INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD)
© 2026 IJNRD | Volume 11, Issue 7, July 2026 | ISSN: 2456-4184 | IJNRD.ORG

A REVIEW ON NANOSIZED DRUG CRYSTALS

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ABSTRACT:

The barrier function of skin and the non-optimal physicochemical properties of drugs present challenges to the skin penetration of many drugs, thus motivating the development of novel drug delivery systems. Recently, nanocrystal-based formulations have been investigated for topical drug delivery and have demonstrated improved skin penetration. This review highlights barriers in skin penetration, current techniques to improve topical delivery and application of nanocrystals in conquering obstacles for topical delivery. Nanocrystals can improve delivery through the skin by mechanisms including the creation of a higher concentration gradient across skin resulting in increased passive diffusion, hair follicle targeting, formation of diffusional corona, and adhesion to skin.

KEYWORDS:

Nanocrystals, Nanosuspensions, Nanocrystal-based formulations ,Topical drug delivery

1)INTRODUCTION:

Topical drug delivery is defined as the delivery of a drug to a particular location in the skin to exert local therapeutic action and minimal systemic absorption. In addition, it overcomes the limitations of oral and/or parenteral routes. By contrast, transdermal drug delivery involves the diffusion of the drug across the various skin layers in order to exert a systemic effect [1] Nanocrystals are nanoscopic crystals of a parent drug, of sub-micron particle size (100–1000 nm), that facilitate the efficient transport of the drug into or in between the cells [2] [3]

NCs are nanosized drug particles, and the process of nanocrystallization is used to improve the aqueous solubility and bioavailability of poorly water-soluble drugs [4]. NCs are entirely made up of drug particles with sizes below 1000 nm, which are conventionally produced either through top-down or bottom-up approaches. Physicochemical properties are altered due to the smaller particle sizes, which further results in increased kinetic solubility.

Moreover, an increase in the particle curvature of NCs results in elevated dissolution pressure, which eventually raises solubility [5].In this review, major challenges in DDD across the skin barrier, mechanism of action of dermal NCs, advantages of using NCs in enhancing DDD, NC preparation methods, and applications of NCs in the treatment of various skin disorders have been discussed. Nanocrystals are nanoscopic crystals of a parent drug, of sub-micron particle size (100–1000 nm), that facilitate the efficient transport of the drug into or in between the cells [6], [7]

Several researchers have investigated the application of nanocrystals for topical delivery and have observed their potential in improving skin penetration. A limited number of reports have described the potential for the use of nanocrystals to improve topical delivery [8], [9], [10]. Nanocrystal-based cosmetic products that contain poorly soluble antioxidants such as ‘Juvedical® age-decoder cream’ containing rutin by Juneva (St Margrethen, Switzerland) and ‘Cellular Serum Platinum Rare’ containing hesperidin by La Prairie (Zürich, Switzerland), and that offer anti-aging and skin protection properties were introduced in 2007 [11]]. The recent research indicates the good scope of nanocrystal-based formulations for topical delivery.

1.1PRINICIPLES BEHIND NANOCRYSTALS TECHNOLOGY:

The effectiveness of nanocrystals is based on several physicochemical principles:

a. Increased Surface Area

According to the Noyes–Whitney Equation, dissolution rate increases with surface area. Particle size reduction significantly enhances drug dissolution.

b. Increased Saturation Solubility

Small particles exhibit higher saturation solubility due to increased surface curvature and surface energy, described by the Ostwald–Freundlich Equation.

c. Enhanced Adhesion to Biological Membranes

Nanocrystals exhibit improved contact with biological surfaces, promoting drug absorption and permeation.

d. Enhanced Dissolution Rate

The dissolution rate is described by the Noyes–Whitney equation:

$$\frac{dC}{dt} = \frac{DA(C_s - C)}{h}$$

Where:

- D = diffusion coefficient
- A = surface area
- Cs = saturation solubility
- C = concentration at time t
- h = diffusion layer thickness

An increase in surface area (A) significantly enhances dissolution

1.2)CHARACTREZIATION OF NANOCRYSTAL:

a. Particle Size Analysis

Measured using:

- **Dynamic light scattering (DLS)**
- **Laser diffraction**

b. Zeta Potential

Evaluates surface charge and colloidal stability.

c. Morphology

Examined by:

- Scanning electron microscopy (SEM)
- Transmission electron microscopy (TEM)
- Atomic force microscopy (AFM)

d. Crystallinity

Analyzed using:

- X-ray diffraction (XRD)
- Differential scanning calorimetry (DSC)

e. Dissolution Studies

Determine enhancement in dissolution behavior compared with conventional formulations.

f. Saturation Solubility

Assesses the increase in apparent solubility resulting from nanosizing

1.3)STABILIZATION OF NANOCRYSTALS:

Nanocrystals possess high surface energy and tend to aggregate. Stabilizers are therefore essential.

COMMON STABILIZERS:

- Polyvinylpyrrolidone (PVP)
- Hydroxypropyl methylcellulose (HPMC)
- Poloxamers
- Tween 80
- Sodium dodecyl sulfate (SDS)

NATURAL STABILIZERS:

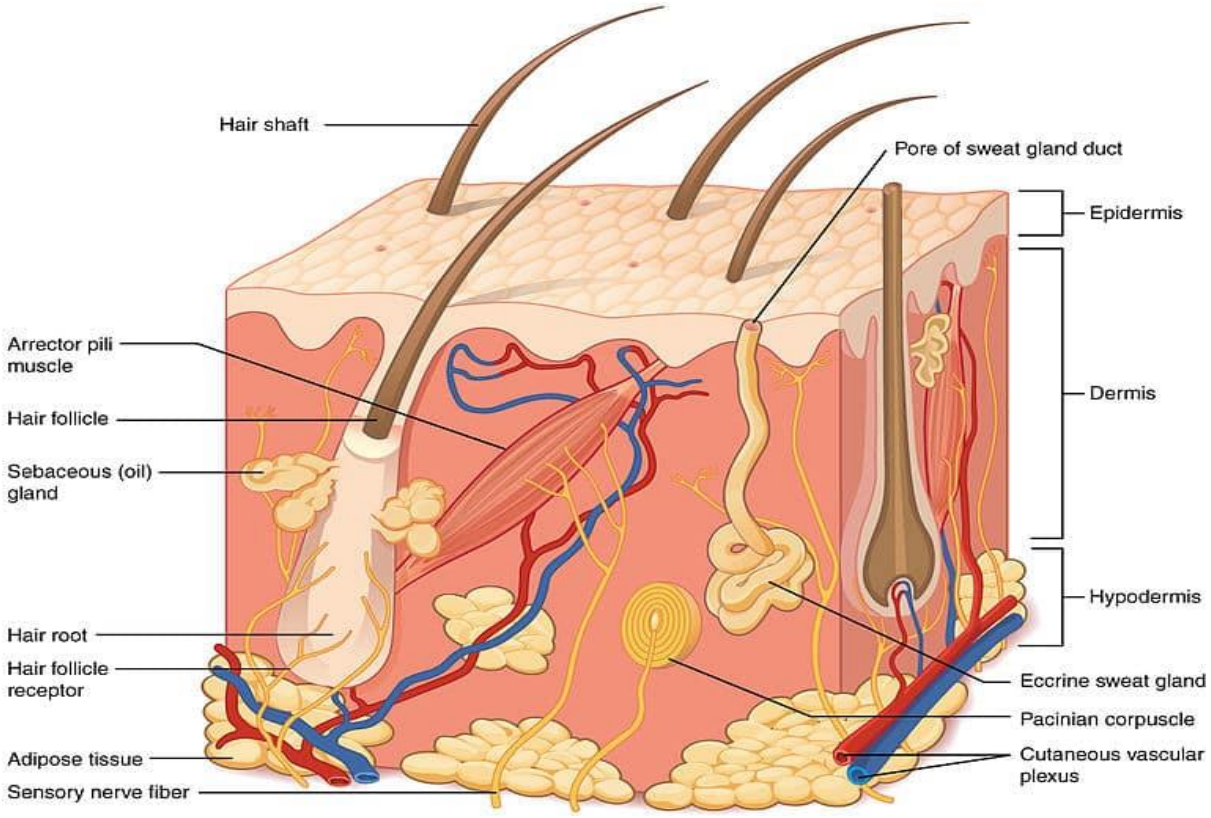
1. Steric stabilization
2. Electrostatic stabilization
3. Electrosteric stabilization

