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Original Review Article

NANOCRYSTALS: A NOVEL APPROACH IN THE DELIVERY OF HYDROPHOBIC DRUGS

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Abstract

The distribution of medications into the relevant layers of the skin is referred to as dermal delivery. The delivery pathway has the potential to improve the active ingredients' local bioavailability at their drug target. Nanocrystal-based formulations for dermal distribution have recently received a lot of attention due to their increased skin penetration. According to current research on nanocrystal for topical delivery, it could be a novel approach for all formulators struggling with poorly soluble drugs. Nanocrystals are a step forward from typical nanocarriers, offering 100 percent drug loading, a huge surface area, and the potential for follicular targeting. The skin structure and physiology, nanocrystal fabrication methods, and applications are discussed in this review.

Keyword: Nanocrystals, Dermal drug delivery, Nanocrystal, Methods.

INTRODUCTION

The delivery of a pharmaceutical substance to a specific location on the skin to exert local therapeutic activity with limited systemic absorption is known as topical drug delivery. The drug is delivered topically to treat both acute and chronic skin infections and diseases[1]. Skin is the largest organ of the human body and outermost covering. The medication is administered through the skin when local delivery is intended. Therapeutics can be used as standalone or supplementary therapy for treating various skin problems such as inflammation of the skin, allergies, infection of the skin, acne, and psoriasis, thus reducing the need for systemic administration of the medication[2,3]. Delivery of drugs through the skin has some advantages such as patient compliance, avoiding first-pass metabolism, reduced systemic adverse effects, minimal drug-drug interactions, and the possibility of delivering a drug through in a sustained or controlled manner[4]. Passive diffusion is the primary mechanism for absorption into the skin, and a sufficient amount of dissolved active substance within the formulation is required for successful passive diffusion, as only dissolved molecules can be taken up[5,6].

However, drug delivery via the skin is challenging due to the barrier properties of the skin's outermost layer (stratum corneum), which prevents drug molecules from passing through. As a result, some of the most stringent physicochemical requirements imposed by this route, such as molecular weight, partition coefficient, lipophilicity, and ionization, limit its usage to only a few drugs with a specific set of features[7,8]. Traditional formulations with micronized active components, such as gels, creams, ointments, and lotions, are effective for medication delivery to the skin, but the

barrier function leads to inadequate penetration[9].

In the delivery of small molecules, overcoming poor water solubility and associated poor bioavailability is a serious challenge. Poor bioavailability affects effective topical delivery as well as oral bioavailability. As a result, many nanotechnologies assisted approaches such as liposomes, transfersomes, ethosomes, niosomes, nanoemulsions, solid lipid nanoparticles, polymeric nanoparticles, and nanocrystals have been used to overcome this issue and enhance the topical delivery[10,11].

Drug nanocrystals are pure drug particles with the highest drug loading of any nano-based formulation. Drug nanocrystals have particle sizes ranging from 1nm to 1000nm, and are stabilized by polymeric or surfactant-based stabilizers. Nanocrystals may have a crystalline or amorphous structure[12]. Nanocrystals are commonly prepared in a dispersion medium containing stabilizers, resulting in a colloidal form, and these systems are also referred to as nanosuspensions. Most stabilizers are assumed to lower the risk of nanoparticle aggregation by adsorbing onto the surfaces of nanocrystals[13].

Drug nanocrystals have a greater surface area than pure drug particles, which improves their contact with biological membranes and gives them mucoadhesive characteristics when applied to the skin. Nanocrystals have a high saturation solubility, resulting in a higher concentration gradient and the potential for passive penetration following application to the skin[14-16]

Several drug products of oral nanocrystals has already entered the market. Rapamune® (Sirolimus, Pfizer), Emend® (Aprepitant, MSD), and Tricor® (Fenofibrate, AbbVie) are just a few of the oral nanocrystals medicine products that have hit the market. However, nanocrystal-based pharmaceutical formulation for dermal use has yet to enter the market. Nonetheless, a variety of cosmetics based on the nanocrystal principle are already in the market. Juvedical (Juvena), Edelweiss (Audorasan), and Platinum rare (laprairie) are some of the examples[17-19]. Even though there are numerous papers detailing the principles of nanocrystals for oral and dermal applications, there is relatively little research in the field of nanocrystals for dermal application[20, 21].

SKIN STRUCTURE

Skin is the body's largest organ, covering roughly $2m^2$ and accounting for 15 percent of total adult body weight[22]. It is composed of numerous layers, each with a different composition and structure. Three layers make up the human skin: the epidermis, the dermis, and the hypodermis. The epidermis is made up of four layers, the stratum corneum (topmost layer), followed by the stratum granulosum, stratum spinosum, and stratum basale.

