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AN OVERVIEW ON NANOCRYSTAL TECHNOLOGY AND DRUG DELIVERY SYSTEM

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ABSTRACT

Nanotechnology in pharmaceuticals has pioneered the way for disease detection and therapies. Its ramifications in the field of health care are becoming recognized, as it allows for faster and less expensive treatments. It is possible to achieve efficient drug targeting and movement through barriers using nanotechnology. Scientists must resolve several serious issues such as safety, bioethical issues, toxicity hazards, and physiological and pharmacological challenges. In conclusion, regulators should develop clear criteria to reduce/balance the risks associated with therapeutic outcomes. The purpose of this brief review is to provide detailed illustrations on innovative applications, Nanocrystal Preparation methods, Evaluation criteria, and Nanogel Advantages and Disadvantages.

Keywords *– Nanogel, Nanocrystals, Nanotechnology, Evaluation.*

1. INTRODUCTION

Nanoscience has recently begun to rapidly increase and become incredibly important in all sectors of modern science, resulting in improvements in human health, opportunities for profit, and incredible changes in living standards and well–being. Nanotechnology's application in a variety of therapeutic areas has transformed the field of medicine, in which nanoscale particles with dimensions ranging from 1 to 100nm are designed as biomedical research tools. [1-3] Nanomedicine and nano delivery systems are a young but rapidly growing discipline in which small materials are employed as diagnostic tools or to deliver therapeutic drugs to specific sites in a controlled manner. [4]

2. NANOCRYSTAL FORMULATION

Nanocrystals were initially developed in the ninth and tenth centuries, and despite their high efficacy, their commercial availability is limited. Because of the rising number of poorly soluble medications in the drug development process, safe formulation, and pharmacoeconomic value, nano- crystal pharmaceuticals have received attention as a difficult strategy. Pharmaceutical companies

can potentially benefit from nanocrystal technology by possibly reworking a product line of an existing formulation. Nanocrystals were originally presented in the nineteenth century, and despite their excellent efficacy, their commercial availability is limited. Because of a rising number of poorly soluble medications in the drug development process, safe formulation, and pharmaco-economic value, nanocrystal pharmaceuticals have attracted attention as a difficult method. Pharmaceutical companies can potentially benefit from nanocrystal technology by possibly reworking a product line of an existing formulation.

Nanocrystals were first postulated in the nineteenth century, and their commercial availability is limited despite their high efficacy. Nano- crystal medicines have attracted attention as a difficult technique due to the increased number of poorly soluble medications in the drug development process, safe formulation, and pharmacoeconomic value. Pharmaceutical firms may be able to gain from nanocrystal technology by redesigning an existing formulation's product range.

Nanocrystals are atom aggregates that form a "cluster" and are smaller than one metre. The average size is between 10 and 400 nanometre's. Physically and chemically, they are between bulk solids and molecules. The effective surface area of a particle increases as its size decreases, enhancing solubility and bioavailability. Sustained pharmaceutical release can be achieved with a lower dose to the patient. Nanocrystals can be made using both top-down and bottom-up methods. Pearl/ball milling, high-pressure homogenization, microfluidizer technology, piston gap homogenization, and spray drying are examples of bottom-up procedures, whereas high-pressure homogenization, microfluidizer technology, piston gap homogenization, and spray drying are examples of top-down procedures. Improved dissolving properties in nanocrystal-loaded solid dosage forms may help to increase the bioavailability of poorly soluble drugs in patients.

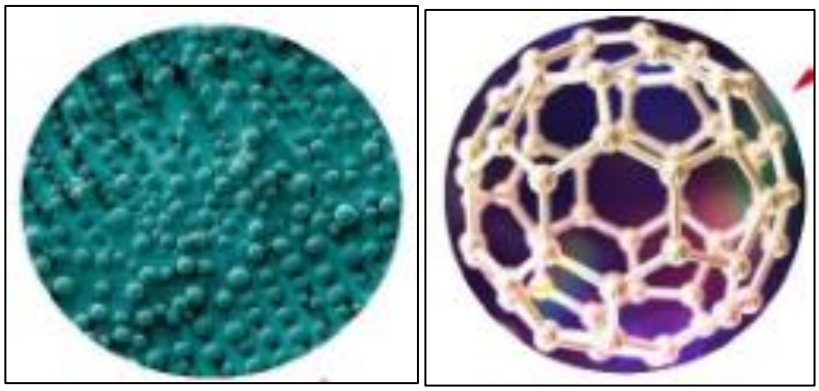

Fig.1. Structure of nanocrystal and nanoparticle

Aloe vera is the subject of numerous research to demonstrate its antiviral, antibacterial, and other effects as a pain reliever, anti-inflammatory, and wound healing agent. Aloe vera is one of the plants that has antibacterial properties. In fruits like oranges, grapes, sweet cherries, and papaya, Aloe vera gel is used as an edible coating material because research has shown that it has antifungal and antimicrobial activity, which can prevent moisture loss and firmness loss, control respiratory rate and maturation development, delay oxidative browning, and reduce microorganism proliferation. [6]

3. METHODS OF NANOCRYSTAL PREPARATION

The methods for producing nanosized particles, such as direct crystallisation employing high supersaturation (bottom-up methodology), particle breaking (top-down technique), and crystallisation in a confined environment, are briefly discussed in this Review (bottom-up technique).