2)SECTION SNIPPETS

2.1. STRUCTURE AND PHYSIOLOGY OF THE SKIN:

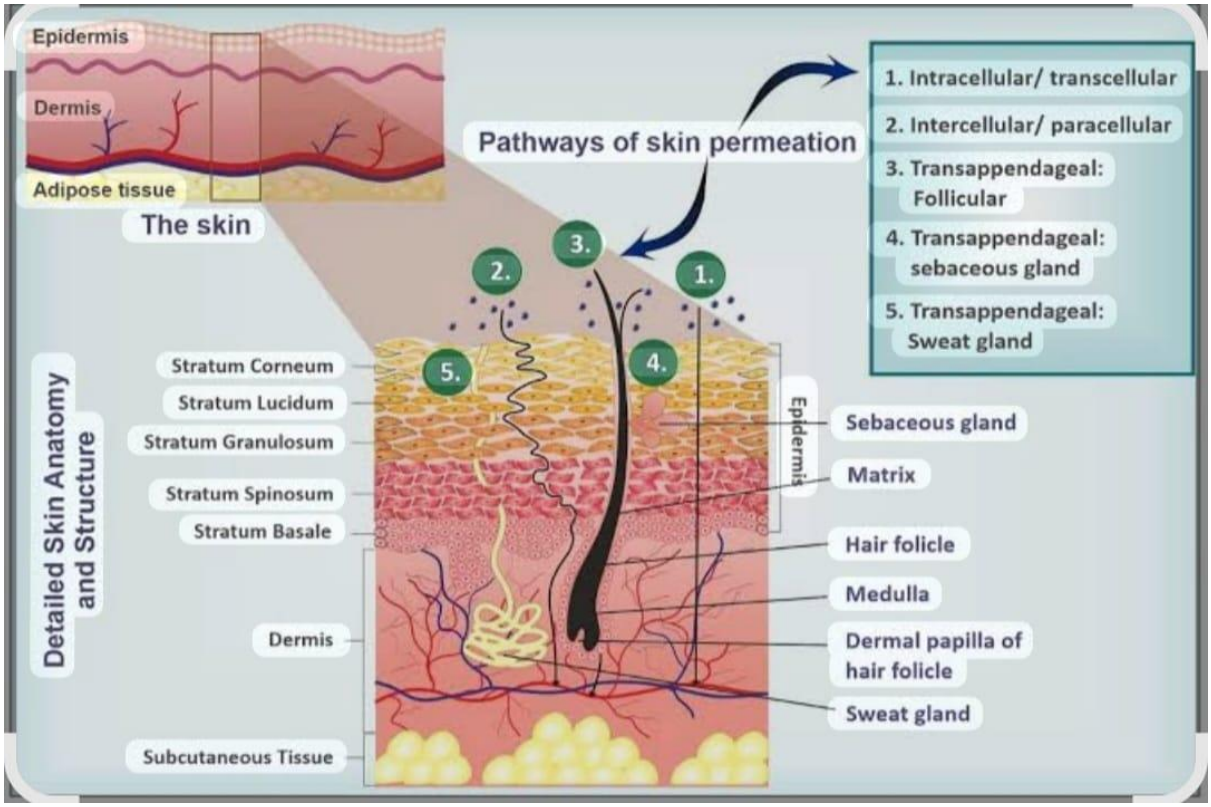
Skin is the largest organ of the body, covering a body area of nearly 1.8 m^2 and comprising 16% of total body weight [12]. It is composed of several layers that differ in their composition and structure. Starting from the deepest, the layers include the hypodermis, dermis and epidermis. The dermis is a hydrophilic layer that is irrigated by the blood circulation. It is composed of a gel in which a dense network of fibers (collagen and elastin) provides mechanical strength to the skin The skin is the largest organ of the human body, covering approximately 1.5–2.0 m^2 in an adult and accounting for about 15% of total body weight. It acts as a protective barrier between the body and the external environment while performing essential physiological functions such as thermoregulation, sensation, immune defense, and prevention of water loss.

STRUCTURE OF SKIN:



2.2) ROUTES OF DRUG PENTRATION AND CHALLENGES IN DERMAL DRUG DELIVERY:

Skin is the body's largest organ, which is composed of 16% of total body weight and covers around 1.8 m^2 of body area [13]. The skin has three different layers, including the epidermis, dermis, and hypodermis. The structure and composition of these layers are different [14]. The dermis layer is made of a dense network of fibers, including elastin and collagen. The drugs that reach the dermis later can also be passed into the systemic circulation. The outermost layer of skin is the epidermis, which is further divided into the viable epidermis (a living hydrophilic layer) and SC (a hydrophobic layer) [15]. SC is also known as a horny layer, which is composed of dead cells [16'17]. SC represents the utmost challenge for active drug penetration through the viable skin. SC is made of 15–20 layers of corneocytes entrenched in a lipid matrix, and this matrix is composed of cholesterol, free fatty acids, and ceramides. Since SC is located in the outermost layer of the epidermis, therefore this layer serves as a barrier that restricts the therapeutic efficacy of numerous drugs via serving as a barrier for drug molecules [18,19]. Drugs pass across these barriers through specific routes, including transcellular (intracellular), intercellular (paracellular), and transappendageal routes



Typically, lipophilic or hydrophobic molecules penetrate through the corneocytes via the transcellular route, while hydrophilic drugs preferentially penetrate through the SC via the intercellular route. On the other hand, drugs usually cross the skin appendages (including hair follicles, sebaceous glands, and sweat glands) through the transappendageal route [20,21]. Indeed, the uniquely intact skin structures play a role as a major barrier for most of the drugs.

