International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1415-1434 www.ijprajournal.com ISSN: 2249-7781

Nanocrystal Hydrogel - a promising approach for dermal drug delivery system

Akshay Tambe*, Rajveer Bhaskar, Monika Ola, Ramarao Suryawanshi,
Department of Pharmaceutics, Quality Assurance& Industrial PharmacyR. C. Patel Institute of Pharmaceutical Education and Research, Shirpur 425405, Maharashtra State, India

Submitted: 15-05-2023 Accepted: 30-05-2023

ABSTRACT
Nowadays Gels appear to be more advantageous in both cosmetics and pharmaceutical preparations when compared to other semisolid formulations. In gel, hydrogels are systems comprising three-dimensional, physically or chemically bonded polymer networks entrapping water in intermolecular space, inrecent research in nanotechnology, nanocrystals have offered a unique set of properties for drug delivery including high drug loading capacity, combinatorial delivery, controlled and sustained drug release, prolonged stability and lifetime, and targeted delivery. To further enhance the therapeutic index, especially for localized applications, nanocrystals have been increasingly combined with hydrogels to form a hybrid biomaterial system for controlled drug delivery.nanocrystals arecomposed of 100% drug without any matrix material, typically with a size preferably less than 100 nm. Drug nanocrystals can be considered a universal formulation approach for the delivery of poorly soluble drugs.Nanocrystal-based formulations for dermal distribution have recently received a lot of attention due to their increased skin penetration. According to current research on nanocrystals for topical delivery, it could be a novel approach for all formulators struggling with poorly soluble drugs.EspeciallySuperficial fungal infection in immunocompromised patients can lead to many disorders and complications. Currently, new topical treatment options are critically needed to treat these fungal infections. Consequently, this review discusses and development of hydrogel incorporated with nanocrystals could be a new approach with improved activity and increased dermal delivery for drugs with poor aqueous solubility rather than coarse drug-containing gel.

Keywords: Nanocrystals; Hydrogel;Antifungal Activity; Nanocrystal-based formulations; Topical drug delivery

A fungus is one of the main causes of skin illness worldwide. It is reported that 40 million people in developing and emerging countries have fungal infections.Fungi affect the skin's surface first, and then, through desquamation, they reach the deeper layer. [1]One of the fungi that causes the most superficial cutaneous infections is the Candida species, which has a fungal infection.[2] [3]Fungal infections expressed in the deeper layer of skin arecalled “cutaneous mycoses”[4]."Subcutaneous mycosis" refers to a fungal infection that has penetrated deeper skin tissue [5]Antifungal drugs are employed for treating both deep and superficial fungal infections. Infections caused by fungi are frequently seen in the various skin layers, as shown in **Figure 1(A)**

The most effective method for treating the most common skin dermatophytes is the topical application of anti-fungal medications, which guarantees direct access and a greater rate of retention at the target[6].Topical administration also minimizes systemic toxicity and avoids pre-systemic metabolism[7]. Site-specific drug administration, less systemic toxicity, increased patient compliance, increased treatment effectiveness, and improved bioavailability are further benefits of topical delivery[8]. On the other hand, topical use of anti-fungal medications may result in unfavorable skin reactions, such as allergic rash and itching. Moreover, conventional formulations require high doses and frequent administration, which is linked to a higher risk of both local and systemic toxicity. because of this, a novel medication delivery mechanism is being considered with the aim of lowering local side effects and boosting therapeutic efficacy[9]. The current review is focused on topical nanocarrier technology for cutaneous application of anti-fungal drugs. One of the most extensively researched topical formulations in pharmaceutical research are novel drug delivery systems (NDDS). Due to its exceptional capacity to encapsulate a wide range of medications, improve disease-specific localization,

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1415-1434 www.ijprajournal.com ISSN: 2249-7781

decrease dose frequency, and promote clinical efficacy, NDDS is able to manage the release kinetics of encapsulated drugs. To maintain acceptable therapeutic performance, it is necessary to comprehend the precise mechanism of antifungal treatments while adopting a suitable topical formulation. Fungal cells use ergosterol as a growth agent to encourage growth. The anti-fungal properties of azoles are correlated with their capacity to prevent ergosterol formation. Particle size, surface charge, and lipophilicity are variables of penetration depth into various skin layers.[10]. The capacity to absorb and hold significant amounts of water in an aqueous environment without itself dissolving in water makes hydrogels[11,12].Wichterle developed the first hydrogels in 1960 using a cross-linked hydroxyethyl methacrylate (HDMA). Hydrogels are good alternatives for flexible/wearable substrates because of their superior biocompatibility, flexibility, and stretchability[13].In addition to being employed in medicinal applications, hydrogels are frequently found in hygiene products, food additives, and soil conditioners.[14]In essence, the hydrogel is made of heterogeneous mixtures of two (or more) phases, with water serving as the dispersed phase and a solid three-dimensional network as the solid phase, respectively.In additional to having a high tensile strength and toughness, hydrogel has a high Young's modulus of 1 MPa.Due to its benefits in speed, accuracy, and flexibility, 3D printing has recently been examined as a useful and promising technology for the fabrication of cellulose nanocrystals-based hydrogel shown in **figure.1(B)**Hydrogels have become more prevalent in several scientific disciplines since they are very compatible with the majority of biological molecules and substrates. [18] [19]. Hydrogels can be made from a variety of materials. Among them are polymers, biocompatible substances like proteins and carbohydrates, as well as inorganic and conductive substances.High mechanical strength, surface area and hydrophilic nature are the main features of functional hydrogels that have played a pivotal role in trapping selective wastewater contaminants. The method of adsorption by hydrogel, which can be either physical (physisorption) or chemical (chemisorption), is strongly involved in the normal pattern and electrostatic interaction [20] [21].It was reported that increasing the degree of cross-linking within the hydrogels, the adsorption capacity of the hydrogels is reduced.Water, an active pharmaceutical ingredient, and a stabilizer make up nanocrystal dispersions. Because stabilizers that inhibit the reaggregation of the active drug ingredient are present, they are physically stable.As a potential technique nanosuspension has been applied more and more widely to increase the solubility of poorly soluble drugs lately. By using the nanocrystal technology to reduce the drug particle size into the nano (sub-micron) range, the solubility was enhanced.Without compromising their essential structural integrity, hydrogels can interact with and hold substantial volumes of water. Despite having a high affinity to water, they are not dissolved due to the equilibrium state of hydrogels that may depend on the cross-link's interactions with water, internal moisture transport, diffusion characteristics, and mechanical strength. One of the most promising methods for improving the biopharmaceutical performance of hydrophobic drugs is the formulation of pharmaceuticals in nanocrystals. Nanocrystals have been increasingly used to enable drug delivery via a wide range of routes, such as parenteral injections, ophthalmic, intranasal, and pulmonary. Initially intended to increase the absorption of medications delivered orally. Conventional medication delivery systems typically address systemic toxicity and issues of repeated dosages. For a number of years, hydrogels have been utilised as a drug carrier to decrease the issues with traditional drug delivery. Due to their biocompatibility, physicochemical characteristics, and intended interaction with living environments, they have been regarded as one of the most dependable families of biomaterials. The variety and adaptability of hydrogels make them exceptional not just in the field but also in the manufacture of contact lenses, tissue engineering, and other applications. Another factor that makes hydrogels a good medication delivery vehicle is their unique ability to hold water inside of their network. [22].Many medications have difficulties penetrating the skin due to the barrier function of the skin and the non-optimal physicochemical features of the drugs. This has led to the development of innovative drug delivery systems. Lately, formulations based on nanocrystals have shown enhanced skin penetration in topical medication delivery studies.This review focuses on skin penetration barriers, modern methods to enhance topical distribution, and the use of nanocrystals to overcome these barriers.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1415-1434 www.ijprajournal.com ISSN: 2249-7781

Advantages of nanocrystal-based Hydrogel formulation: -

Nanocrystal based hydrogel providesGood dispersibility, high crystallinity and self-assembly [23], Advantages of the nanostructure, biocompatibility, biodegradability, and tuneable surface chemistry[24], Cellulose nanocrystal-based hydrogels can provide stronger bioavailability and better drug loading capacity owing to their open pore structure and high surface area, Hydrogels have thus far gained acceptance due to their inherent advantages, such as their wide variety of precursors and additives, low toxicity, easy form control, and biological compatibility.It is capable. Improved dosage proportionality, increased oral bioavailability, and decreased food impacts.Drug products with nano dimensions can be employed at a lower concentration and can result in an early commencement of bioactivity, which is one of the advantages of nanocrystal pharmaceuticals over their conventional equivalents. Increased rate of absorption, Rapid effect, Reduction in the required dose.Due to the extremely small particle size, the nanocrystal-based hydrogel can also be delivered topically, resulting in 100% bioavailability. reduced variability between fed and unfed, quick, easy, and affordable formulation development, More dependability; ongoing crystal structure. As the particle size of the active drug material is reduced to the nano size range while maintaining the drug's crystal form, nanocrystal technology increases the intensity at which substances dissolve. more stability. Because a stabilizer is used to stop the reaggregation of active drug ingredients during manufacturing, these systems are stable. The addition of surface-active compounds or polymers can stabilize the suspension of drug nanocrystals in a liquid. This principle applies to all drugs that are poorly soluble since they can all easily break down into particles smaller than a manometer. In addition to acting as an efficient barrier against oxygen, regulating food moisture, and even possessing antimicrobial action, hydrogels are a great replacement for conventional packaging. [25]increased dissolution and saturation solubility, low toxicity, and chemical stability.An essential approach to enhance clinical effectiveness and patient acceptance, which is readily available and affordable, is the design of innovative drug delivery methods for the reduction in dose and alleviation of adverse effects. [26].