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Direct crystallisation using supersaturation (bottom-up technique), particle breakdown (top-down technique), and crystallisation in a confined environment are among the ways outlined in this work for creating nanoparticles. [8]

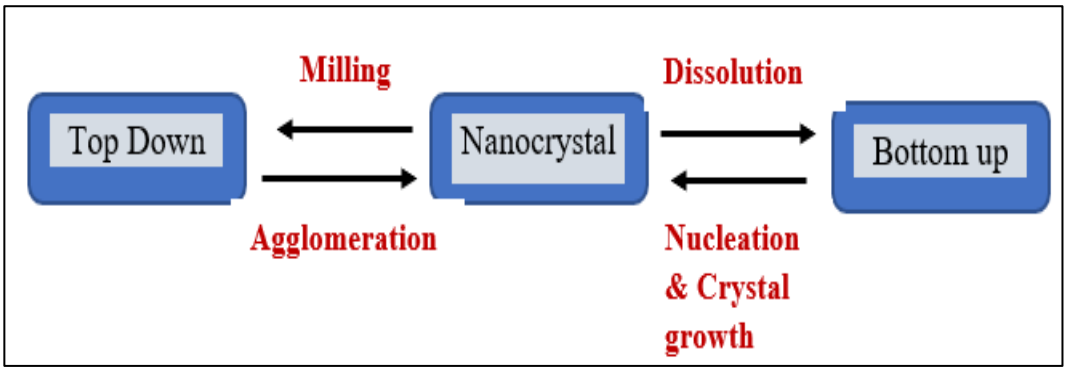

Fig. 2. Nanocrystal method of preparation.

i. Top-down Approach

ii. Bottom-up technique

- Control Flow Cavitation (CFC)
- Spray Drying
- Supercritical Fluid
- Impinging Gel crystallization
- Emulsion Method
- Patterned microwell and gold islands.
- Microfluidics Devices
- Nanocrystals preparation using nonporous particles.

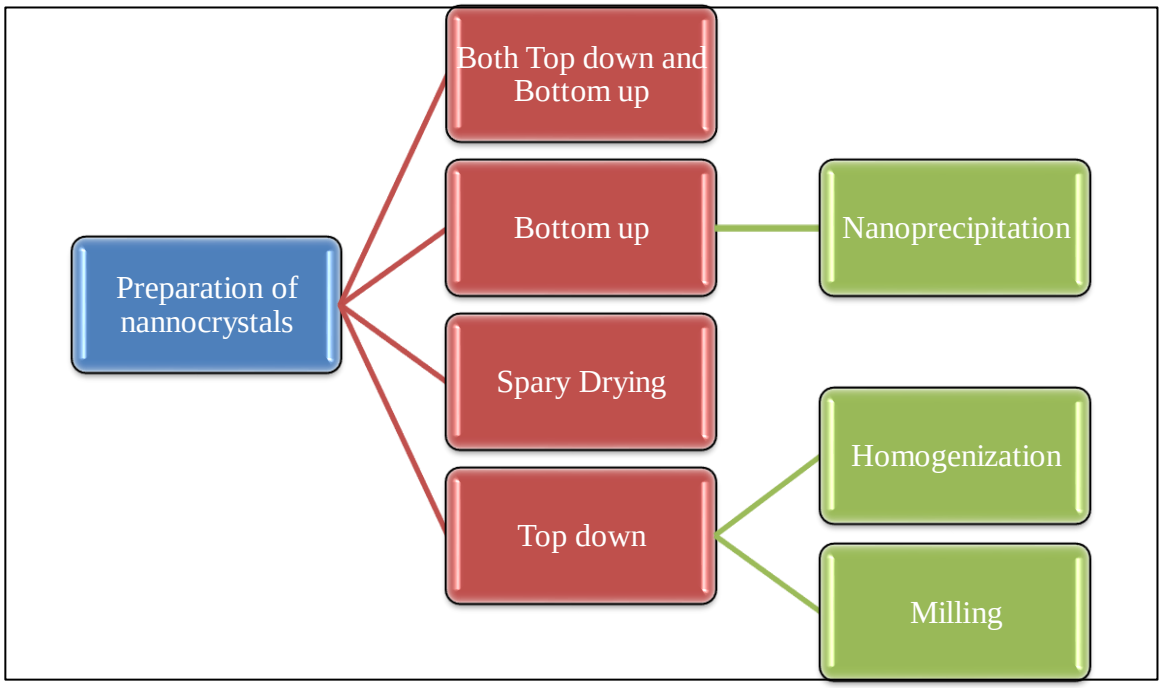

Fig. 3. A schematic illustration of the preparation method of nanocrystals

4. TYPES OF NANOCRYSTAL FORMULATION USED TOPICALLY

When applied topically, many forms of nano-formulations are employed to improve the efficacy and activity of the API. [10]