3) NANOCRYSTALS (NCs):

NCs are nanoscale particles, and their sizes are below 1000 nm [22]. NCs are made up of drug particles only, which are stabilized by stabilizers and kept dispersed in order to avert their aggregations. The common

stabilizers that are used in the formulation of NCs include polymeric, non-ionic, and ionic stabilizers [23]. NC-based formulations can greatly enhance dissolution rate, drug release rate, surface adhesion, saturation solubility, and dermal bioavailability of the drug.

In DDD, physicochemical characteristics (including size, shape, and surface area) of nanostructured particles play an important role in regulating the skin permeation process It has been observed that anisotropic NC shapes, including nanowires or nanorods, have an elongated geometry that offers an outstanding benefit in crossing intercellular spaces of the SC [24]

Moreover, NCs provide numerous advantages, including greater therapeutic loading capacity, low excipient concentration, reproducibility, and facile method of preparation as compared to other nanocarriers, including ethosomes, niosomes, nanoemulsions, solid lipid nanoparticles, and polymeric nanoparticles. Limitations of lipid nanoparticles (such as solid lipid nanoparticles) include drug leakage and low entrapment efficiency because of their recrystallization tendency.

Liposomes were found to be ineffective in penetrating deeper skin layers and might rupture the skin during permeation. On the other hand, niosomes are not suitable for transdermal purposes. In addition, niosomes are expensive, and their manufacturing process is complex.

3.1)TOPICAL NANOCRYSTALS-BASED FORMULATION:

Topical formulation are classified as liquid,semisolid and solid.liquid liquid formulation such as nanosuspensions, and semisolid formulations, such as gels, creams, ointments and lotions can be useful for the topical delivery of nanocrystals.

Numerous excipients are available for topical nanocrystal-based formulations, and they include stabilizers, gelling or thickening agents, emulsifying agents, emollients, ointment bases, permeation enhancers, antioxidants, humectants, buffering agents

3.2)NOVEL APPROCHES FOR IMPROVED TOPICAL DELIVERY NANOCRYSTALS:

Intradermal delivery is an attractive approach for the penetration of drug into the viable layers (viable epidermis and dermis) of the skin by circumventing the SC using a suitable device, such as microneedle (MN). Recently, combination of a nanocrystals and MN was explored to achieve higher amount of drug in the viable layers of the skin and/or sustained release of the drug. MN rollers or arrays are minimally invasive devices with small projections that can disrupt the skin barrier by creating

Improved topical delivery using nanocrystals is an active area of pharmaceutical research. Nanocrystals are pure drug particles typically in the 10–1000 nm range, stabilized by surfactants or polymers. They enhance topical delivery primarily by increasing drug saturation solubility, dissolution rate, skin adhesion, and concentration gradients across the skin.

Some novel approaches include:

a. Surface-Modified Nanocrystals

Researchers are modifying nanocrystal surfaces with polymers, lipids, or targeting ligands to improve skin interaction.

Examples:

- Chitosan-coated nanocrystals enhance adhesion to the skin and increase penetration through the stratum corneum.
- Hyaluronic acid-coated nanocrystals improve retention in skin layers and provide hydration.

Advantages:

- Enhanced residence time.
- Better penetration into deeper skin layers.
- Reduced dosing frequency.

b. Stimuli-Responsive Nanocrystals

These systems release drugs in response to environmental triggers such as:

- pH changes
- Temperature
- Light
- Reactive oxygen species (ROS)

Applications:

- Acne
- Psoriasis
- Infected wounds

Benefits:

- Site-specific drug release.
- Reduced systemic exposure.
- Improved therapeutic outcomes

c. Nanocrystal-Loaded Hydrogels

Combining nanocrystals with hydrogel matrices creates dual-function systems.

Features:

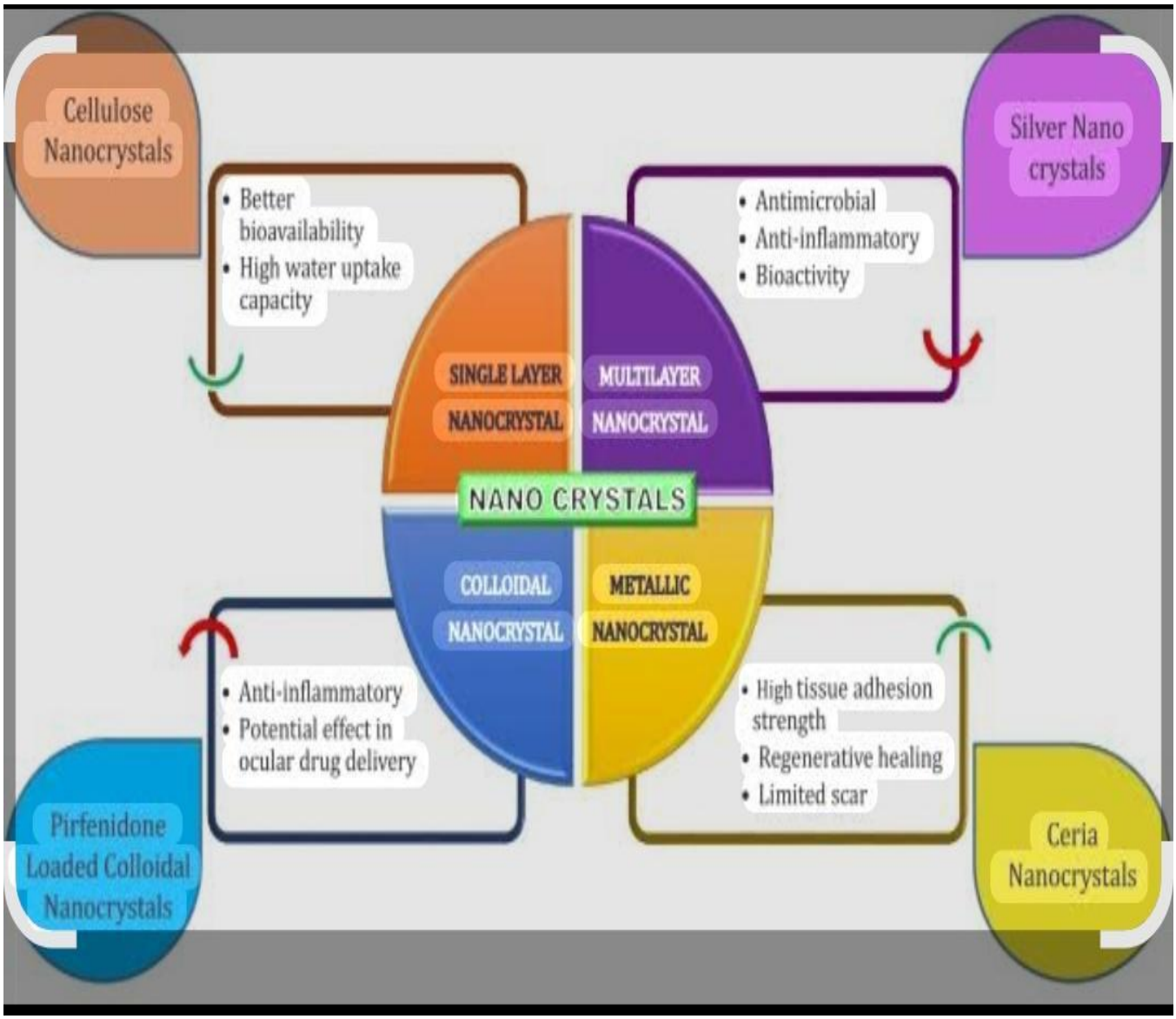
- Controlled drug release.
- Improved skin hydration.
- Enhanced patient compliance.