Problems of hydrogel nanocrystals

- Certain hydrogels' non-biodegradable and non-biocompatible qualities.
- Hydrogels that respond to stimuli too slowly.
- During the initial hydrogel swelling, a quick burst of drug is released.
- Entrapment method used for drug loading has chance of drug deactivation and initial burst release.
- Covalent binding method for drug loading may cause drug deactivation during polymer binding.
- Drug release by diffusion method is a non-specific drug release mechanism.
- Possible toxicity of remaining, unreacted small molecule cross-linkers used in the production of hydrogels.
- Using hydrogels to reduce the delivery of hydrophobic drugs.
- Incorporation of drug-loaded colloidal carriers in semisolid dosage forms such as hydrogels is so difficult.

Solution

- synthesis of hydrogels with hydrolysable moieties, such as PEG-PLGA-PEG, that are biocompatible and biodegradable (Chemically altered).
- Make thinner and smaller hydrogels which are fast-acting.
- Prior to gelation, drugs can be physically or covalently attached to the polymer chains (tethering method).
- Use linkers, in which drug release could be tuned, instead of direct covalent binding drug to polymer.
- To regulate the release of drugs from hydrogels, use triggers that are chemically and physiologically triggered.
- Use polymer-polymer cross-linking method by formation of Schiff base or Michael addition.
- Preparation of a novel nanoparticles and hydrogel composite drug delivery system or introduce hydrophobic domains directly into the hydrogel network.
- Application of mixed delivery system (Liposome in-hydrogels) to improve release profiles [27] [28].

Technique of formulating nanocrystal

Drug nanocrystal preparation essentially entails a nanosizing technique to increase the oral bioavailability of poorly water-soluble drugs. Drug

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1415-1434 www.ijprajournal.com ISSN: 2249-7781

nanocrystals are defined as drug crystals that are fewer than 2000 nm in size, according to the first patents in this field. Active pharmaceutical ingredients, surface-active agents, and polymers needed for stability are all present in nanocrystal dispersions together with a dispersion medium (water, aqueous solutions, or nonaqueous media). Other compounds, like buffers, salts, and sugars, can be added if necessary. Nanocrystal production is divided into three categories: bottom-up, top-down techniques. In addition, novel techniques that combine the two basic techniques have been developed that is combination technique. Various methods for nanocrystal production are shown in **figure.3** [29], advantages and disadvantages of this technique are shown in **Table.1.**

1) Top-Down technique

Wet bead milling and high-pressure homogenization are the two basic manufacturing top-down technological methods. [30].As they don't need organic solvents and are relatively easy to scale up manufacturing, this technology has been used to make the majority of previously reported anticancer drugs. [31].In conclusion, top-down processing can be used to process drugs that are insoluble in both the aqueous and organic phases. It works swiftly and is frequently utilised for commercially available drug nanocrystals.

A) Wet Bead Milling

Wet bead milling utilizes stabilizers, water, and high-intensity mechanical force to break down the drug into nanoparticles. [32].The particle size of the nanocrystals has the greatest impact on the milling beads size. [33].Wet bead milling, which enables for temperature control during the preparation process, is particularly well suited for producing thermally unstable drug nanocrystals. It operates easily to obtain a uniform product. To achieve the desired particle size range, stabilisers and wetting agents must still be added, and multiple cycles must be performed.The resultant product, however, has drawbacks such as contamination from grinding beads and poor physical storage stability based on by agglomeration. [34].The majority of drug nanocrystals that have been successfully developed for industrial use, such as the first pentoxifylline capsule Verelan®PM, the fenofibrate tablet Tricor® used to treat hypercholesterolemia, and the anti-inflammatory drug Naprelan®, are made by milling[35].

B) High Pressure Homogenization

High-pressure homogenization causes drug particles to be severely sheared, collided, and cavitated in a homogenization chamber (HPH). It can be categorised as micro fluidization, IDD-P™, Dissocubes®, and Nanopure® depending on the instruments and solution utilised. For the homogenization of suspensions, IDD-P™ employs a jet homogenizer.A piston gap homogenizer is used by Dissocubes® to homogenise aqueous medium. In decreased non-aqueous medium, Nanopure® is appropriate for the manufacturing of easily hydrolyzed pharmaceuticals. [36]Most importantly, the procedure can be more effectively integrated with other techniques to lower the necessary homogenization pressure and the number of homogenization cycles. Costly equipment and challenging procedures make it tough to scale up. [37].High pressure may adversely affect a variety of properties, including the stability of some amorphous nanosuspensions, the number of amorphous states present, and changes to crystal structure. [38]The presently marketed paliperidone palmitate intramuscular suspension Invega Sustenna, Triglide® fenofibrate tablets, and Luteolin nanocrystals are made using the HPH process[39].

C) Laser Ablation

Recently, a novel method for preparing nanocrystals called laser ablation has been devised. During laser ablation, the solid target is subjected to laser light; the material that is ejected condenses into nanoparticles in the liquid around it. Then, stirred suspensions of microparticles are broken up into nanoparticles using laser energy [40].There are three different types of laser processing times: femtosecond laser irradiation, which can generate more nanoscale particles, and nanosecond, picosecond, and picosecond laser irradiation. [41]The laser intensity, scanning speed, suspension characteristics, and other factors all have an impact on particle size. Although no organic solvents are used in this process, employing too much power could cause a small quantity of the drug to undergo oxidative degradation and change its crystal structure. The development of nanosuspensions containing paclitaxel, megestrol acetate, and curcumin has all been accomplished using this technique. [42].

D) Ultrasound

Ultrasound is a good method for breaking up larger drug particles via the vibration of

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1415-1434 www.ijprajournal.com ISSN: 2249-7781

the sound wave. By causing acoustic cavitation in the solution and swiftly distributing the drug solution, ultrasound has been demonstrated to improve nucleation [43]. It is also frequently used in conjunction with other procedures due to its simplicity of use and good reproducibility in the laboratory [44]. Mixing, nucleation, growth, and agglomeration are the main processes impacted by ultrasound-assisted precipitation of nanoparticles. [45].[46].

2. Bottom-up technique

Precipitation and evaporation are the basic bases of bottom-up technology[37]. The basic principle is to obtain drug nanocrystals from supersaturated drug states and then regulate the size distribution of the nanoparticles using the proper techniques [47].Controlling crystal formation is the most efficient method for precisely regulating drug particle size. A variety of physical methods, such as high gravity-controlled precipitation, have been used to control crystal formation. These methods provide more control over particle attributes than top-down methods provide[48].Bottom-up technology is simple in theory and in practise, but scaling it up is difficult due to its low reproducibility. The technique may also involve the use of organic solvents.

A) Liquid Antisolvent Precipitation

Liquid antisolvent (LAS) precipitation produces nanocrystals by mixing an aqueous antisolvent with a solution stream (organic phase) that contains an insoluble substance. The most frequently described form of nanoprecipitation is solution-antisolvent[49]. Two steps can be used to prepare the optimised nanocrystals. However, the process also involves recrystallization of unstable crystal particles, which causes nanocrystals to aggregate and precipitate[50]. Organic solvents should not be used to produce drugs that are neither insoluble in non-aqueous solvents nor soluble in aqueous solvents due to the issue of solvent residues. This technique is now being used in several research to obtain suspensions of hydrochlorothiazide and budesonide[51].

B) Precipitation Assisted by Acid-Base Method

The drug is typically dissolved in a weak acid solution as the acid phase and a weak base in a solution containing a stabilizer as the base phase in the carbon dioxide-assisted precipitation method using acid-base reactions. To produce carbon dioxide, the acid phase is gently introduced to the base phase. Subsequently, vapour effervescence is used to precipitate the drug nanocrystals. [52].As organic solvents are not used in this method, it is more environmentally friendly. However, it can only be utilised with insoluble pharmaceuticals whose solubility is connected with pH and stable to acids-bases [53].