- **Nanogel:** Many medications have trouble permeating the skin due to the skin's barrier function and the pharmaceuticals' non-optimal physicochemical properties, necessitating the development of novel drug delivery systems. Nanocrystal-based formulations for topical medication administration have recently been studied and found to have better skin penetration. [11]
- **Nano emulsion:** Nano-emulsions/Sub-micron emulsions (SMEs)/Mini-emulsions: Nano-emulsions/Sub-micron emulsions (SMEs)/Mini-emulsions are thermodynamically stable transparent or translucent oil-water dispersions stabilised by an interfacial coating of surfactant and cosurfactant molecules with globule sizes less than 100 nm. Nano emulsions are being used to administer vaccinations, DNA-encoded pharmaceuticals, antibiotics, cosmetics, and topical medications through a range of routes, including oral, pulmonary, intranasal and ophthalmic, and transdermal. [12,13]

- **Hydrogels:** Hydrogels are a three-dimensional (3D) network of hydrophilic polymers that can expand and store a large amount of water while maintaining structural integrity due to chemical or physical cross-linking of individual polymer chains. [14]

- **TDDS Nanocrystals:** TDDS Nanocrystals: The skin's stratum corneum serves as a good barrier, preventing most drugs from penetrating the epidermis and making passage difficult. Fortunately, several non-invasive approaches can boost drug penetration across this barrier significantly. Nanocarriers have emerged as a viable and intriguing option for broadening the

range of drugs that can be administered transdermal. A variety of nanocarriers can carry lipophilic and hydrophilic drugs through the stratum corneum, with the potential for local or systemic effects to treat a number of illnesses. [15]

- **Carbon-Based Nanoparticles:** Fullerenes, carbon nanotubes, graphene and its derivatives, graphene oxide, nanodiamonds, and carbon-based quantum dots are all carbon-based nanomaterials. Because of their odd structural dimensions and remarkable mechanical, electrical, thermal, optical, and chemical capabilities, these materials have attracted interest in a range of sectors, including biomedical applications. Among them include cell and tissue imaging, as well as therapeutic molecule delivery for disease treatment and tissue healing. Because of their broad one-photon property, biocompatibility, and ease of functionalization, carbon-based nanomaterials have been identified as possible imaging agents for tumour diagnostics. The intrinsic two-photon fluorescence feature of carbon-based nanomaterials in the long wavelength range (near-infrared II) enables for deep-tissue optical imaging. [16]
- **Polymeric nanoparticles: S**mall particles having a diameter of 1 to 1000 nm that can be loaded with active chemicals or surface-adsorbed onto the polymeric core are known as polymeric nanoparticles (NPs). Nanocapsules and nanospheres, which have different morphological structures, are both referred to as "nanoparticles." Polymeric NPs have shown a lot of promise in terms of delivering drugs to precise regions for the treatment of a range of diseases. [17]