Common polymers:

- Carbopol
- Poloxamer
- Sodium alginate.

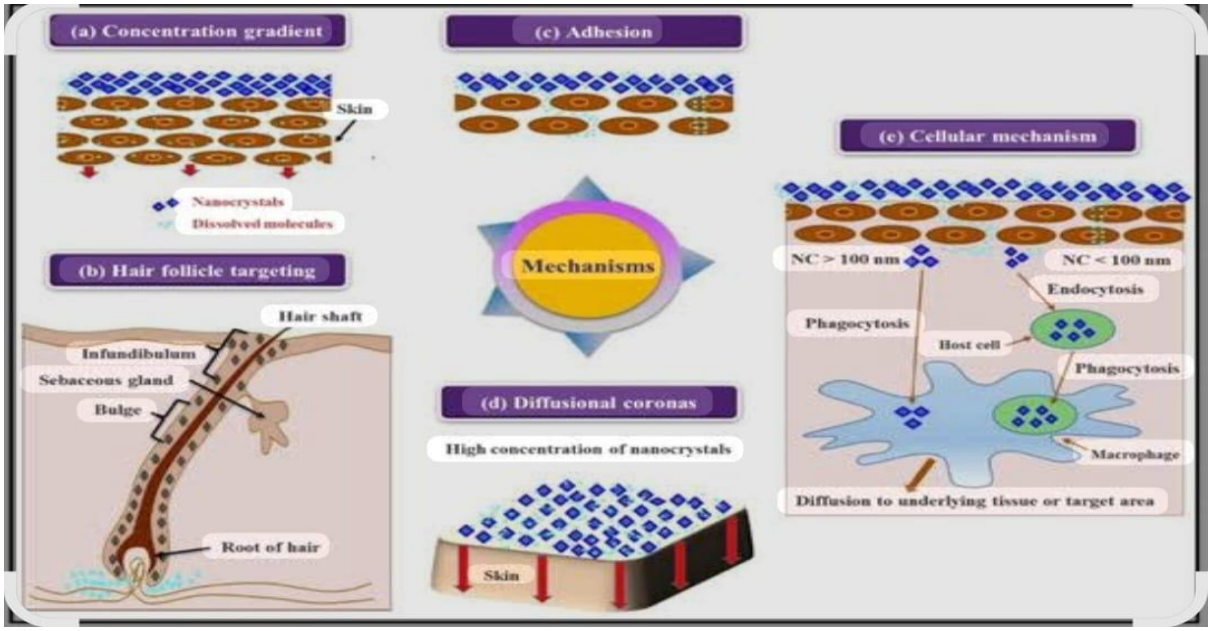
4)MECHANISM OF ACTION OF DERMAL NANOCRYSTALS:

NCs have various unique features, including bioadhesion, improved permeation, and enhanced penetration through a membrane. These properties of NCs were utilized to develop oral and intravenous formulations. In addition, the use of NCs in DDD gained interest following the formulation of poorly soluble antioxidants, including hesperidin, apigenin, and rutin as nanosuspensions (NSs) for usage in anti-aging and skin protective products [25]. NCs are only admixed to the water phase of o/w lotions and dermal creams. In March 2007, the first products with rutin were launched in the market, for example, Juvedical products (age-decoder face fluid and face cream). Subsequently, Platinum Rare products containing hesperidin were made available in 2009 [25].



Formulations of rutin NCs were compared in vivo to a cream containing a water-soluble rutin derivative.. Still, NC-based formulations exhibited higher sun protection factors than water-soluble derivatives. Active ingredients penetrated from the water phase into the skin are promptly replaced by rapidly dissolving active ingredients from the NCs; hence, they play a role as a depot in the water phase [25]

4.1)PENETRATION OF DRUG:



Indeed, this mechanism can be used to formulate topical products. When diclofenac sodium NS was delivered through the transdermal route in a Yucatan micropig skin model, it exhibited enhanced permeability flux of the drug across the skin by up to 3.8-fold than the control.

Hesperetin NCs also showed significantly higher in vitro antioxidant properties in a free radical scavenging assay; thus, they can be utilized as an efficient adjuvant in topical or skin care preparations.

Previously this theory was demonstrated by generating antiseptic lipid nanoparticle sprays by utilizing cetylpyridinium chloride as an antiseptic and cationic surfactant. Administration through rectal and vaginal routes can be used to treat local sexually transmitted diseases by evenly spreading the drug in the local area [25].

Nanocrystals generally **do not penetrate intact skin as whole particles to a significant extent**. Instead, they enhance drug penetration through several mechanisms:

4.2) Increased Saturation Solubility and Concentration Gradient:

Nanocrystals have a very large surface area, which increases the apparent saturation solubility of the drug. This creates a higher concentration gradient between the formulation and the skin, driving passive diffusion according to Fick's law.

a) Enhanced Dissolution Rate

The reduced particle size accelerates drug dissolution at the skin surface.

Effect: Rapid generation of a highly concentrated drug solution ("supersaturated state"), increasing penetration into the epidermis and dermis

b)Follicular Penetration

Hair follicles and sebaceous glands act as reservoirs for nanoparticles.

Optimal size range: Approximately 200–700 nm for efficient follicular accumulation.

Effect:

- Deep deposition within follicles.
- Sustained drug release.
- Improved treatment of follicle-associated diseases such as acne and alopecia

c)Increased Adhesion to the Skin:

Nanocrystals exhibit stronger adhesion to the skin due to their small size and large contact area.