C) High Gravity Controlled Precipitation

A development in the gravity-controlled precipitation method, high gravity-controlled precipitation (HGCP), creates more uniform and compact drug nanocrystals. [54]. This method allows for continuous mixing and reacting of the drug suspension in the equipment.However, this method's actual usefulness is limited because mixing causes continuous nucleation when the feed stream is locally oversaturated near the turbulent edge.

D) Supercritical Fluid Method

Via the rapid vaporization of a supercritical fluid (such as CO2) that is atomized under reduced pressure through a nozzle with a small aperture, drugs dissolve in the fluid and precipitate nanocrystals in the supercritical fluid (SCF) method [55]. According to the role that supercritical fluid performs in the crystallization process, two supercritical fluid technologies are used: rapid expansion of supercritical solution (RESS) and supercritical antisolvent (SAS).Supercritical fluids are used extensively, nevertheless, and they are only appropriate for drugs that can be dissolved in them. [50].

E) Emulsion Polymerization Method

In order to create an O/W emulsion, the active pharmaceutical ingredient (API) is first dissolved in volatile organic solvents or solvents that are partially mixed with aqueous as the dispersed phase. The organic solvent is then dropped into the aqueous phase and emulsified, typically with the addition of stabilisers. Controlling the emulsion droplet size is simple. To obtain drug nanocrystals, the emulsions are then evaporated, mixed, and extracted. The quality of the final product is significantly influenced by elements like the emulsifier, stirring rate, evaporation rate, temperature gradient, and pH value. This emulsion polymerization process is suitable for laboratory operations but not for a

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1415-1434 www.ijprajournal.com ISSN: 2249-7781

large-scale pilot production because it needs homogenization or ultrasonic aid [55].

3) Combination technique

Due to the qualities of various drugs and the features of the equipment, there are always a number of restrictions on employing a single preparation technology to produce the necessary nanocrystals. Combinative technology, which combines top-down and bottom-up technologies in a certain way, helps to overcome the drawbacks of a single preparation method and increases particle size reduction effectiveness. The Nano edge® technology, created by Baxter [56]and the Smart Crystal® technology, created by Abbott/Soliqs in Ludwigshafen, Germany, are two different types of combination technology.

Nano edge Technology

The first integrated technique for particle size reduction developed for the development of nanodrugs was nano edge technology. The precipitation method is used in conjunction with the HPH method. The initial crystal particles are produced through precipitation, which reduces high-pressure homogenizer slit obstruction and improves the efficiency of particle size reduction during homogenization. The HPH method's homogenization step then further crushes the particles, preventing secondary growth, resolving the problems with the precipitation method's uneven particle size distribution and Oswald ripening, and improving the physical stability of the nanocrystal particles [58].

A) Smart Crystal technology

The basic components of Smart Crystal technology are a pre-treatment stage and a high-pressure homogenization step. Pre-treatment procedures that HPH can use include wet bead milling, spray drying, freeze drying, and precipitation. [59].An established second-generation technique for preparing nanocrystals is smart crystal technology. For the purpose of creating drug nanocrystals, the combined method in this technology specifically takes the form of collection. [60]. The approaches H69, H42, H96, and combination technology (CT) are all explored.

3. B-1 H69

H69, which combines nanoprecipitation and HPH techniques, is comparable to Nano Edge technology. The creation of nanocrystals in the high-pressure homogeneous cavitation area leads to extremely small and homogeneous particle sizes[61].

3.B-2 H42 and H96

Spray drying, freeze drying, and HPH methods are respectively combined with H42 and H96. A spray/freeze-dried solution comprising the insoluble drug and stabilizer is equally dispersed in the stabilizer skeleton first and then redispersed in water using HPH. This process creates drug nanocrystals. Combining both decreases particle agglomeration and increases processing effectiveness. It is appropriate for mass production[62].

3.B-3 CT

CT combines top-down and bottom-up technologies. The rotor-stator and milling techniques are the two most popular wet bead milling types [63]. As an illustration, the former uses a combination of rotor-stator high-speed shear and HPH technology to create nanocrystals. The drug suspension is initially pre-treated utilising a rotor-stator high-speed shear to produce stable and homogeneous suspensions. The nanocrystals are subsequently homogenised at high pressure.Acyclovir nanocrystals with a mean particle size of 400–500 nm was produced by Wadhawan et al. [64]using a high-pressure homogenizer, hydroxypropyl cellulose as a stabiliser, and wet bead milling, it was possible to create crystalline acyclovir nanocrystals with a mean particle size of 400–500 nm.

B) Other New Combinative Technology

1. Precipitation-lyophilization-homogenization (PLH) method

Precipitation-lyophilization-homogenization, or PLH, is a combination of these processes. Morakul et al. [65]By employing sodium dodecyl sulphate (SDS) and poloxamer 407 as co-stabilizers, clarithromycin nanocrystals were produced.

2. High gravity antisolvent precipitation process (HGAP)

Antisolvent precipitation technique is integrated with HGCP technology to create HGAP. Once the drawbacks of product impurities are minimised, the advantages of the HGCP are kept [66].

3. Microjet reactor technology (MRT)

MRT and HPH are equivalent. The drug solution is mixed in the high-pressure chamber and sprayed into the reaction chamber through the

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1415-1434 www.ijprajournal.com ISSN: 2249-7781

nozzle's narrow aperture as a high-speed fluid. Turbulence is produced in the reaction chamber by convective shear. The impacts of cavitation, impact, and shear work together to reduce the product particle size.The antisolvent and solution mixing ratios, jet pressure, stabiliser dosage, temperature, and other variables all affect MRT. This approach enables continuous, vast output. Nonetheless, it is impossible to disregard the path blockage and energy consumption [42].

4. Evaporative precipitation into aqueous solution (EPAS)

The EPAS approach dissolves the API in the low-boiling-point solvent while heating it above its boiling point. Following that, the heated solution is sprayed into heated stabilised aqueous solutions [46]. Chen et al. [67]"Cyclosporine," EPAS generated a suspension of amorphous nanoparticles. The material dissolves quickly due to its low crystallinity, small nanoparticle size, and hydrophilic stabilizers.

5. Antisolvent precipitation-high pressure homogenization method

Huang et al. [68]We combined the antisolvent precipitation method and HPH method to produce celecoxib nanocrystal suspensions with a particle size of 283.67 20.84 nm using polyvinylpyrrolidone K30 (PVP K30) and SDS as crystal stabilisers. In comparison to celecoxib in its raw form and the physical mixture, celecoxib nanocrystals demonstrated a much better solubility.

6. Ultrasound probe-high pressure homogenization method

Jin et al. [69]Using an ultrasound probe, HPH, and a fluidized drying process, it was decided to combine the surfactant poloxamer 188 as a steric stabilizer and SDS as an electrostatic stabilizer to create baicalin nanocrystals with an average particle size of 248 6 nm and PDI 0.181±0.065. Pharmacokinetic tests on rats revealed a considerable increase in the drug's in vivo bioavailability.

7. Rotary evaporation method-high pressure homogenization method

Zuo [70]By using the rotary evaporation-HPH technique, curcumin-artemisinin cocrystal nanomedicine was produced. After optimization, the nanomedicine's particle size was 234.6 nm.The solubility and stability of curcumin-artemisinin cocrystal nanomedicine were significantly improved when compared to raw curcumin, curcumin-artemisinin cocrystals, and curcumin nanocrystals.

8. Melt quench-high pressure homogenization method

Yu [71] also produced nano amorphous indomethacin using the combination melt quench-high pressure homogenization method. The prepared suspension had particles that were 245 nm in size. The nanosuspensions have dramatically improved solubility.

9. Antisolvent precipitation-ultrasound method

Fenofibrate nanocrystals were produced by Zhang et al. [72]The ultrasound probe precipitation technique is used to produce fenofibrate nanocrystals. Ultrasonic probes, however, have a few drawbacks, including the possibility of leaving behind metal particles, which makes them unsuitable for use in industrial manufacturing.

- **Nanocrystal-based formulation developed for topical delivery** are shows in table no.2 [76]

Role of stabilizer in nanocrystal Hydrogel formulation

Nanocrystal stability, however, has hampered their research and manufacturing.Small particle size is the main source of the instability of nanocrystal preparations, and the high surface energy that is brought on by small particles causes thermodynamic instability, which eventually causes aggregation and Ostwald ripening.

Causes of instability of nanocrystals

1. Aggregation - One of the primary causes of its low stability is crystal aggregation.
2.Ostwald ripening - Due to variations in solubility, crystals of different particle sizes develop.
3.Sedimentation - Larger particles naturally settle under the influence of gravity, and their settling velocity.