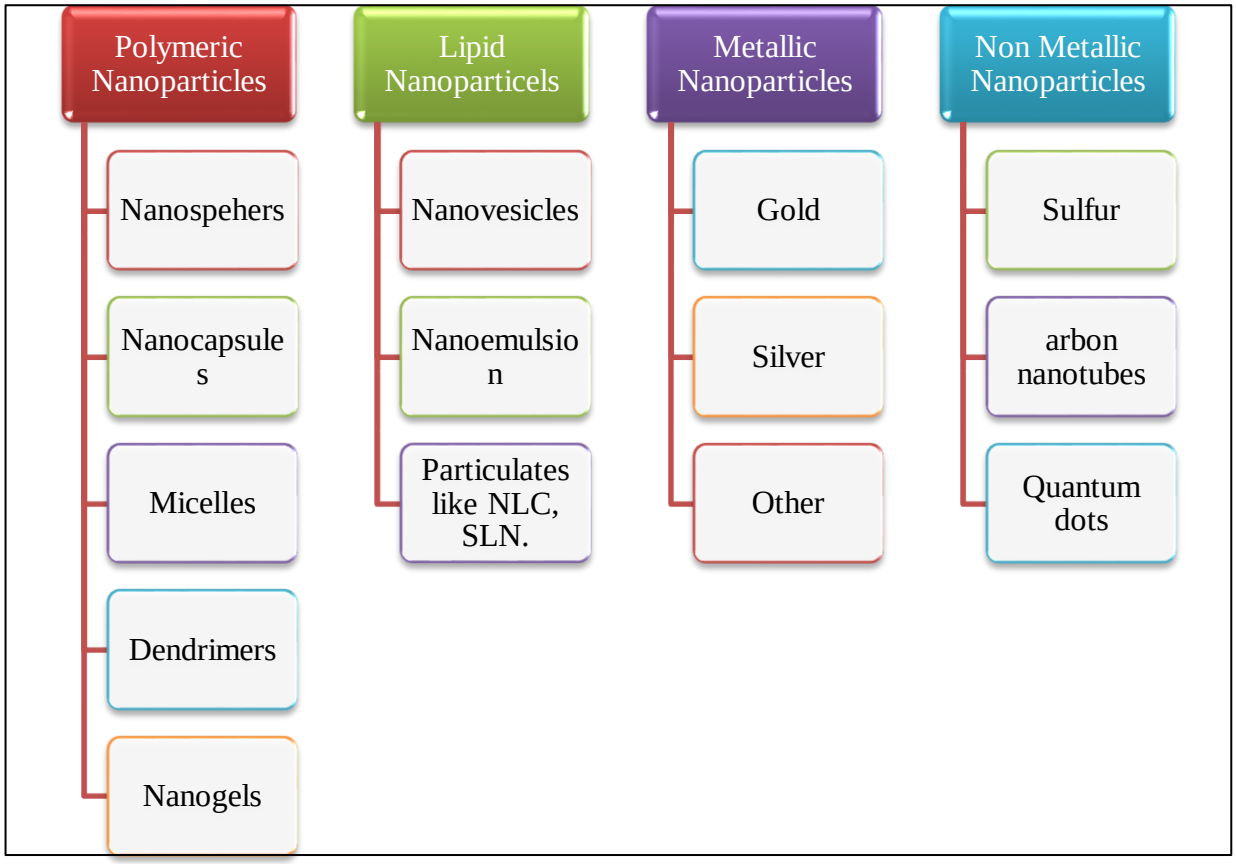

Fig. 4. Various types of nanoparticles

Many techniques for addressing the bioavailability limitations of poorly soluble medications have been developed over time. As a result of recent developments in nanotechnology, science and business have been approaching this issue by formulating pharmaceuticals as nanocrystals, which contain "pure drugs and a minimal of surface-active chemicals essential for stability."

According to their definition, "carrier-free submicron colloidal drug delivery systems with a mean particle size in the nanometer range, typically between 10–800 nm." The main advantage of these nanoparticles was that they lowered particle size to nanoscale dimensions, which increased particle surface area in contact with the dissolving media and hence increased bioavailability. This method has proven to be effective, as seen by the enormous number of such pharmaceutical goods. Despite the fact that nanocrystals are a "carrier-free" system, surface active compounds are needed to prevent colloidal particles from aggregating and enhancing stability. Furthermore, in recent years, nanocrystal characteristics and technologies have aroused researchers' interest as a technique of generating colloidal particles with altered biological properties, and their focus is now geared toward changing medicine delivery and targeting. [18]

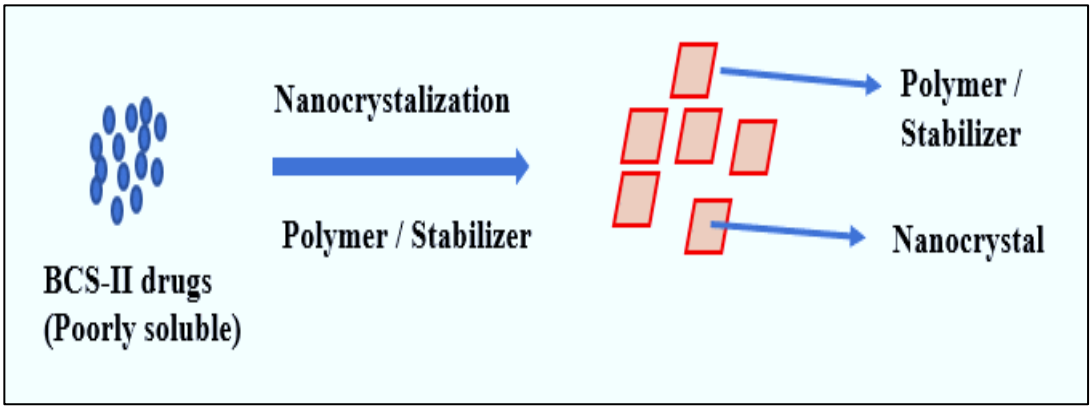

Fig. 5. A schematic diagram of the process of nanocrystalization of poorly soluble drugs that improves their physicochemical properties.

