-Nos-Ag2+ nanocrystals is bigger than 25.33 ± 3.52 nm is mean particle size of noscapine-Ag2+ nanocrystal. In zeta-potential Nos-Ag2+ nanocrystals is higher than Red-Br-Nos-Ag2+ nanocrystals (-25.3 ± 3.11 mV >-15.2 ± 3.33). BothThe modified nanocrystals have an asymmetrical or somewhat spherical form. Nanocrystals both have an amorphous architectures. The interaction of Ag2+ nanocrystal with drug molecule has been demonstrated by FT-IR spectroscopy. The improved cytotoxicity, apoptosis, and cellular absorption of modified nanocrystals were used to gauge their greater therapeutic effectiveness. The value of IC50 of noscapine-Ag2+ is 16.6mM which is lower than 38.5 as well as Red-Br-Nos-Ag2+ is 6.5mM lower than 10.3 . Internalisation of both nanocrystal performs cellular morphological change results in gathering within membrane-bond cytoplasmic vacuoles and expanded lysosomes, which in effect activated caspase to cause mitochondria to induce apoptosis. That concludes the transport of noscapinoides to melanoma cancer cell the nanocrystal are used(19).

Rosa Pireddu , Carla Caddeo , Donatella Valenti , Francesca Marongiu, Alessandra Scano , Guido Ennas , Francesco Lai a, Anna Maria Fadda , Chiara Sinico discussed that to treating skin antiphlogistic as well as better permeation and to produce higher bioavailability nanosuspension of diclofenac with poloxamer 188 as a stabilizer is developed with wet media milling method. They show an average diameter of 279nm. They were is examined in ex-vivo with help of Franz cells and skin of a mice is correlated against diclofenac acid suspension. The nanocrystals topical antiphlogistic effectiveness was examined with In-vivo against typical inflammatory results in the prevention of hydropsy as well as WBC infiltration. They show a less polydispersity index (0.17) and showing different crystalline shape as the original bulk powder. When both coarse suspension and conventional product are correlation to nanocrystal it performs grater assemblage of medication by transdermal delivered it analysed by ex-vivo. In in-vivo oedema both nanocrystal and conventional product are statistically equal. The nanocrystal having grater restraining myeloperoxidase (86%) than conventional medication (16%)(20) Huamin Liang , Fengming Zou , Qingwang Liu , Beilei Wang , Liyi Fu ,Xiaofei Liang , Jing Liu , Qingsong Liu discussed that the nanocrystal have grater advantages but it have flaw of unstable and uncontrolled release. Study of nanoparticle entrapping other nanoparticle which as Nano crystal core is entrapped in the liposomal shell which give higher advantages. CHMFL-ABL-053 is a lipophilic drug which is entrapped in nanocrystal core in NC@Lipo. Wet ball milling and probe sonication were used to manufacture surface PEGylated (053-NC@PEG-Lipo) and folic acid-functionalized (053-NC@FA-

Lipo) formulations. High drug loading, improved stability, as well as longer circulation in vivo compared to 053-NC. In K562 xenograft mice, 053-NC@PEG-Lipo and 053-NC@FA-Lipo showed much greater in vivo antitumor activity than free 053, with tumour growth inhibition rates (TGI) of up to 98%. They produced greater TGI In-vivo as well as more successful tumour cell targeting In-vitro. The NC@Lipo expresses great advantages for the delivery of poorly water soluble medication at targeted site(21).

Patrik Scholz, Cornelia M. Keck discussed that a novel technique termed ARTcrystal1-technology, which employs a high-speed stirring step performed in lower pressure with the help of high-pressure homogenization with lower cycle number, was evaluated for the production of nanocrystals. This technique was used to process three antioxidants, rutin, hesperidin, and apigenin. The outcomes were contrasted with size those produced using conventional high pressure homogenization. The ability to create nanosuspensions of all three compounds was discovered, with average diameters and PdIs of fist container 431 nm/0.27, second container 717 nm/0.21, and third container 262 nm/0.31. The outcomes were par with or even superior to those attained using the traditional approach. If the HSS procedure is further improved, it may become even more effective than standard high pressure homogenization(22).

Yang Liu, Leaf Huang, and Feng Liu discussed that we just proposed a PTX nanocrystal preparation that overcomes multidrug resistance (MDR) to cancer treatment utilising D-R-tocopheryl polyethylene glycol 1000 succinate (TPGS) as the only excipient. According to data we known, this is the primary investigation on PTX nanocrystals that can reverse MDR. The P-gp inhibitor TPGS also aids in stabilising the nanocrystals and reversing MDR. We used transmission electron microscopy to examine the size and form of nanocrystals, and powder X-ray diffraction to examine the crystalline structure. The clinical paclitaxel formulation, Taxol, had a worse drug release profile. We also examined the nanocrystals' cytotoxicity and anticancer properties in xenograft models. With the use of apoptotic tests, we discovered that PTX/TPGS nanocrystals had a more notable therapeutic impact which as resistant of Taxol to the cancer cell in presents of in vivo and in vitro reading. This kind of nanocrystal may offer a fresh approach to medication delivery and the management of drug resistance(23).

Yao Liua, Wei Liua, Sha Xionga, Jingshan Luoa, Ye Lic, Yuying Zhaoa, Qun Wanga, Zexin Zhangd, Xiaojia Chenb,□, Tongkai Chena,□ discussed that parkinson's disease, this is a significant contributor to neurodegeneration in older individuals, has been getting a lot of attention lately. The disease is caused by a decrease in dopamine-producing neurons, making it difficult to deliver anti-PD drugs orally because of their minimal exposure and flow of medications characteristics of the neurons. In order to efficiently concentrate Ginkgolide B (GB), a potent anti-Parkinsonism chemical, in the blood and brain, nanocrystals were utilised to speed up the dissolution rate and solubility of GB. The nanocrystals were tiny, dispersed fast, improved cellular absorption, and exhibited no toxicity in zebrafish. They also protected neurons from MPP+-induced toxicity. According to fluorescent imaging, the zebrafish's brain and stomach both contained NCs. Rats administered the GB-NCs had greater plasma levels and improved drug dispersion in the neurones compared to the control groups. Finally, the GB-NCs therapy enhanced behavior, decreased dopamine deficit, as well as improves levels of dopamine metabolites in the MPTP-induced Parkinsonism model. GB-NCs are effective drug carriers for delivering anti-PD treatments to neurons, according to this study's findings in its entirety(24).

2. CONCLUSION

It's clear that solubility isn't the only important thing here. Greater solubility and dissolution velocity improve bioavailability of medicines with a limited therapeutic window. Additionally, the necessity for potentially harmful surfactants is eliminated with nanocrystal technology. Additionally, nanoparticles have a rapid commencement of action, which is particularly advantageous for medications that must start working rapidly. Additionally, nanocrystals allow for the administration of lower dosages, minimizing adverse side effects. High drug nanocrystal load tablets can take a while to produce, and more effective methods are required. More medications will become poorly soluble in the future, and nanocrystal technology will play a crucial role in making these pharmaceuticals soluble and accessible. Additionally, it will be feasible to alter the surface of the nanocrystals to create a sustained or focused release.

Acknowledgement
We thank the Department of Pharmaceutics for the unrestricted participation and assistance with the data gathering procedure. My guide deserves special

recognition for the unwavering moral support and inspiration.

Funding: Nil
Authors Contributions: All the authors contributed equally.
Consent for Publication: Not applicable.
Conflict of Interests: Declared none

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