Formability mechanism of nanocrystal suspensions

1. Drug-related factors - Drugs physical and chemical characteristics, such as cohesive energy, enthalpy, log P, polymorphism, and log P. Not all drugs can produce stable suspensions of nanocrystals.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1415-1434 www.ijprajournal.com ISSN: 2249-7781

2. Drug polymorphism - Amorphous forms of drugs are more soluble and susceptible to Ostwald ripening than crystalline forms, which makes them more unstable and causes a rise in drug particle size.
3. Drug hydrophobicity - Strongly hydrophobic drugs have the benefit over hydrophilic drug nanocrystals in that stabilizers can more easily cover the nanocrystals.
4. Drug enthalpy and cohesive energy - Low enthalpy drugs are more likely to aggregate while being stored.
5. Stabilizing agent related factors –The use of appropriate stabilizers can lower surface tension and stop nanocrystal aggregation.

- The instabilitymechanismsofnanocrystals show in**figure 1(C).**[77]& nanocrystal formulation some main instabilities are shown in **table.3**.
- Agglomeration/aggregation is a technique to increase particle size, decrease surface energy, and minimize the total energy. It is explained by the excess in Gibbs's free energy that is characteristic of particles of nano dimensions.
- Stabilizers provide ionic or steric barriers, fully cover nanoparticles, and prevent agglomeration.
- To stabilize drug nanosuspension, researchers exploit amphiphilic excipients (frequently surfactants) or polymers with hydrophilic and hydrophobic domains that favour the interaction between particles and wetting liquid.
- Non-ionic surfactants and non-charged polymers can create a steric barrier around the particles to avoid aggregation while ionic surfactants and charged polymers can inhibit aggregation by electrostatic repulsion [78].

A) Electrostatic stabilization

The process of electrostatic stabilisation involves the adsorption of ionic charges on the surface of the colloidal particles, which produces positively repelling interactions between the particles. Electrolytes or strong acid conditions can inhibit the stability of a nanosuspension system maintained by electrostatic repulsion [79]. Because it is straightforward and inexpensive, electrostatic stabilisation is commonly employed. There are, however, drawbacks to this approach. It performs effectively in an aqueous environment and loses effectiveness when the formulation is dried since the ionization state is no longer maintained [78].In **Figure.1(D).** Shows theAction mechanism of electrostatic stabilization

B) Steric stabilization

Steric stabilization includes the attachment or adsorption of non-ionic amphipathic polymers to the surface of the particle to inhibit aggregation. It happens when chemically bonded or adsorbed polymeric molecules. [79]. In **Figure.1(E).** Shows the Action mechanism of steric stabilization & in nanocrystal formulation have different types of modifiers are shown in **Table.4**

Nanocrystal-loaded gel effective against fungal infection in vitro antifungal study

1. Luliconazole

Luliconazole drug (LZL), Luliconazole nanocrystal (LNC), D-GEL, and N-GEL have all shown in vitro antifungal activity. The mean zone of inhibition (ZOI) for Candida albicans was determined to evaluate antifungal activity. LNC, with a ZOI diameter of 41.20±0.6110mm, was shown to be more effective at killing fungus than LZL, which had a ZOI diameter of 35.98± 0.8172 mm. In addition, the ZOI of N-GEL was higher (44.25±0.57mm) than that of D-GEL (36.83±0.83mm)[80]

2. Itraconazole

A study on the antifungal activity of this formulation using Candida albican (CA) cultures was done to determine its potential as a treatment option for fungal keratitis. After 48 hours of incubation, administering a thermosensitive in situ gel basis (without ITZ) had no effect in reducing the fungal bioburden. The integration of ITZ-NCs into the thermosensitive in situ ocular gel exhibited enhanced antifungal action, according to bioburden fungal observations made 48 hours later. percentage decline in the population of CA was only 59% after 48 h in without itraconazole nanocrystal & After 24 hours, there was a 63% drop in the fungal population as a percentage. A greater degree of decrease of 93% was seen after 48 hours (0.4 log CFU). Zone of inhibition shows in the **figure.2(A)**[81]

3. zinc ferrite

By using the disc diffusion susceptibility method, the antifungal activity of nanocrystalline zinc ferrite ($ZnFe_2O_4$) powders was tested against pathogenic Candida albicans. The antifungal efficacy of nanocrystalline zinc ferrite ($ZnFe_2O_4$) powders was examined against pathogenic Candida albicans utilising the disc diffusion susceptibility method. Zone of inhibition shows in **figure.2(B)**[82]

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1415-1434 www.ijprajournal.com ISSN: 2249-7781

4. Clotrimazole (CTZ)

The produced Clotrimazole nanocrystals were tested against C. albicans for antifungal activity. As shown in **Figure 2(C)**, the commercial CTZ cream (Candid, clotrimazole 1% w/w, Glenmark Pharmaceuticals Ltd., India) demonstrated an inhibitory zone that was superior to the CTZ by itself at 7.5± 70 and 5.2±0.52 mm, respectively. Due to its limited solubility, CTZ-API may not have been able to disperse, resulting in the fact that it displayed a small zone of inhibition. The CTZ nanocrystals, however, displayed a maximal inhibition zone measuring 22.0 ±0.64 mm. [83].

5. Gentamicin Conjugated Cellulose

The results indicated that gentamicin-conjugated cellulose nanocrystals were effective against Candida albicans. Its zone of inhibition is 32±0.76 mm shown in **figure.2(D)** [84]

CONCLUSION

The threat of fungal infections to human health is ongoing and getting worse. Antifungal chemotherapeutics were used inappropriately and irrationally, which led to the growth of multidrug-resistant fungal infections, undesired toxicity, and poor therapeutic efficacy. Recent literature findings revealed that numerous research initiatives are actively working on innovative and alternative drug delivery technologies. In this instance, skin absorption of the drugs and overall therapeutic effectiveness are significantly influenced by the formulation of topical carriers. A novel strategy to the treatment of fungal skin infections is suggested by the ongoing advances in nanotechnology. Antifungal drugs clinical potential is limited by potential adverse effects, patient non-compliance, and reduced bioavailability at the target site with prolonged use, Safe and efficient new drug delivery technologies that lower the dose while increasing the drug's concentration in the targeted organ with a low systemic concentration are greatly desired to address this problem. Studies on the in vitro skin penetration and retention of drugs showed that nanocrystal-loaded hydrogel could clearly improve the amount of drug retention in the skin layers when compared to the standard formulation. The effectiveness of current drug delivery systems can be improved by this unique drug delivery technology's optimized properties, which include decreased particle size, greater apparent solubility, enhanced dissolution rate, and selective site targeting. The development of an effective product for topical distribution only necessitates a few simple processes and the direct incorporation of nanocrystals into the semisolid dosage form. Topical nanocrystals can deliver drugs for immediate release or controlled release and have great potential for use in the treatment of superficial and deep skin disorders. They can also target certain skin regions, enhance photo and chemical stability, and reduce systemic side effects. Thus, it's possible to conclude that hydrogels based on nanocrystals have a great deal of potential for topical delivery of both new and established drugs.

Future prostate And Recent Advances

Further research can be done toproperly investigate these formulations, additional research is required, such as in-depth pharmacokinetic investigations, histological studies, and toxicity studies. It is important to investigate new approaches for introducing nanocrystals into the skin's deeper layers. The topical administration of pharmaceutical nanocrystals is not currently covered by any formal regulatory guidelines. A regulatory guideline, however, is expected to be made available soon. Although there are various cosmetic items on the market, the pharmaceutical industry has not yet marketed any topical drugs based on nanocrystals. The development of such items can be accelerated by industry and academic cooperation. Preclinical research should be combined with essential in-vitro and ex-vivo studies in future studies to determine the efficacy of formulations in the appropriate animal model. Recently, List of globally marketed nanomedicines approved by the FDA and the EMA are shown in **table. 5.**, Now a day, some nanocrystal-based formulation has patents has been done this are mention below **Table.6.**[90].

REFERENCES

[1]. Ameen, M., 2010. Epidemiology of superficial fungal infections. Clinics in dermatology, 28(2), pp.197-201.
[2]. Havlickova, B., Czaika, V.A. and Friedrich, M., 2008. Epidemiological trends in skin mycoses worldwide. Mycoses, 51, pp.2-15.
[3]. Zhang, A.Y., Camp, W.L. and Elewski, B.E., 2007. Advances in topical and systemic antifungals. Dermatologic clinics, 25(2), pp.165-183.
[4]. A.O. Goldstein, K.M. Smith, T.J. Ives, B. Goldstein, Mycotic infections. Effective management of conditions involving the

skin, hair, and nails, Geriatrics 55 (2000) 40–42, 45.

[5]. Queiroz-Telles, F., McGinnis, M.R., Salkin, I. and Graybill, J.R., 2003. Subcutaneous mycoses. Infectious Disease Clinics, 17(1), pp.59-85.

[6]. Sathyan, G., Ritschel, W.A. and Hussain, A.S., 1995. Transdermal delivery of tacrine: I. Identification of a suitable delivery vehicle. International journal of pharmaceutics, 114(1), pp.75-83.