Effect:

- Longer residence time on the skin.
- Increased local drug concentration.
- Greater opportunity for drug absorption.

d)Interaction with Skin Lipids:

Some nanocrystals are stabilized with surfactants or polymers that can interact with the lipid matrix of the stratum corneum.

Effect:

- Temporary disruption or fluidization of skin lipids.
- Increased drug diffusion through intercellular pathways

4.3)Main Skin Penetration Pathways:

Drugs released from nanocrystals can enter through:

1. **Intercellular route** – between corneocytes through lipid domains.
2. **Transcellular route** – directly through skin cells.
3. **Appendageal route** – via hair follicles and sweat gland

FACTORS AFFECTING PENTRATION:

FACTOR	INFLUENCE
Particle size	Small particles generally improve skin more effectively
Drug liphophilicity	Moderately lipophilic drug pentrate skin more effectively
Surface charge	Positive charge may increses interaction with negatively charged skin
Stabilizer type	Can effect adhesion,hydration,and lipid interaction
Vehicle composition	Gels,and hydrogels influence drug and retetion

4.4)Conventional Drug Delivery Systems:

Conventionally, vehicles have been used to enhance the penetration of drugs through the SC. These vehicles should be inert, non-allergenic, non-irritating, cosmetically acceptable and should allow adequate release of

drug into the skin. Various vehicles act by blocking transcutaneous water loss, forming an occlusive film and hydrating the skin to facilitate the absorption of the drug into the skin. Surfactants and aqueous or hydro-alcoholic solvents have also been employed in these vehicles

When discussing nanocrystals, "conventional drug delivery systems" usually refers to traditional formulations used before nanocrystal technology was introduced.

CONVENTIONAL SYSTEM	CHARACTERISTICS	LIMITATION FOR POORLY SOUBLE DRUGS
Solutions	Drug completely as micron sized particle	Low solubility may prevent adequate drug loading
Suspensions	Drug dispered as micron-sized partic;es	Slow dissolution and poor soluble bioavability
Creams	Emulsions-based semisolid formulation	Limited penetration of poorly soluble drugs
Gels	Water-based semisolid system	Limited loading of hydrophobic drugs
Lotions	Low visicosity topical preparation	Short skin residence time
Tablets	Oral solid doage forms	Poor absorption of poorly souble

5)NANOCRYSTALS-BASED FORMULATION:

Topical formulations are classified as liquids, semisolids and solids. Liquid formulations, such as nanosuspensions, and semisolid formulations, such as gels, creams, ointments and lotions can be useful for the topical delivery of nanocrystals. Numerous excipients are available for topical nanocrystal-based formulations, and they include stabilizers, gelling or thickening agents, emulsifying agents, emollients, ointment bases, permeation enhancers, antioxidants, humectants, buffering agents

Nanocrystals are rarely administered alone; they are incorporated into various dosage forms depending on the therapeutic goal. These formulations can be classified as follows:

a)Nanosuspensions

The simplest nanocrystal formulation, consisting of drug nanocrystals dispersed in an aqueous medium and stabilized by surfactants or polymers.

Components

- Drug nanocrystals
- Stabilizers (e.g., poloxamers, PVP, HPMC)
- Water

Advantages

- High drug loading
- Simple preparation

b) Nanocrystal-Loaded Gels:

Nanocrystals are incorporated into gel bases for topical application.

Common gel bases

- Carbopol

- HPMC
- Poloxamer
- Sodium alginate

Advantages

- Improved skin retention
- Better patient acceptability

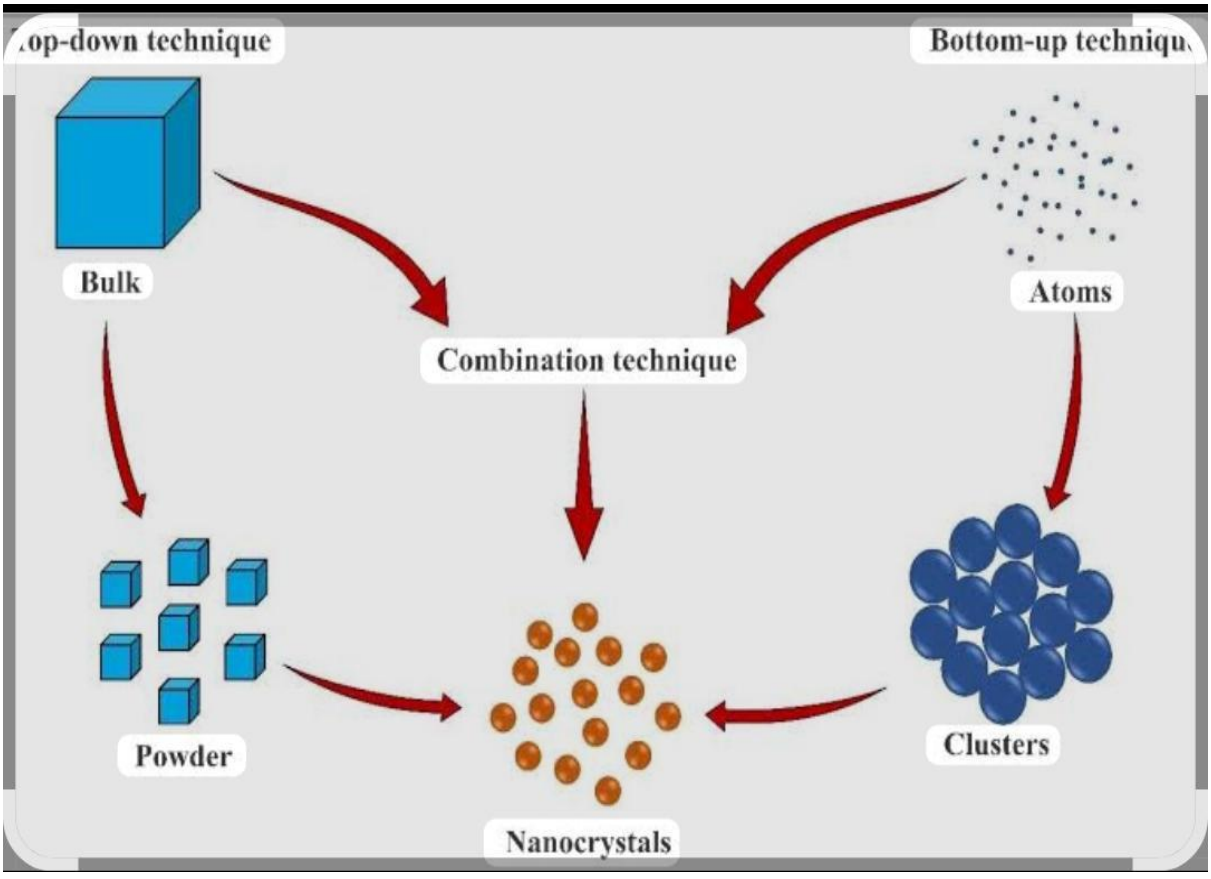
6)NANOCRYSTALS PREPARATION TECHINQUES:

NCs are typically prepared either through bottom-up techniques (by altered crystallization/antisolvent precipitation) or top-down techniques (by mechanical breakage/attrition of a crystalline powder.Although top-down techniques are widely used in commercial applications, these methods have some inherent disadvantages that require the development of alternative methods. On the other hand, bottom-up techniques are not fully established for commercial applications; nonetheless, it has greater potential to generate small-size drug NCs while requiring less energy.