Table - 1. Physiochemical properties of NCs

Physiochemical Properties	**Advantages**	**Disadvantages**
Permeability	Increasing permeation across the skin	Drug release rate is limiting factor
Saturation Solubility	Increased saturation solubility then conventional particles	Not Applicable
Stability	Increased physical stability due to stabiliser	• Problem related to long term stability • Sedimentation and compaction
Dissolution Rate	Increased dissolution and bioavailability	Nanocrystals that are shrinked due to size.
Adhesiveness	Increased adhesiveness	Not Applicable

5. EVALUATION PARAMETERS OF NANOCRYSTALS:

The following parameters discussed in the section below.

5.1 X-ray diffraction (XRD):

Nanocrystals' morphology and crystalline state can be used to investigate morphological and polymorphism changes. To assess the crystallinity of pharmaceuticals, the X-ray diffraction (XRD) technique is often utilised. The change in polymorphic state was used to confirm the formulation of the nanocrystal. The X-ray diffraction patterns of the crystalline compounds are compared to the pure sample. Each crystalline substance has its own pattern, which is reflected in the resulting mixture. The distinctive fingerprint of a substance is represented by its X-ray diffraction pattern.

5.2 Morphological Examination:

SEM and TEM are electron microscopic techniques used to examine the shape, size, and morphology of NCs. A wet sample of sufficient concentration is required for TEM study, but the resultant nanosuspension must be turned into dried powder via lyophilization or spray drying for SEM investigation, resulting in agglomeration. Mannitol is often employed as a cryoprotectant to prevent particle agglomeration and contact during the lyophilization process. Agglomeration is accepted in the final particle up to a certain point in the permissible range. [21,22]

5.3 Thermal Analysis:

Differential scanning calorimetry is one of the most essential technologies for understanding the thermal behaviour of drug nanocrystals (DSC). To test the thermal behaviour, the drug crystallinity and the production of nanocrystals with excipients are compared. For drugs that exist in a range of polymorphic forms, this research is crucial. Many top-down procedures, such as high-pressure homogenization, result in amorphous particles, which increase saturation solubility. DSC can be divided into two types based on their operation mechanisms: heat-flux DSC and power-compensated DSC. [23,24]

5.4 Raman Spectroscopy:

Raman spectroscopy is a technique that uses the inelastic scattering of monochromatic light from a laser source. In inelastic scattering, the frequency of photons in monochromatic light changes due to interaction with the sample. It is used to determine the crystalline or amorphous portions of nanostructured materials by characterizing phase transitions and phases of many types of nanoparticles and other nanomaterials (e.g., nanocrystal). It's also used to figure out whether nanomaterials have faults, their size and shape, and whether nanostructured materials are homogeneous or heterogeneous. Only a few of the applications include fundamental structural studies, drug excipient compatibility research, formulation characterization, quantitative analysis, and surface modification in nano formulation. [25]

5.5 FT-IR Spectroscopy:

The FT-IR method is used to evaluate a drug's chemical characteristics as well as its interactions with different excipients. Spray-dried curcumin powders for pulmonary drug delivery were produced and evaluated by Liandong and his colleagues. FT-IR spectroscopy investigations of curcumin nanocrystal and the generated spray dry powder of curcumin nanocrystal were

conducted to investigate the change in chemical properties and crystalline structure. Based on the position of the peaks in the formulation compared to the pure drug, the data showed that milling and spray drying the product had no effect on the chemical property of curcumin as in spray-dried powder. [25]

5.6 Particle Size and Polydispersity Index:

Particle size and distribution influence other characteristics such as dissolving rate, saturation solubility, physical stability, and therapeutic efficacy. The surface energy of smaller particles is higher, which favors particle aggregation. The most frequent techniques for detecting particle size include microscopy, static light scattering techniques, and dynamic light scattering techniques [26].

5.7 Particle Surface Charge:

The particle surface charge has an impact on physical stability. There is more electrostatic repulsion between charged particles when there are more of them, which leads to improved physical stability. The particle surface charge is estimated using the zeta potential, which is determined by particle electrophoretic mobility in an electric field. The particle surface charge is determined using the colloid titration. Surface function-al group dissociation, commonly known as the Nernst potential, causes particle surface charge. The degree of functional group dissociation is determined by the pH of the suspension; consequently, the pH of the suspension or media determines the zeta potential. [25]

5.8 Permeation Study:

The enhanced dissolution and saturation solubility of nanocrystals also suggest improved skin adherence and medication delivery across the skin membrane. Nanocrystals of the correct size (about 700 nm) can easily deposit and operate as a depot inside such shunts. The chemical can pass through and diffuse into the surrounding cells for long-term release. For the formulation of the poorly soluble medicament for cutaneous distribution, factors such as particle size, transporters, and stabilizer interactions are considered.