[7]. Magdum Chandrakant, S., Naikwade Nilofar, S. and Shah Rohit, R., 2009. Preparation and evaluation of fluconazole topical microemulsion. Journal of Pharmacy Research, 2(3), pp.557-562.

[8]. Esentürk, İ., Balkan, T., Özhan, G., Döşler, S., Güngör, S., Erdal, M.S. and Sarac, A.S., 2020. Voriconazole incorporated nanofiber formulations for topical application: preparation, characterization and antifungal activity studies against Candida species. Pharmaceutical development and technology, 25(4), pp.440-453.

[9]. Silva, H., Luz, G.M., Satake, C.Y., Correa, B.C., Sarmento, V.H., Oliveira, G.H.D., Carvalho, F.C., Chorilli, M. and Gremião, M.P.D., 2014. Surfactant-based transdermal system for fluconazole skin delivery. Journal of Nanomedicine & Nanotechnology, pp.1-10.

[10]. Nair, S.K., Basu, S., Sen, B., Lin, M.H., Kumar, A.N., Yuan, Y., Cullen, P.J. and Sarkar, D., 2019. Colloidal gels with tunablemechano morphology regulate endothelial morphogenesis. Scientific reports, 9(1), pp.1-17.

[11]. Mondal, M., Ibrahim, H. and Haque, M., 2019. Cellulosic hydrogels: a greener solution of sustainability. Cellulose-based superabsorbent hydrogels, pp.3-35.

[12]. Pakdel, P.M. and Peighambardoust, S.J., 2018. A review on acrylic based hydrogels and their applications in wastewater treatment. Journal of environmental management, 217, pp.123-143.

[13]. Karimzadeh, Z., Mahmoudpour, M., Rahimpour, E. and Jouyban, A., 2022. Nanomaterial based PVA nanocomposite hydrogels for biomedical sensing: Advances toward designing the ideal flexible/wearable nanoprobes. Advances in Colloid and Interface Science, p.102705.

[14]. Gao, W., Zhang, Y., Zhang, Q. and Zhang, L., 2016. Nanoparticle-hydrogel: a hybrid biomaterial system for localized drug delivery. Annals of biomedical engineering, 44, pp.2049-2061.

[15]. Sultan, S. and Mathew, A.P., 2018. 3D printed scaffolds with gradient porosity based on a cellulose nanocrystal hydrogel. Nanoscale, 10(9), pp.4421-4431.

[16]. Sinha, V. and Chakma, S., 2019. Advances in the preparation of hydrogel for wastewater treatment: A concise review. Journal of Environmental Chemical Engineering, 7(5), p.103295.

[17]. Hoare, T.R. and Kohane, D.S., 2008. Hydrogels in drug delivery: Progress and challenges. polymer, 49(8), pp.1993-2007.

[18]. Zhao, F., Yao, D., Guo, R., Deng, L., Dong, A. and Zhang, J., 2015. Composites of polymer hydrogels and nanoparticulate systems for biomedical and pharmaceutical applications. Nanomaterials, 5(4), pp.2054-2130.

[19]. Lu, P., & Hsieh, Y. L. (2010). Preparation and properties of cellulose nanocrystals: Rods, spheres, and network. Carbohydrate Polymers, 82(2), 329–336.

[20]. Liang, M., Ge, X., Dai, J., Ren, P., Wei, D., Xu, L., Zhang, Q., He, C., Lu, Z. and Zhang, T., 2021. High-strength hydrogel adhesive formed via multiple interactions for persistent adhesion under saline. ACS applied bio materials, 4(6), pp.5016-5025.

[21]. Zhao, F., Yao, D., Guo, R., Deng, L., Dong, A. and Zhang, J., 2015. Composites of polymer hydrogels and nanoparticulate systems for biomedical and pharmaceutical applications. Nanomaterials, 5(4), pp.2054-2130

[22]. Paukkonen, H., Kunnari, M., Laurén, P., Hakkarainen, T., Auvinen, V.V., Oksanen, T., Koivuniemi, R., Yliperttula, M. and Laaksonen, T., 2017. Nanofibrillar cellulose hydrogels and reconstructed hydrogels as matrices for controlled drug release. International journal of pharmaceutics, 532(1), pp.269-280.

[23]. Kesharwani, P., Bisht, A., Alexander, A., Dave, V. and Sharma, S., 2021. Biomedical applications of hydrogels in drug delivery system: An update. Journal of Drug Delivery Science and Technology, 66, p.102914.

[24]. Karvinen, J. and Kellomäki, M., 2022. Characterization of self-healing hydrogels for biomedical applications. European Polymer Journal, p.111641.

[25]. Hydrogels as Novel Drug Delivery Systems; Limitations and Solutions Parisa Ghasemiyeh 1,3, Soliman Mohammadi Samani 2,3, Amir Azadi

[26]. Ran, Q., Wang, M., Kuang, W., Ouyang, J., Han, D., Gao, Z. and Gong, J., 2022. Advances of Combinative Nanocrystal Preparation Technology for Improving the Insoluble Drug Solubility and Bioavailability. Crystals, 12(9), p.1200.

[27]. Lu, Y., Li, Y. and Wu, W., 2016. Injected nanocrystals for targeted drug delivery. Acta Pharmaceutica Sinica B, 6(2), pp.106-113.

[28]. Chen, Z., Wu, W. and Lu, Y., 2020. What is the future for nanocrystal-based drug-delivery systems? Therapeutic Delivery, 11(4), pp.225-229.

[29]. Raval, A.J. and Patel, M.M., 2011. Preparation and characterization of nanoparticles for solubility and dissolution rate enhancement of meloxicam. International Research Journal of Pharmaceuticals, 1(2), pp.42-49.

[30]. Liu, T., Müller, R.H. and Möschwitzer, J.P., 2015. Effect of drug physico-chemical properties on the efficiency of top-down process and characterization of nanosuspension. Expert opinion on drug delivery, 12(11), pp.1741-1754.

[31]. Jarvis, M., Krishnan, V. and Mitragotri, S., 2019. Nanocrystals: A perspective on translational research and clinical studies. Bioengineering & translational medicine, 4(1), pp.5-16.

[32]. Yang, X., Gao, L., Guo, Q., Li, Y., Ma, Y., Yang, J., Gong, C. and Yi, C., 2020. Nanomaterials for radiotherapeutics-based multimodal synergistic cancer therapy. Nano Research, 13, pp.2579-2594.

[33]. Shegokar, R. and Müller, R.H., 2010. Nanocrystals: industrially feasible multifunctional formulation technology for poorly soluble actives. International journal of pharmaceutics, 399(1-2), pp.129-139.

[34]. Srivalli, K.M.R. and Mishra, B., 2016. Drug nanocrystals: A way toward scale-up. Saudi Pharmaceutical Journal, 24(4), pp.386-404.

[35]. Keck, C.M. and Müller, R.H., 2006. Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. European journal of pharmaceutics and biopharmaceutics, 62(1), pp.3-16.

[36]. Liu, J., Sun, Y., Cheng, M., Liu, Q., Liu, W., Gao, C., Feng, J., Jin, Y. and Tu, L., 2021. Improving oral bioavailability of luteolin nanocrystals by surface modification of sodium dodecyl sulfate. AAPS PharmSciTech, 22, pp.1-11.

[37]. Joshi, K., Chandra, A., Jain, K. and Talegaonkar, S., 2019. Nanocrystalization: an emerging technology to enhance the bioavailability of poorly soluble drugs. Pharmaceutical nanotechnology, 7(4), pp.259-278.

[38]. Sugiyama, T., Asahi, T. and Masuhara, H., 2004. Formation of 10 nm-sized Oxo (phtalocyaninato) vanadium (IV) Particles by Femtosecond Laser Ablation in Water. Chemistry letters, 33(6), pp.724-725.

[39]. Tian, Y.; Peng, Y.; Zhang, Z.; Zhang, H.; Gao, X. Research progress on preparation technology of nanocrystal drugs. Acta Pharm. Sin. 2021, 56, 1902–1910.

[40]. Guo, Z., Zhang, M., Li, H., Wang, J. and Kougoulos, E., 2005. Effect of ultrasound on anti-solvent crystallization process. Journal of Crystal Growth, 273(3-4), pp.555-563.

[41]. Chen, J. The Pharmacokinetics Evaluation and Preparation of Hydrochlorothiazide and Valsartan Nanocrystals. Master's Thesis, Guangdong Pharmaceutical University, Guangzhou, China, 2016.

[42]. Thorat, A.A.; Dalvi, S.V. Liquid antisolvent precipitation and stabilization of nanoparticles of poorly water-soluble drugs in aqueous suspensions: Recent developments and future perspective. Chem. Eng. J. 2012, 181–182, 1–34.