Nanocrystal preparation methods can be divided into top-down and bottom-up techniques. The size reduction of relatively large particles into smaller particles are known as top-down technique

whereas bottom-up techniques consist of the growth of small particles from individual molecule . The driving force for the growth of a crystal from individual molecules is supersaturation.

6.1 TOP-DOWNTECHNIQUES:



a)Milling:

Most of the NC products that are available in the market are prepared by using wet ball milling (WBM) [26]. WBM method uses mechanical attrition to wet particles by using an aqueous solution of surfactants and

shearing as well as ground via using milling balls in a milling container. WBM results in reduced particle sizes, which might reach a few hundred micrometers

However, the traditional milling process can be modified to generate NCs [26]. Furthermore, the manufacturing process can be reproducible. Major drawbacks of this manufacturing process include decreased crystallinity, long operation time, high energy input, and contamination from erosion of metal milling pearls or balls [26].

However, polymeric beads can be used to minimize the contamination and erosion. On the other hand, jet milling is used to manufacture microparticles without using organic solvents

b) High-pressure homogenization(HPH):

In a chamber, two fluid streams of particle suspensions collide under high pressure in the case of HPH, which results in the collision of particles following particle rupture. In piston-gap homogenizers, nanosized solid particles are manufactured by forcing a suspension of drug particles with a piston by a thin gap under high pressure. The turbulent flow and high shear forces break the particles, and the particle outcome is determined by the number of piston-moving cycles, particle hardness, and the power of homogenization.

Nevertheless, HPH needs complex equipment, high-energy input, and high process temperature, which may experience a possible breakdown of the components and might have less yield as compared to wet milling [27]

c)Ultrasound:

In the case of ultrasound, drug particles are fragmented into smaller particles by the vibration of acoustic waves. Nucleation can be enhanced through ultrasound via the generation of acoustic cavitation in solution and the rapid dispersal of the drug solution. This method is highly reproducible and can easily be operated in laboratory settings.

Ultrasound-guided precipitation of nanoparticles changes agglomeration, growth, nucleation, and mixing processes [28]. Various factors affect the size of NCs, including the cavitation depth, horn immersion depth, horn length, and ultrasound treatment [29,30].

d) Laser ablation (LA):

LA is comparatively a newer process for NC preparation. In the case of LA, a laser beam is focused on a solid target to eject materials. Subsequently, the ejected materials form nanoparticles in the surrounding liquid. The mixed suspensions of microparticles are then fragmented into nano-sized particles through laser-induced fragmentation [31]. Depending on the duration of the laser pulse, LA can be grouped into femtosecond, picosecond, and nanosecond laser irradiation.

Several factors affect the particle sizes, including properties of the suspension, scanning speed, and laser intensity. No organic solvent is involved in LA; however, a small fraction of the drug might go through oxidative degradation and alterations in crystal states because of extreme power. LA has already been utilized in the preparation of curcumin, megestrol acetate, and paclitaxel NSs [29,32].

*6.2)*BOTTOM-UP TECHNIQUES*:*

a). Control flow cavitation(CFC):

CFC makes the best process condition for NC preparation after regulating the density, location, size, and implosion intensity of bubbles in the cavitation zone. The controlled energy released by the microbubble implosions and the capacity to regulate the energy of cavitation are the desired distributions of particle sizes to be achieved [33].

In addition, to generate micro- and nanostructured materials, CFC turns destructive force into constructive with high-intensity energy force [33]. CFC is a highly effective and scalable technique with outstanding reproducibility and excellent process control [27,34].

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b). High gravity controlled precipitation (HGCP):

HGCP is the improved version of the precipitation method that uses gravity regulation to prepare smaller and more uniform drug NCs. There are several factors that influence particle size, including volumetric flow rate, rotational speed, and reactant concentration. The drug suspension in the device can be circulated for long-term reaction and mixing.

Nevertheless, continuous nucleation is achieved because of the local oversaturation of the feed stream at the turbulent edge during mixing, which limits the use of the HGCP method in industrial applications [35]. So far, HGCP has been effectively utilized in laboratory-scale preparation of sorafenib and salbutamol sulfate [29,36].

c). Spray drying:

Spray drying is a single-step method for the conversion of pastes, slurries, suspensions, emulsions, and solutions into powders in a continuous manner. This method also permits the generation of particles with controlled morphological aspects and sizes.

However, the conventional spray drying method is limited to the generation of particles with sizes between 2 µm and 5 µm [27].

d). Microfluidization:

The microfluidization method has been developed on the basis of the dynamics of carefully designed microchannels through which liquids go through high-pressure collision up to 1700 bar (25,000 psi) [37]. The active chemicals and lipids are mixed by the compressed air-driven pump at very high velocities in the selected microchannels, which further generates stable nano-sized delivery systems ranging from 50 to 100 nm [38].

At present, single-step dual-channel and two-step single-channel microfluidizers are commonly used in industries The use of a single-step dual-channel microfluidizer is more advantageous than the two-step single-channel microfluidizer since it consumes less energy and less expensive oil and lipid materials utilized in the preparation of Ncs

e).Liquid antisolvent precipitation(LAP):

In order to generate NCs, the LAP method mixes a solution stream (organic phase) dissolved with an insoluble drug along with an aqueous antisolvent. Most commonly, the solution–antisolvent technique is used for nanoprecipitation. This method is cost-effective and simple as it contains only nucleation and growth steps [30].

There are two steps for preparing optimized NCs. Nevertheless, LAP involves the recrystallization of unstable crystal particles, which results in precipitation and aggregation of NCs [39].

Moreover, the problem of solvent residues arises due to the usage of organic solvents in the manufacturing process; therefore, LAP is not suitable for drugs that are neither insoluble in non-aqueous nor soluble in aqueous solvents. The LAP method has previously been used to prepare suspensions of budesonide and hydrochlorothiazide [29].

f). Combination technique:

The combination technique involves the use of any of the two above-mentioned techniques. Various combinations, including HPH followed by milling, spray-drying, and further processed by homogenization or milling, freeze-drying followed by milling, and precipitation followed by HPH are some combination techniques that are commonly utilized to obtain better production and product benefits [40]. shows a number of patented topical NCs and production techniques.

g) Antisolvent Precipitation (Solvent–Antisolvent Method)

This is the most widely used bottom-up technique.