The dermis, which lies beneath the epidermis, ensures that the skin is flexible and that the body's temperature is maintained. It is made up primarily of collagen fibers interspersed with elastic fibers, all of which are surrounded by a proteoglycan and glycoprotein matrix. The dermis contains blood arteries, lymphatic channels, and sensory nerves. Any substance that makes it to the dermis has the potential to enter the systemic circulation. The dermis and hypodermis lying beneath the epidermis are irrelevant for the penetration of drug substances for dermal therapy [23,24].

NANOCRYSTAL FOR TOPICAL DELIVERY

The nanocrystal drug may have a crystalline or amorphous state. One of the most

important characteristics of nanocrystal drugs is that they are made entirely of the drug. Unlike polymeric nanoparticles, no carrier materials are used in the preparation of nanocrystal. Dispersion of nanocrystal drugs in an aqueous solution is also called nanosuspension[25-27].

Nanocrystals are prepared in a dispersion medium containing a stabilizer. A stabilizer is a significant excipient that plays an important role in the formulation of the nano-crystal. They prevent the aggregation of drug particles by adsorbing at the interface. Stabilizers are of different types, they can be ionic (Sodium dodecyl sulfate), nonionic (vitamin ETPGS, tweens, poloxamers), or polymeric (hydroxypropyl cellulose, polyvinyl pyrrolidone, hydroxypropyl methylcellulose, polyvinyl alcohol). In order to stabilize the nanocrystals, nonionic and polymeric stabilizers provide steric hindrance, whereas ionic stabilizers provide electrostatic repulsion[28-30]

The utilization of nanotechnology in the cosmetics industry has been demonstrated, as evidenced by the market share of several nanotechnology-based products. Commercially available nanoparticle-based cosmetics comprising titanium dioxide, zinc oxide, resveratrol, and other ingredients are available. However, drug nanocrystal formulation for dermal use is yet to be commercialized. The goals of developing nanocrystal-based formulations are to enhance product stability, penetration, efficacy, and tolerance, as well as to make the product more aesthetically appealing. Nanocrystal-based products have been found to penetrate deeper into the skin[31,32].

Nanocrystals increase the concentration gradient by increasing the saturation solubility of drugs which shows potential for passive penetration after application. The molecules penetrating the skin from nanocrystal-based products are rapidly recouped by new molecules dissolving from the nanocrystal depot[33].

Many of the nanocrystal-based products were licensed and approved by various regulatory bodies some of them are Rapamune®(sirolimus), Cesamet®(nabilone), Emend (aprepitant), Tricor(fenofibrate), etc. Few nanocrystal-based products, such as Semapimod®(Guanylhudrazone), Paxceed®(Paclitaxel), Theralux®(Thymectacin), and Nucryst®(Silver), and plenty of other products in the developmental stage [34].

Nanocrystals have a number of advantages when it comes to topical delivery which are as follows[35,36,37].

- Because they are made entirely of pure drug particles, they have a high drug loading.
- Nanocrystals can be stabilized by the low concentration of surfactants.
- They possess higher solubility and dissolution rate than the conventional particles.
- They have the ability to adhere to cell membranes or surfaces.
- There is no need for co-solvents or a wide range of pH for solubilization.
- Flexible production process.
- Higher therapeutic drug concentration at the application site.
- Nanocrystal shows higher penetration into the skin over microparticles.

METHODS PREPARATION OF NANOCRYSTALS

Nanocrystal production is divided into two categories: bottom-up and top-down techniques. In addition, novel techniques that combine the two basic techniques have been

developed. Various methods for nanocrystal production are reported in figure 1

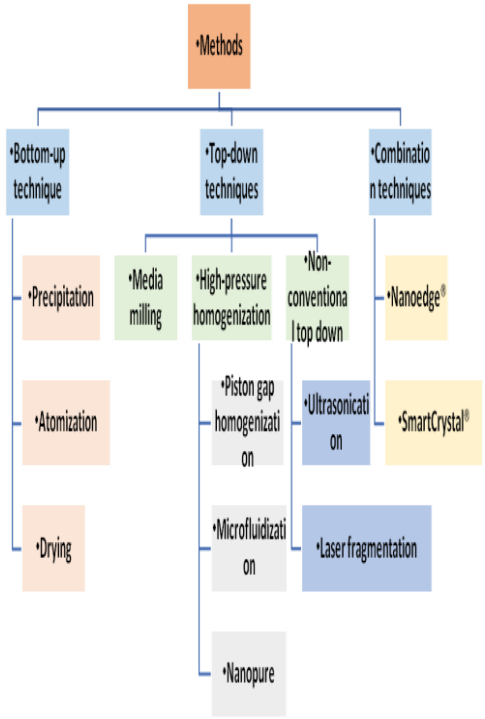

Figure 1. Methods of preparation of Nanocrystals[38]

1) Bottom-up techniques:

Controlled precipitation and evaporation principles are used in the bottom-up approach. This method is characterized by a simple instrument, low energy consumption, minimal heat generation, and minimal cost. Both thermostable and thermolabile active ingredients could benefit from this method. Some bottom-up approaches to nanocrystal production are listed below.