[43]. Sinha, B.; Müller, R.H.; Möschwitzer, J.P. Bottom-up approaches for preparing drug nanocrystals: Formulations and factors

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1415-1434 www.ijprajournal.com ISSN: 2249-7781

affecting particle size. Int. J. Pharm. 2013, 453, 126–141.
[44]. Technical Guidelines for Nanomedicine Quality Control Research (for Trial Implementation). Available online: https://www. nmpa.gov.cn/ (accessed on 18 March 2021).
[45]. Chow, A.H.L.; Tong, H.H.Y.; Chattopadhyay, P.; Shekunov, B.Y. Particle Engineering for Pulmonary Drug Delivery. Pharm. Res. 2007, 24, 411–437.
[46]. Yue, P.; Liu, Y.; Xie, J.; Chen, Y.; Yang, M. Review and prospect on preparation technology of drug nanocrystals in the past thirty years. Acta Pharm. Sin. 2018, 53, 529–537.
[47]. Ding, Y.; Kang, B.; Wang, J. Preparation and in vitro evaluation of budesonide inhalation nanosuspension. Chin. J. Pharm. 2017, 48, 1131–1137.
[48]. Han, X.; Wang, M.; Ma, Z.; Xue, P.; Wang, Y. A new approach to produce drug nanosuspensions CO2-assisted effervescence to produce drug nanosuspensions. Colloids Surf. B. Biointerfaces 2016, 143, 107–110.
[49]. Mou, D.; Liao, Y.; Zhou, X.; Wan, J.; Yang, X. Advances in Nanocrystal Medicine. Her. Med. 2020, 39, 1257–1261.
[50]. Chen, J.F.; Wang, Y.H.; Guo, F.; Wang, X.M.; Zheng, C. Synthesis of Nanoparticles with Novel Technology: High-Gravity Reactive Precipitation. Ind. Eng. Chem. Res. 2000, 39, 948–954
[51]. Zheng, A.; Shi, J. Research progress in nanocrystal drugs. J. Int. Pharm. Res. 2012, 39, 177–183.
[52]. Kipp, J.E.; Wong, J.C.T.; Doty, M.J.; Rebbeck, C.L. Microprecipitation Method for Preparing Submicron Suspensions .2001. Available online: https://patents.google.com/patent/US7037528B2/en (accessed on 18 March 2021).
[53]. Pardhi, V.P.; Verma, T.; Flora, S.J.S.; Chandasana, H.; Shukla, R. Nanocrystals: An Overview of Fabrication, Characterization and Therapeutic Applications in Drug Delivery. Curr. Pharm. Des. 2018, 24, 5129–5146
[54]. Möschwitzer, J.P. Drug nanocrystals in the commercial pharmaceutical development process. Int. J. Pharm. 2013, 453, 142–156.
[55]. Romero, G.B.; Chen, R.; Keck, C.M.; Müller, R.H. Industrial concentrates of dermal hesperidin smartCrystals®—Production, characterization & long-term stability. Int. J. Pharm. 2015, 482, 54–60.
[56]. Gholap, A.; Borude, S.; Mahajan, A.; Amol, M.; Gholap, D. Smart Crystals Technology: A Review. Pharmacologyonline 2011, 3, 238–243.
[57]. Li, Y.; Wang, Y.; Yue, P.F.; Hu, P.Y.; Wu, Z.F.; Yang, M.; Yuan, H.L. A novel high-pressure precipitation tandem homogenization technology for drug nanocrystals production—A case study with ursodeoxycholic acid. Pharm. Dev. Technol. 2014, 19, 662–670.
[58]. Möschwitzer, J.; Müller, R.H. New method for the effective production of ultrafine drug nanocrystals. J. Nanosci. Nanotechnol. 2006, 6, 3145–3153.
[59]. Malamatari, M.; Taylor, K.M.G.; Malamataris, S.; Douroumis, D.; Kachrimanis, K. Pharmaceutical nanocrystals: Production by wet milling and applications. Drug Discov. Today 2018, 23, 534–547.
[60]. Wadhawan, J.; Parmar, P.K.; Bansal, A.K. Nanocrystals for improved topical delivery of medium soluble drug: A case study of acyclovir. J. Drug Deliv. Sci. Technol. 2021, 65, 102662.
[61]. Morakul, B.; Suksiriworapong, J.; Chomnawang, M.T.; Langguth, P.; Junyaprasert, V.B. Dissolution enhancement and in vitro performance of clarithromycin nanocrystals produced by precipitation–lyophilization–homogenization method. Eur. J. Pharm. Biopharm. 2014, 88, 886–896.
[62]. Sinha, B.; Müller, R.H.; Möschwitzer, J.P. Bottom-up approaches for preparing drug nanocrystals: Formulations and factors affecting particle size. Int. J. Pharm. 2013, 453, 126–141.
[63]. Chen, X.; Young, T.J.; Sarkari, M.; Williams, R.O.; Johnston, K.P. Preparation of cyclosporine A nanoparticles by evaporative precipitation into aqueous solution. Int. J. Pharm. 2002, 242, 3–14.
[64]. Huang, T.; Lin, Q.; Qian, Y.; Xu, X.; Zhou, J. Preparation and Characteristics of Celecoxib Nanocrystals. Chin. J. Pharm. 2015, 46, 358–363.

[65]. Jin, S.; Yuan, H.; Jin, S.; Lv, Q.; Bai, J.; Han, J. Preparation of baicalin nanocrystal pellets and preliminary study on its pharmacokinetics. China J. Chin. Mater. Med. 2013, 38, 1156–1159.

[66]. Zuo, X. Preparation of New Nano pharmaceutical Combination Method and Its Preparation. Master's Thesis, Qingdao University of Science & Technology, Qingdao, China, 2019.

[67]. Yu, X. Preparation and Formulation of Novel Drug Nanoparticles Based on High Efficient Solubilization. Master's Thesis, Qingdao University of Science & Technology, Qingdao, China, 2021.

[68]. Zhang, H.; Meng, Y.; Wang, X.; Dai, W.; Wang, X.; Zhang, Q. Pharmaceutical and pharmacokinetic characteristics of different types of fenofibrate nanocrystals prepared by different bottom-up approaches. Drug Deliv. 2014, 21, 588–594.

[69]. Gong, T., Patel, S.K., Parniak, M.A., Ballou, B. and Rohan, L.C., 2019. Nanocrystal formulation improves vaginal delivery of CSIC for HIV prevention. AapsPharmscitech, 20, pp.1-13.

[70]. Atia, N.M., Hazzah, H.A., Gaafar, P.M. and Abdallah, O.Y., 2019. Diosmin nanocrystal–loaded wafers for treatment of diabetic ulcer: in vitro and in vivo evaluation. Journal of Pharmaceutical Sciences, 108(5), pp.1857-1871.

[71]. Chang, T.L., Zhan, H., Liang, D. and Liang, J.F., 2015. Nanocrystal technology for drug formulation and delivery. Frontiers of Chemical Science and Engineering, 9, pp.1-14.

[72]. Bansal, S., Bansal, M. and Kumria, R., 2012. Nanocrystals: current strategies and trends. Int J Res Pharm Biomed Sci, 4, p.10.

[73]. Jarvis, M., Krishnan, V. and Mitragotri, S., 2019. Nanocrystals: A perspective on translational research and clinical studies. Bioengineering & translational medicine, 4(1), pp.5-16.

[74]. Li, J., Wang, Z., Zhang, H., Gao, J. and Zheng, A., 2021. Progress in the development of stabilization strategies for nanocrystal preparations. Drug Delivery, 28(1), pp.19-36.

[75]. Gigliobianco, M.R., Casadidio, C., Censi, R. and Di Martino, P., 2018. Nanocrystals of poorly soluble drugs: drug bioavailability and physicochemical stability. Pharmaceutics, 10(3), p.134.

[76]. Shete, G., Jain, H., Punj, D., Prajapat, H., Akotiya, P. and Bansal, A.K., 2016. Stabilizers used in nano-crystal based drug delivery systems. Journal of Excipients and Food Chemicals, 5(4).

[77]. Kumar, M., Shanthi, N., Mahato, A.K., Soni, S. and Rajnikanth, P.S., 2019. Preparation of luliconazole nanocrystals loaded hydrogel for improvement of dissolution and antifungal activity. Heliyon, 5(5), p.e01688.

[78]. Permana, A.D., Utami, R.N., Layadi, P., Himawan, A., Juniarti, N., Anjani, Q.K., Utomo, E., Mardikasari, S.A., Arjuna, A. and Donnelly, R.F., 2021. Thermosensitive and mucoadhesive in situ ocular gel for effective local delivery and antifungal activity of itraconazole nanocrystal in the treatment of fungal keratitis. International journal of pharmaceutics, 602, p.120623.

[79]. Sharma, R.K. and Ghose, R., 2015. Synthesis and characterization of nanocrystalline zinc ferrite spinel powders by homogeneous precipitation method. Ceramics International, 41(10), pp.14684-14691.