Process

- Drug is dissolved in a suitable organic solvent.
- The solution is added to an antisolvent (usually water) containing stabilizers.
- Rapid mixing creates supersaturation.
- Drug precipitates as nanocrystals

h) Sonoprecipitation

Process

- Antisolvent precipitation is combined with ultrasonication.
- Ultrasound promotes rapid nucleation and prevents aggregation.

i)Evaporative Precipitation into Aqueous Solution (EPAS)

Process

- Drug dissolved in volatile solvent.
- Solution sprayed into heated aqueous phase.
- Rapid solvent evaporation causes nanocrystal formation.

7)APPLICATION OF NANOCRYSTALS- BASED FORMULATION:

Topical nanocrystal-based formulations have been explored for a wide variety of applications such as skin inflammation, fungal conditions, skin infections, psoriasis, frostbite, anti-aging treatments and anti-acne effect. The details of significant results and current progress relating to the application of nanocrystal-based formulations

7.1) NANOCRYSTALS-BASED FORMULATION :

a. Melanoma:

Melanoma is a type of skin cancer that involves malignant neoplasm of the melanocytes [41]. Melanocyte produces melanin (the natural skin pigment), and they are located in the basal layer of the epidermis [42,43]. Noscapine is a phthalide isoquinoline alkaloid derived from the opium poppy.

This alkaloid was found to prevent the proliferation of cells and mediate apoptosis in B16LS9 melanoma cells. However, noscapine suffers from various problems, including poor water solubility as well as poor oral bioavailability.

Noscapinoids (synthetic derivatives of noscapine) were incorporated in silver NCs to overcome these drawbacks because silver decreases the extent of UV-induced DNA damage and apoptosis.

In addition, this nanogel downregulated cyclin D1, proliferating cell nuclear antigen, EP3, and cyclooxygenase-2, as well as limited the cell cycle and inflammatory pathways than quercetin alone [44].

In addition, this nanogel downregulated cyclin D1, proliferating cell nuclear antigen, EP3, and cyclooxygenase-2, as well as limited the cell cycle and inflammatory pathways than quercetin alone[44] [24,45]

b.pain and inflammation:

Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) used in the treatment of acute pain and inflammation; nonetheless, this drug suffers from poor solubility, which leads to the prolonged onset of action that hinders its development[46,47]. Meloxicam NCs were effectively manufactured by nanoprecipitation, which resulted in greater transdermal permeability and over double the elevation in plasma level area under the curve over 24 h as compared to normal formulation [48].

Collectively, the DDD of meloxicam NCs was found to be beneficial. Curcumin is an effective and natural anti-inflammatory agent [49], and its NCs were developed owing to its poor solubility in water and oil. Skin-friendly curcumin NCs with an average particle size of around 200 nm were developed by using Plantacare stabilizers and the smartcrystal technique . In a study, analgesic and anti-inflammatory activities of a nanogel of flurbiprofen (an NSAID) NCs were evaluated in rat models. Stabilizer, Plantacare 2000 (BASF, Ludwigshafen, Germany) and the wet milling method were used to generate flurbiprofen NS

In another study, NCs of 18β-Glycyrrhetinic acid, a pentacyclic triterpene that occurs in plants, were prepared by HPH to treat inflammatory skin disorders [50]. These NCs were characterized by photon correlation spectroscopy (PCS), scanning electron microscopy, thermogravimetric analysis, and X-ray diffractometry.

The average particle size of 18β-Glycyrrhetinic acid NCs was 552.0 ± 9.8 nm, and the polydispersity index (PI) was 0.13–0.10. The solubility and skin penetration capacity of these NCs were greatly increased after nano crystallization. However, thermal stability and crystallinity were decreased [50].

c. Psoriasis:

Psoriasis, an autoimmune condition, is a chronic and inflammatory skin condition. As DDD involves lower chances of systemic adverse reactions caused by the drug, it is the preferred route for mild-to-moderate psoriasis management [51]. Researchers prepared NCs of apremilast (an immunosuppressive drug) by using the wet milling method to enhance its DDD.

Apremilast NCs exhibited two times greater saturation solubility than the micronized apremilast. As compared to oral apremilast preparations, apremilast NCs were found to increase the skin distribution of apremilast to treat psoriasis without adverse effects [52]. In a study, methotrexate (an anti-metabolite) NCs were prepared by using the bottom-up technique to target and maintain its release at the skin application site [53]

The average particle size of methotrexate NCs was 678 ± 15 nm, which exhibited prolonged in vitro drug release over a 72 h period. In addition, methotrexate NCs were also incorporated into the shafts of disintegrating microneedles arrays with a drug loading of 2.48 mg per array, which resulted in the deposition of 25.1% of the packed methotrexate NCs in the epidermis.

d. Bacterial Infections:

Topical antibiotics are used to treat various bacteria-caused infections [54]. However, there is a need for the development of novel therapeutic approaches to cure skin infections because of the emergence of bacterial antibiotic resistance. In a study, researchers developed fusidic acid (antistaphylococcal antibiotic) NCs by using the nanoprecipitation method to treat skin infections [55].

Since fusidic acid shows low water solubility, researchers converted them into NCs to improve its saturation solubility, local bioavailability, and effectiveness for DDD.. As compared to commercial cream, fusidic acid NC cream exhibited better in vivo antibacterial properties and wound healing [55].

In another study, NCs of nitrofurazone (a topical antibiotic) were prepared by using the wet milling method, which was then converted into gels for extensive assessment. After the gel formation by using carbopol formulation, a scanning electron microscope (SEM) showed that nitrofurazone formed rectangular-shaped particles.

In order to overcome these problems, silver sulfadiazine NCs were gradually encapsulated within chitosan hydrogels. Silver sulfadiazine NCs loaded hydrogels showed enhanced antibacterial properties in vitro owing

to the larger contact area along with low cytotoxicity. On the other hand, it was revealed by in vivo studies that the quickest healing time, optimum collagen deposition, and nearly full re-epithelialization were observed in wounds cured by silver sulfadiazine NCs loaded hydrogels [56].

e.Fungal infection:

Fungal infections are responsible for causing over 1.5 million deaths every year; therefore, strong research is required in this field to develop novel therapeutics [57]. In a study, luliconazole (a topical antifungal agent) NCs were developed by using the nanoprecipitation method and then incorporated into a hydrogel to increase the dissolution and antifungal properties.

Luliconazole NCs showed increased skin absorption and drug retention. In addition, luliconazole NCs showed greater antifungal action than conventional luliconazole, along with 5-fold greater solubility and 4-fold increased dissolution.