5.9 Dissolution:

The thermodynamic supersaturated state and apparent solubility represent the most stable crystalline form of the drug in each medium at a given temperature and pressure. This increased solubility is described using several terms such as apparent or kinetic solubility. Because the apparent solubility of nanosized particles is greater than the thermodynamic solubility of the substance, dissolution of nanocrystalline material produces a supersaturated solution. This phenomenon is known as the "spring effect." [26]

6. NANOCRYSTAL APPLICATIONS

Nanocrystals have been used in a variety of ways in pharmaceutical drug delivery systems. As shown schematically in Fig. 06, the sections below go over the different applications of nanocrystals in depth.

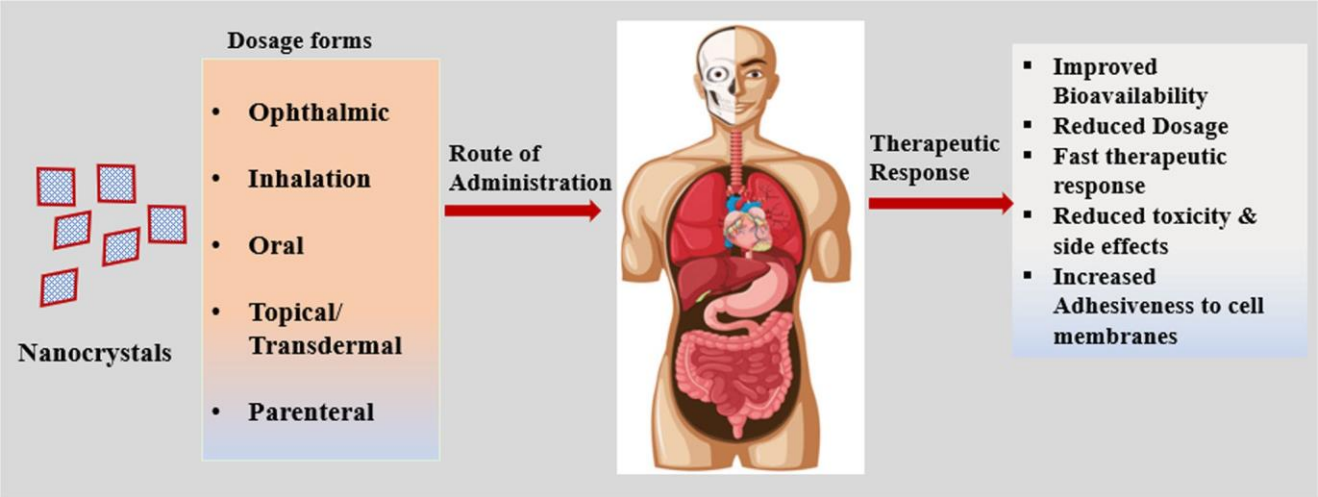

Fig. 6. A schematic illustration related to the application of nanocrystals via various routes

Drug administration to the skin has been demonstrated to be effective for local therapy in the treatment of a variety of dermatological conditions, including fungal infection. The fundamental challenge that topical antifungal drugs encounter is their ability to reach the required layers of the skin via the stratum corneum, the first layer of the skin, for a highly effective and successful therapy.

Aloe vera is a major natural gel technique since manufactured gels have so many negative consequences when compared to natural gels. Aloe vera is a medical plant with antifungal properties, and aloe vera gel extract has a better absorption rate than other commercially available gels. Aloe gel also promotes wound healing and cell growth, and the complete extract of the plant contains antifungal and antibacterial properties. The aloe vera extract has been engineered to be extremely resistant to a variety of bacterial and fungal diseases.

Drug nanocrystals are crystalline nanoparticles that are completely drug-free. Because of the porosity in the gel matrix, the hydrogels are also crosslinked in a three-dimensional configuration, which has the advantage of allowing the loading of hydrophobic or hydrophilic medications. Formulation preparation as nanocrystal aloe gel enhances bioavailability and skin penetration by increasing solubility and prolonging retention at the site of action.

Nanocrystals applied topically have a synergistic effect, creating depots in hair follicles and boosting penetration. The enhanced penetration is due to the nanocrystals' higher saturation solubility. As a result, using natural aloe gel instead of synthetic hydrogel with nanocrystals, rather than coarse drug-containing gel, could be a new technique for medicines with limited aqueous solubility with increased therapeutic efficacy and broader cutaneous distribution.

7. EVALUATION OF GEL

pH:

A 1.0 g gel was properly weighed and dispersed in 100 mL filtered water. A digital pH metre that had been calibrated with a standard buffer solution at 4.0, 7.0, and 9.0 before usage was used to determine the pH of the dispersion. Three pH readings were collected, and the average values were calculated.