[80]. Patel, V., Sharma, O.P. and Mehta, T.A., 2019. Impact of process parameters on particle size involved in media milling technique used for preparing clotrimazole nanocrystals for the management of cutaneous candidiasis. AAPS PharmSciTech, 20, pp.1-15.

[81]. Gülsu, A. and Yüksektepe, E., 2021. Preparation of gentamicin conjugated cellulose nanocrystals and evaluation of efficacy on different microorganisms. AvrupaBilimveTeknoloji Dergisi, (27), pp.1105-1112.

[82]. Andrews, P.L.R., Kovacs, M. and Watson, J.W., 2001. The anti-emetic action of the neurokinin1 receptor antagonist CP-99,994 does not require the presence of the area postrema in the dog. Neuroscience letters, 314(1-2), pp.102-104.

[83]. Narayan, R., Pednekar, A., Bhuyan, D., Gowda, C., Koteshwara, K.B. and Nayak,

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1415-1434 www.ijprajournal.com ISSN: 2249-7781

U.Y., 2017. A top-down technique to improve the solubility and bioavailability of aceclofenac: in vitro and in vivo studies. International journal of nanomedicine, 12, p.4921.

[84]. Boyce, R.D., Collins, C., Clayton, M., Kloke, J. and Horn, J.R., 2012. Inhibitory metabolic drug interactions with newer psychotropic drugs: inclusion in package inserts and influences of concurrence in drug interaction screening software. Annals of Pharmacotherapy, 46(10), pp.1287-1298.

[85]. Wappler, F. S1-Leitlinie maligneHyperthermie. Der Anaesthesist 2018, 67, 529–532.

[86]. Epstein, N.E., 2015. Preliminary study showing safety/efficacy of nanoss bioactive versus vitoss as bone graft expanders for lumbar noninstrumented fusions. Surgical Neurology International, 6(Suppl 10), p.S318.

[87]. https://ipindiaservices.gov.in/PublicSearch/PublicationSearch/Search

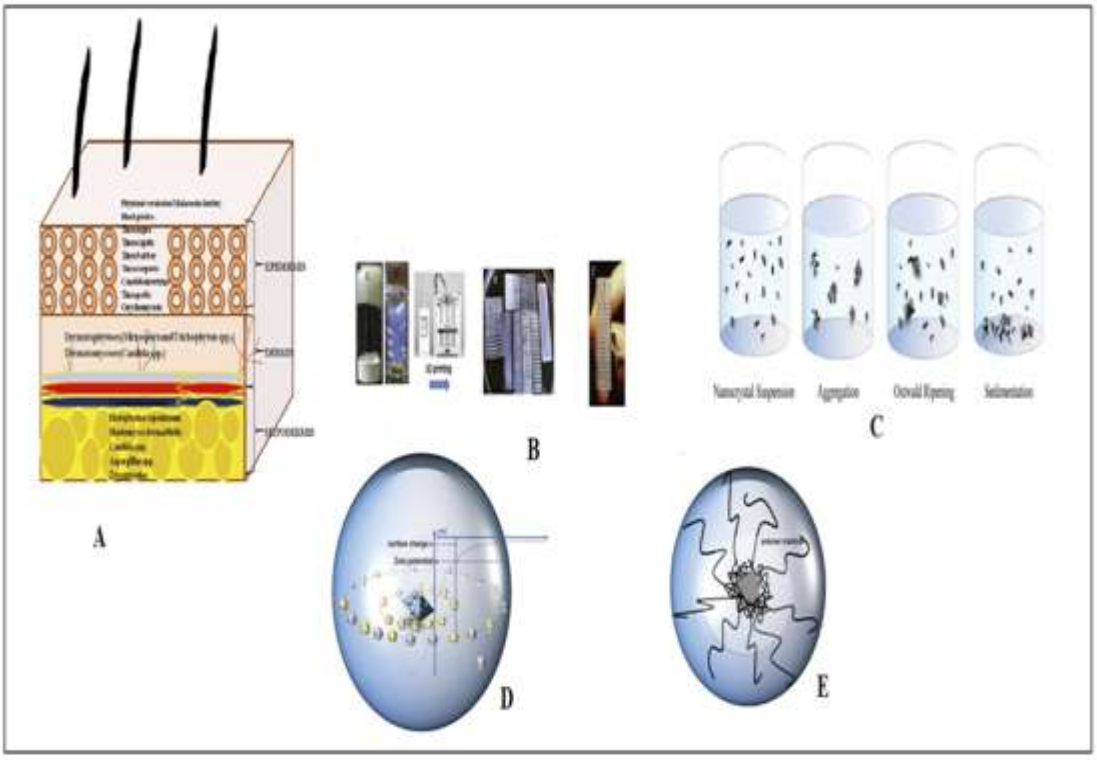

Figure.1. A. Layers of skin with fungal infection [8], **B.** Diagrammatic depiction of the processing route for 3D printed CNCs/SA/gelatin hydrogel scaffolds [18], **C.** Instability mechanisms of nanocrystals [78], **D.** Action mechanism of electrostatic stabilization [79], **E.** Action mechanism of steric stabilization [79]

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1415-1434 www.ijprajournal.com ISSN: 2249-7781

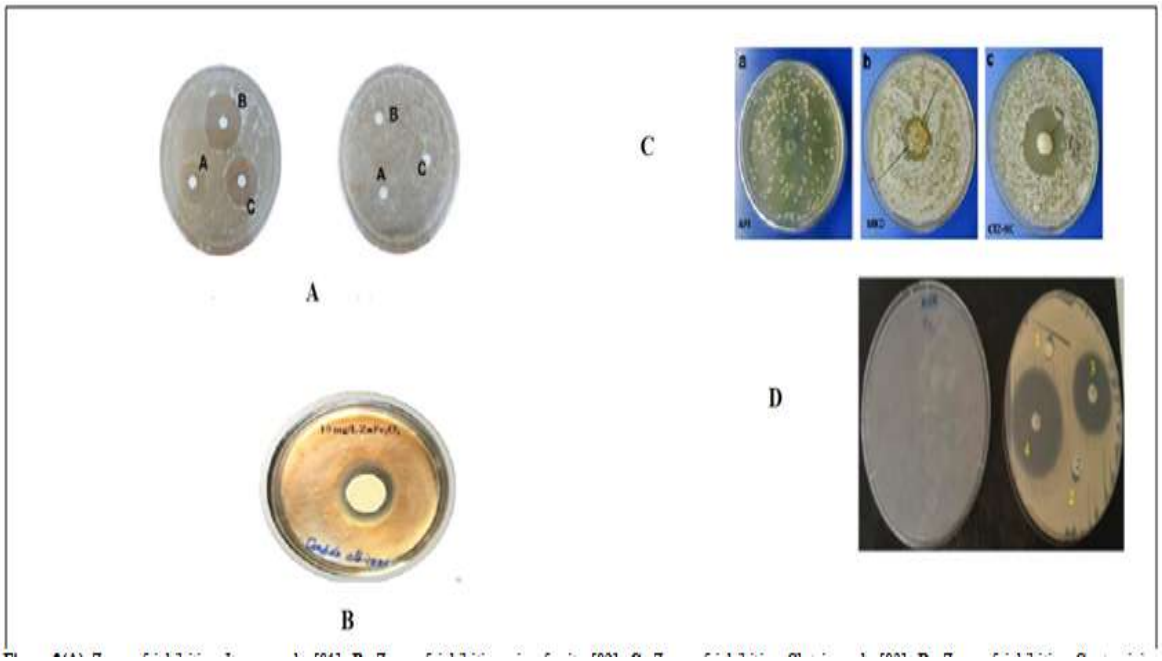

Figure.2(A) Zone of inhibition Itraconazole [81], **B.** Zone of inhibition zinc ferrite [82], **C.** Zone of inhibition Clotrimazole [83], **D.** Zone of inhibition Gentamicin Conjugated Cellulose [84]