Luliconazole hydrogel also caused negligible irritation in Wister rats [58]. In another study, nanogel of the clotrimazole (a topical broad-spectrum antifungal agent) NCs were prepared by using media milling to treat fungal infections [59]

f. Eczema:

Eczema or atopic dermatitis is a skin condition that causes inflamed, dry, and itchy skin [60]. Beclomethasone (a corticosteroid) NCs were prepared in a study by using the antisolvent nanoprecipitation method to treat eczema.

These NCs showed 745.5 times greater saturation solubility than even pure beclomethasone dipropionate. The local skin accumulation efficiency of beclomethasone NCs was 6.20, which was significantly higher than the local skin accumulation efficiency of 0.25 of the brand formula [61].

g. Skin Aging:

Skinagaing is a complicated process where skin deteriorates with age because of the synergistic effects of environmental factors, hormonal deficiency, photo-aging, and chronological aging [62,63]. In a study, caffeine NCs were prepared by HPH or the pearl milling method to prevent fiber formation and crystal development, as supersaturation tends to generate medium solubility drugs.

These NCs were developed based on the low-energy milling method along with ideal stabilizers and reduced dielectric constant dispersion media.

h. Herpes Simplex Virus (HSV) Infections:

HSV can cause infections in different parts of the human body, most commonly the mouth and genital areas [64]. Researchers developed acyclovir (an antiviral drug) NCs via wet media milling in a high-pressure homogenizer to enhance DDD.

These NCs were found to be crystalline naturally and had particle sizes ranging from 450 to 550 nm. Saturation solubility of acyclovir NCs was 1.6-fold higher than acyclovir in micronized form. Both NS and nano cream of acyclovir showed 6.3-fold and 2.4-fold higher skin permeation than the conventional preparations, respectively [65].

i. Skin Manifestations of Tick Bites:

Ticks can play a role as a vector of disease-causing agents in humans. Azithromycin (a macrolide antibiotic) NCs were prepared to control skin infection after tick bites [66]. Azithromycin NCs were found to be stable at 4 °C for a year.

PCS, laser diffraction, and light microscope were used to characterize the azithromycin NCs, which revealed that these NCs were in the nanometer range.

j. Hyperpigmentation:

Hyperpigmentation is a common skin condition that involves the appearance of darker patches on the skin [67]. In a study, glabridin (an important flavonoid extracted from licorice root) NCs were developed to enhance drug penetration through the skin.

These researchers prepared glabridin NSs by using an anti-solvent precipitation–homogenization process. The average particle size of the NSs was 149.2 nm, and the PI was 0.254. The developed nano formulation significantly ameliorated the penetration of glabridin through rat skin without lag phase in both in vitro and in vivo.

k.Diabetic Foot Ulcer:

Diabetic foot ulcer is a major complication of diabetes mellitus, which can further lead to hospitalization and even amputation of the lower limb if not treated in a timely manner. Diosmin is a natural compound found in some plants that shows strong antiulcer, anti-inflammatory, anticancer, and antioxidant properties.

Diosmin NC-loaded sodium alginate wafers were prepared to treat diabetic ulcers in rats. These NC-loaded wafers exhibited high porosity, mucoadhesion properties, and prolonged degradation time.

Curcumin is a good antimicrobial agent that shows no toxicity, and nanocellulose is widely used in wound dressing since it shows good compaction properties as well as excellent absorbing ability.

l.Acne Vulgaris:

Acne vulgaris is an inflammatory skin condition of the pilosebaceous follicle. In a study, azelaic acid (a saturated dicarboxylic acid) NC hydrogel composed of Pluronic F-127 and hyaluronic acid delivered azelaic acid into the SC and inner skin layer to treat acne and rosacea [68].

It was observed that the hydrogel prepared with 15% Pluronic F-127, 1% hyaluronic acid, and 10% lyophilized NC azelaic acid solution showed effective rheological properties and drug delivery required for an in situ gelling framework for skin exposure [68].

Tretinoin (a vitamin A derivative) NCs were developed by precipitation method in a different study to increase the cutaneous targeting of tretinoin and to enhance photostability.

m. Frostbite-Related Infections:

Individuals with frostbite are at risk of wound infections caused by bacteria. A nanogel loaded with Ganoderma lucidum (a medicinal mushroom) NCs was manufactured by researchers through the HPH method for DDD to treat frostbite [69]. Particle size analysis and SEM demonstrated that Ganoderma lucidum NS retained their particle sizes after formulating gel with carbopol.

8)PHYSICAL STABILITY AND DETERMINATION OF PARTICLES OF PARTICLE SIZE IN TOPICAL FORMULATION:

The physical stability of topical nanocrystal-based formulation is crucial during production, storage and shipping to ensure safety and efficacy. Nanocrystals can be homogeneously dispersed in either aqueous or lipid phase of the vehicle depending on the composition. Numerous instabilities, such as agglomeration, Ostwald ripening, modification of solid form and dissolution of the active ingredient leads to loss of the beneficial properties of nanocrystals

Advantages of Pharmaceutical Nanocrystals:

- Improved solubility and dissolution rate.
- Enhanced bioavailability.

- High drug-loading capacity.
- Reduced food effects.
- Flexibility in administration routes.
- Potential reduction in dose and side effects.
- Scalable manufacturing processes.

Limitations:

- Physical instability due to particle aggregation.
- Crystal growth during storage (Ostwald ripening).
- Requirement for stabilizers.
- Manufacturing costs.
- Challenges in long-term stability.

Future Perspectives:

Future developments are likely to emphasize:

- Personalized nanomedicine.
- Improved stabilization strategies.
- Smart nanocrystal systems with controlled release.
- Regulatory harmonization for nanotechnology-based pharmaceuticals.
- Artificial intelligence-assisted formulation optimization.

9)CONCLUSION:

Pharmaceutical nanocrystals represent one of the most effective approaches for enhancing the delivery of poorly water-soluble drugs. By improving solubility, dissolution rate, and bioavailability, nanocrystals can significantly enhance therapeutic efficacy while reducing dose-related side effects. Advances in manufacturing technologies, characterization methods, and targeted delivery strategies continue to expand their applications across multiple routes of administration.

As pharmaceutical research increasingly focuses on poorly soluble drug candidates, nanocrystal technology is expected to play an even greater role in the development of future drug products.

Nanocrystal is a novel drug delivery technology that provides a versatile approach for improved topical delivery of poorly soluble and medium soluble drugs. This novel drug delivery technology possesses optimized characteristics such as smaller particle size, increased apparent solubility, enhanced dissolution rate and selective site targeting that can improve the performance of existing drug delivery systems.

NCs make them a preferred choice for screening during the initial and discovery phases to assess the presence of any correlation between the bioavailability and particle size of a drug. So far, a range of dermal NCs have been developed in various studies that have been evaluated in terms of their skin penetration capacity

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