Spreadability:

One of the prerequisites for a topical formulation to meet the optimum characteristics is that it spreads well. When applied to the skin or an affected portion, it's a term that describes the area across which a formulation distributes quickly. The medical efficacy of a formulation is also affected by its spreading value. A 0.5 g of gel was placed within a 1 cm diameter circle pre-marked on a 20 20 cm glass plate, which was then covered with a second glass plate to assess the spreadability of the formulation. A weight of 500 g was allowed to lie on the upper glass plate for 5 minutes. As a result of the spreading, the gel's diameter rose.

Extrudability:

To test extrudability, a closed collapsible tube containing the formulation was firmly squeezed at the crimped end. When the cap was removed, the formulation extruded and the pressure dissipated. The weight in grammes necessary to extrude a 0.5 cm ribbon of the formulation in 10 seconds was estimated. In grammes, the average extrusion pressure was measured.

Viscosity:

The viscosity of the formulations without dilution was assessed using the R/S CPS Plus Rheometer (Brookfield Engineering Laboratories, Inc., Middleboro, MA, USA) with spindle #C 50-1 and software RHEO3000.

Homogeneity:

The created formulations were visually evaluated for homogeneity after the gel was placed in the container. They were inspected for the presence of aggregates and the appearance of aggregates.

8. NANOCRYSTAL ALOE GEL

- Nanocrystal Aloe gel enhances mechanical strength and modulates medicine release therapy.
- Aloe vera possesses antifungal, antibacterial, and hypoglycemic properties.
- It strengthened antifungal action and increased cutaneous delivery for drugs with weak water solubility because aloe vera gel penetrates directly into the deeper layers of the skin, allowing it to fight, decrease, control, or eliminate infections.
- Aloegel from NC improves drug penetration and skin retention at infection sites.
- To boost the absorption of poorly soluble medications, improved cell membrane adherence is required. [27]

9. DISADVANTAGES OF NANOCRYSTALS

- Nanocrystals have a limited stability, and because this process involves crystallisation, some medications or medicinal chemicals may be difficult to crystallise.
- Increasing the risk of systemic absorption and negative consequences
- Incompatible with drugs that are soluble in water. [28]

10. CONCLUSION

Other methods for increasing the rate of dissolution, solubility, permeability, and oral bioavailability of poorly soluble drug particles include solid dispersions, co-solvency, and particle reduction to submicron levels. The nanocrystal approach can meet these requirements while also providing a superior delivery system with fewer adverse effects than other traditional delivery techniques. The information on various qualities, characterization methodologies, and pharmaceutical uses in drug delivery systems is summarized in this paper.

11. ACKNOWLEDGEMENT

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12. CONFLICT OF INTEREST

Authors have no conflicts of interest to disclose.

REFERENCES

1. Roy I, Ohulchanskyy TY, Pudavar HE, et al. Ceramic–based nano particles entrapping water–insoluble photosensitizing anticancer drugs: a novel drug–carrier system for photodynamic therapy. J Am Chem Soc. 2003;125(26):7860–7865.
2. Samuel I, Mihail C Roco, William Sims Bainbridge. Societal Implications of Nano–science and Nano–technology. Stupp Northwestern University Materials and Life Sciences Building 2225 N, Campus Drive Evanston, IL 60208. 2001. p. 1–280.
3. Sarfaraz S, Bano T, Fatima W. Nanotechnology and it's therapeutic application-a review. MOJ Bioequiv Availab. 2018;5(1):24-27. DOI: 10.15406/mojbb.2018.05.00077.
4. Patra, J. K., Das, G., Fraceto, L. F., Campos, E., Rodriguez-Torres, M., Acosta-Torres, L. S., Diaz-Torres, L. A., Grillo, R., Swamy, M. K., Sharma, S., Habtemariam, S., & Shin, H. S. (2018). Nano based drug delivery systems: recent developments and future prospects. Journal of nanobiotechnology, 16(1), 71. https://doi.org/10.1186/s12951-018-0392-8.
5. Vivek P. Chavda, Chapter 4 - Nanobased Nano Drug Delivery: A Comprehensive Review, Editor(s): Shyam S. Mohapatra, Shivendu Ranjan, Nandita Dasgupta, Raghvendra Kumar Mishra, Sabu Thomas, In Micro and Nano Technologies, Applications of Targeted Nano Drugs and Delivery Systems, Elsevier, 2019, Pages 69-92, ISBN 9780128140291, https://doi.org/10.1016/B978-0-12-814029-1.00004-1.
6. Kumar, S., & Bhatnagar, T. (2014). Studies to Enhance the Shelf Life of Fruits Using Aloe Vera Based Herbal Coatings: A Review, 5, 211–218.