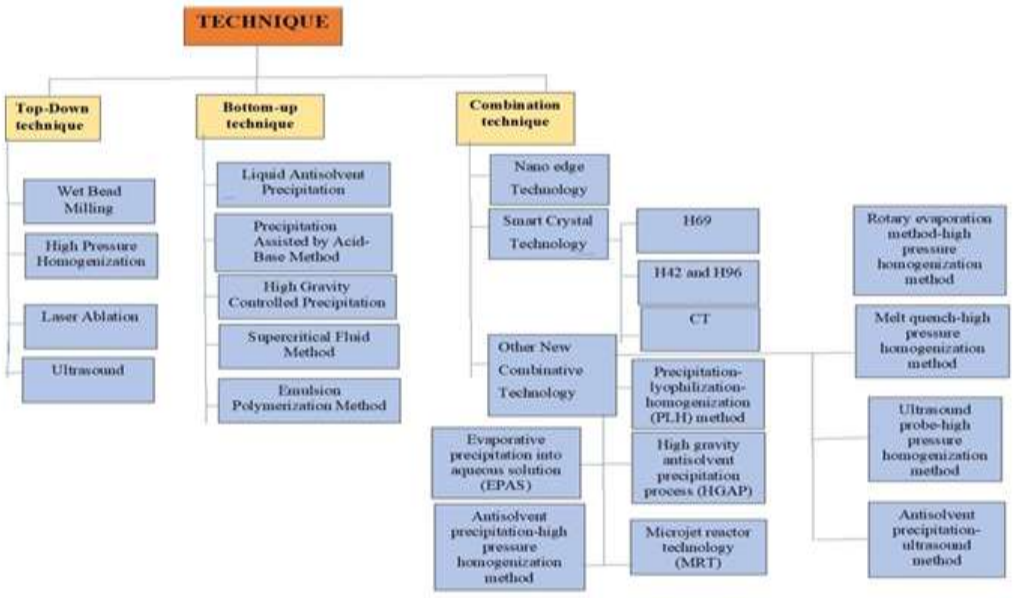

Figure.3. Techniques for nanocrystal production

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1415-1434 www.ijprajournal.com ISSN: 2249-7781

Table 1. Advantages and disadvantages of nanocrystal production techniques([73], [74], [75]

Sr. No	Technique	Advantages	Disadvantages
1	Precipitation	1. Simple and low-cost method 2. Very less energy requirement 3. continuous production is possible	1. Possible growth of particles with time due to Ostwald ripening 2. Requires substantial optimization to find a suitable solvent or antisolvent 3. Insufficient purification process or elimination of harmful solvents
2	Media milling	1. Drugs that are insoluble in both aqueous and non-aqueous solvents can be used. 2. Reduced batch to batch variation 3. Ease of scalability 4. There are no organic solvents required 5. Narrow size distribution	1. Expensive manufacturing process 2. High shear forces and heat build-up could destabilize the drugs 3. Unwanted drug loss 4. Contamination risk from dispersion media 5. High energy requirement
3	High-pressure homogenization (HPH)	Same as mentioned for media milling	1. High energy requirement 2. Contamination risk, which includes machine debris 3. The particles must be micronized and suspended
4	High gravity-controlled precipitation (HGCP)	1.Can produce crystalline particles 2.suspensions can be recycled for prolonged mixing and reaction 3. It has been scaled-up for commercial manufacturing 4. No need to use a stabilizer	Equipment is highly specialized and not widely available
5	Evaporative precipitation techniques	1. Cost-effective 2. easy to operate 3. can be easily scaled for massive production	May not be suitable for heat-labile compounds
6	Rapid expansion of supercritical solution (RESS)	1.Uniform size distribution 2. less processing steps	1. Low solubility of polar drugs in sc-CO2 2. agglomeration of the small particles
7	Supercritical anti-solvent (SAS)	1.This process can take place at near ambient temperatures 2. small particle size; easy scale-up	The presence of residual toxic solvents in the final product

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1415-1434 www.ijprajournal.com ISSN: 2249-7781

8	Spray freezing into liquid (SFL)	1.Highly porous amorphous and smaller size nanocrystals in the form of solid solution are produced 2. Improve dissolution rates and bioavailability of poorly water-soluble APIs	The drug should have a low glass transition temperature (Tg)
9	H69	1.The top-down step reduces the particle size as well as stabilizes the nanocrystals with the applied energy 2. The annealing step promotes the more stable crystalline form	The resulting nanosuspensions contain organic solvent residues
10	CT (Combinative Technology)	1. The reduction of the homogenization pressure and process length 2. The improved physical stability of the nanosuspensions	The particle sizes are relatively bigger than the other combinative processes

Table.2. Nanocrystal-based formulation developed for topical delivery [76]

Sr.no	**Drug**	**Stabilizer used**	**Dosage form**	**Manufacturing technology**	**Application**
1	Luliconazole	Vit.E TPGS and HPMC	Hydrogel	Modified nanoprecipitation	Fungal infection
2	Fusidic acid	PVA 4-88	Cream	Modified nanoprecipitation	antibacterial
3	Azelaic acid	Polysorbate 60	Hydrogel	Wet media milling	Acne rosacea
4	Apremilast	Poloxamer 407	Nanosuspension, nanogel, cream	Wet media milling	Psoriasis
5	Rapamycin	D-a-tocopheryl polyethylene glycol succinate	Tablet	Ball milling	Antifungal

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1415-1434 www.ijprajournal.com ISSN: 2249-7781

6	Naproxen	Vitamin E tocopherol polyethylene glycol succinate, Pluronic F127, sodium lauryl sulfate, di(2- ethylhexyl) sulfosuccinate	Tablet	Milling	anti-inflammatory
7	Paclitaxel	Hydroxylpropyl methylcellulose, polyvinylpyrrolidone, polyethylene glycol 400, Pluronics F127 and F68, sodium lauryl sulfate, Tween 20 and 80, transferrin, immunoglobulin G, human serum albumin	Injection	Antisolvent precipitation, sonication	anticancer
8	Curcumin	Polyvinyl alcohol, polyvinyl pyrrolidone, vitamin E tocopherol polyethylene glycol succinate, sodium lauryl sulfate, Carboxymethylcellulose sodium	Gel	High pressure homogenization	anti-inflammatory
9	Beclomethasone dipropionate	Hydrophobin	nanosuspension	Antisolvent precipitation	antifungal

Table. 3 show the main instability of nanocrystal formulation

Main Instability	**Techniques Provoking the Instability**
particle aggregation	Wet comminution, Lyophilization High-pressure homogenization, Bead milling, Cavi-precipitation Dehydration of the surfactant
amorphization	Spray-drying, Lyophilization, Dry milling, Cryomilling, Wet milling
crystallization	Antisolvent High-pressure homogenization, Nano spray, and drying underwent.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1415-1434 www.ijprajournal.com ISSN: 2249-7781

Table. 4 shows the different types of nanocrystal modifier

Type of Nanocrystal Surface Modifier	Example	Mechanism	Drug—Active Compound	Applied Technology
Ionic surfactants / charged polymers	sodium cholate, sodium deoxycholate, sodium lauryl sulfate, sodium dodecyl sulfate, sodium poly (ethylene imine), chitosan	Electrostatic repulsion (prevent aggregation)	Albendazole, Spironolactone, Curcumin, Nitrendipine, Rutin	Nanoprecipitation High-pressure homogenization Milling Nanoprecipitation method
Non-ionic surfactant/polymers	polyvinyl alcohol, polyvinyl pyrrolidone, polysorbates, Pluronic, poloxamers, triblock-copolymers of polyoxyethylene and polyoxypropylene	Steric barrier against aggregation (prevent aggregation)	Ibuprofen, Hydrocortisone acetate, Apigenin Dexamethasone	Antisolvent precipitation method Wet comminution Pearl milling

Table. 5. List of globally marketed nanomedicines approved by the FDA and the EMA

Drug Name	company	Application	Date of approve
Fosaprepitant[85]	Merk & Co. Inc	antiemetic drug	2008
Rapamycin [86]	Wyeth Pharmaceuticals Inc. (a subsidiary of Pfizer Inc.)	a rare progressive lung disease	2015
Paliperidone [87]	Janssen Pharmaceuticals	schizophrenia	2009
Dantrolene sodium [88]	Eagle pharm	malignant hyperthermia	2014
Hydroxyapatite [89]	RTI Surgical	bone substitute	2005

- **Table.6.** Nanocrystal-based formulation has patents has been done this are mention below [90]

Sr. No.	Title	Application date	Patent number/Application number	Status of patent
1	Atazanavir Nanocrystal Formulation	09/09/2020	393527	Granted
2	Method of synthesis of atomically precise metal cluster-cellulose nanocrystal composite for diffusion controlled simultaneous sensing and scavenging of heavy metal ions in water	19/09/2016	367409	Granted
3	Cellulose nanocrystal templated iron oxyhydroxide based	12/08/2016	343818	Granted

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1415-1434 www.ijprajournal.com ISSN: 2249-7781

	adsorbent for arsenic removal from water and a device there of			
4	"Redox doping of semiconductors by colloidal nanocrystal dopants"	15/07/2014	328951	Granted
5	Nanocrystal titanium alloy and production method for same	21/03/2012	345625	Granted
6	Novel gold-platinum based bi-metallic nanocrystal suspensions, electrochemical manufacturing processes there for and uses for the same	21/10/2013	311966	Granted
7	Nanocrystal nano-emulsion		299583	Granted
8	Nanocrystal-sized cerium-zirconium-aluminium oxide material and method of making the same		202147034077	Published (under Examination for grant)
9	Solubility enhancement and bioavailability improvement of rosuvastatin calcium using nanocrystal-based hydrogel		202121002129	Published (under Examination for grant)
10	Biological self-assembled nanocrystal injection having a lymphatic targeting function and preparation method there of		201947045083	Published (under Examination for grant)