7. Nilesh S. Zarekar, Vishal J. Lingayat, and Vishal V. Pande, "Nanogel as a Novel Platform for Smart Drug Delivery System." Nanoscience and Nanotechnology Research, vol. 4, no. 1 (2017): 25-31.
8. Kulkarni, Samir & Myerson, Allan. (2017). Methods for Nano-Crystals Preparation. 10.1007/978-94-024-1117-1_16.
9. Salma A. Fereig, Ghada M. El-Zaafarany, Mona G. Arafa & Mona M. A. Abdel-Mottalab(2020), Tackling the various classes of nano-therapeutics employed in topical therapy of psoriasis, Drug Delivery, 27:1, 662-680.
10. Khan, Ibrahim, Khalid Saeed, and Idrees Khan. "Nanoparticles: Properties, applications and toxicities." Arabian Journal of Chemistry (2017).
11. Prashantkumar K. Parmar, Jhanvi Wadhawan, Arvind K. Bansal, Pharmaceutical nanocrystals: A promising approach for improved topical drug delivery, Drug Discovery Today, Volume 26, Issue 10, 2021, Pages 2329-2349, ISSN 1359-6446, https://doi.org/10.1016/j.drudis.2021.07.010.
12. Thakur Nishi, GargGarima, Sharma P.K. and Kumar Nitin. Nanoemulsions: A Review on Various Pharmaceutical ApplicationsGlobal Journal of Pharmacology. 2012;6 (3): 222-225
13. Savardekar, P., & Bajaj, A. (2016). Nanoemulsions-a review. Inter J Res Pharm and Chem, 6, 312-322.
14. Bahram, M., Mohseni, N., & Moghtader, M. (2016). An Introduction to Hydrogels and Some Recent Applications. In (Ed.), Emerging Concepts in Analysis and Applications of Hydrogels. IntechOpen. https://doi.org/10.5772/64301.
15. Yu Yi-Qun, Yang Xue, Wu Xiao-Fang, Fan Yi-Bin, TITLE=Enhancing Permeation of Drug Molecules Across the Skin via Delivery in Nanocarriers: Novel Strategies for Effective Transdermal Applications. JOURNAL=Frontiers in Bioengineering and Biotechnology, VOLUME=9, YEAR=2021.
16. Patel, K. D., Singh, R. K., & Kim, H. W. (2019). Carbon-based nanomaterials as an emerging platform for theranostics. Materials Horizons, 6(3), 434-469.
17. Zielińska, A., Carreiró, F., Oliveira, A. M., Neves, A., Pires, B., Venkatesh, D. N., Durazzo, A., Lucarini, M., Eder, P., Silva, A. M., Santini, A., & Souto, E. B. (2020). Polymeric Nanoparticles: Production, Characterization, Toxicology and Ecotoxicology. Molecules (Basel, Switzerland), 25(16), 3731. https://doi.org/10.3390/molecules25163731.
18. Gigliobianco, M. R., Casadidio, C., Censi, R., & Di Martino, P. (2018). Nanocrystals of Poorly Soluble Drugs: Drug Bioavailability and Physicochemical Stability. Pharmaceutics, 10(3), 134. https://doi.org/10.3390/pharmaceutics10030134
19. Young TJ, Mawson S, Johnston KP, Henriksen IB, Pace GW, Mishra AK. Rapid expansion from supercritical to aqueous solution to produce submicron suspensions of water-insoluble drugs. Biotechnology Prog. 2000;16(3):402–7.
20. Mottaleb (2020) Tackling the various classes of nano-therapeutics employed in topical therapy of psoriasis, Drug Delivery, 27:1, 662-680.
21. Song K, Zhu X, Zhu W, Xiaoyan Li X. Preparation and character- ization of cellulose nanocrystal extracted from Calotropis procera biomass. Bioresour Bioprocess. 2019;6(45):1–8.
22. Danley R. New heat flux DSC measurement technique. Thermochim Acta. 2002; 395:201–8.
23. Zucca N, Erriu G, Onnis S, Longoni A. An analytical expression of the output of a power compensated DSC in a wide temperature range. Thermochim Acta. 2002; 143:117–25.
24. Gao L, Zhang D, Chen M. Drug nanocrystals for the formulation of poorly soluble drugs and its application as a potential drug delivery system. J Nanopart Res. 2008; 10:845–62.
25. Li YS, Church JS. Raman spectroscopy in the analysis of food and pharmaceutical nanomaterials. J Food Drug Anal. 2014; 22:29–48.

26. Schnitte M, Staiger A, Casper LA, Mecking S. Uniform shape monodisperse single chain nanocrystals by living aqueous catalytic polymerization. Nat Commun. 2019;10(2592):1–6.
27. Rabinow B. Nanosuspensions in drug delivery. Nat Rev Drug Discov. 2004; 3:785–96.
28. Khan, A. W., Kotta, S., Ansari, S. H., Sharma, R. K., Kumar, A., & Ali, J. (2013). Formulation development, optimization and evaluation of aloe vera gel for wound healing. *Pharmacognosy magazine*, *9*(Suppl 1), S6–S10. https://doi.org/10.4103/0973-1296.117849.