Antisolvent precipitation

The antisolvent precipitation method is the classical bottom-up approach to fabricating nanocrystals. The method employs precipitation in the supercritical solvent or precipitation by the addition of solvent-antisolvent or induces precipitation upon the removal of solvent[39]. The stabilizer which is water-soluble is dissolved in water (antisolvent) and the drug is dissolved in an organic solvent (solvent). The solvent phase is injected quickly into the antisolvent phase followed by continuous stirring using a magnetic stirrer to get the nanocrystals[40].

A) Evaporative precipitation into aqueous solution (EPAS) process:

EPAS method is a novel technique employed for the drugs which are soluble in the water-immiscible solvent. The drug is dissolved in an organic solvent. The organic phase is slowly added to the aqueous solution containing surfactant and polymer. After the mixing procedure, the suspension is stirred until nanosuspension is obtained. The obtained nanosuspension is freeze-dried to sustain the long-term stability of nanocrystals[41].

B) Supercritical fluid technology:

The method uses supercritical carbon-dioxide solution (SCO2), with a critical temperature of 31.1 °C and pressure of 72.9 atm. SCO2 is low polarity supercritical liquid that easily dissolves hydrophobic drugs to form a solution. the expansion of this solution through a fine capillary tube produces fine drug particles. Supercritical fluid's low density, viscosity with enhanced diffusivity, and the expansion mechanism of the solution is the main principle of this technique. Fewer stability problems associated with the liquid samples can be overcome by producing the dried nanocrystal powder. Drying techniques such as spray drying or freeze-drying can be used [42, 43].

2) Top-down techniques:

It involves the size reduction process, where large-sized coarse drug particles are broken down to smaller size particles particularly to the nanometric size range by using media milling techniques or high-pressure homogenization.

Media milling technique: In the milling process, the size reduction of the drug

substance is performed in a liquid suspension form. Coarse drug particles and stabilizer is dispersed in a dispersion medium and is later ground by using grinding agents such as ball, pearl, or bead.

The grinding chamber is rotated at high speed which results in high impact due to ball-ball collision and ball-wall collision. This mechanical attrition decreases the particle size of the drug material to the nanometer range. Generally, zirconium oxide (often yttrium stabilized) or polystyrene beads are used as milling media. The nanocrystals produced from media milling shows well-defined shape and significantly smaller size distribution[44,45].

3) High-pressure homogenization (HPH):

The high-pressure homogenization technique uses Micro-fluidization or piston-gap homogenization principles.

In the micro-fluidization procedure, nanocrystals are decreased in size by colliding with air at a high rate and pressure. In piston gap homogenization, the drug suspension is pumped at high pressure and rate via a thin gap (25 µm or less) inside the piston device [46].

At high pressures ranging from 100 to 2000 bar, the drug suspension is driven through a small homogenization nozzle. Due to the sudden restriction of the drug suspension's flow and the application of high pressure at the same time, cavitation is generated, resulting in the creation of very small particles. A few patented innovations based on this approach include Dissocubes® (piston-gap homogenization technology), Nanopure®(by using water mixtures/nonaqueous media), and IDD-P®(microfluidizer technology)[47].

Combination technology:

The combination technique involves the use of both bottom-up and top-down techniques to generate nanocrystals with uniform shape, narrow size distribution, and easy scalability while avoiding the challenges associated with top-down and bottom-up approaches. Combination technologies have two steps: the first is pretreatment which includes the bottom technique(precipitation), followed by a size reduction procedure that requires high energy such as high-pressure homogenization or ultrasound energy. The Nanoedge^{TM} approach was the first combination technique to be developed, combining solvent/anti-solvent precipitation with HPH. Later, it was replaced by SmartCrystal® technology, a combinatorial process owned by Abbott, USA, in which a number of pre-treatment processes are combined with a final HPH step to produce uniform, nano-sized crystals[48]. H42 technique is a combination of spray drying and high-pressure homogenization, while H96 technique combines lyophilization and high-pressure homogenization. CT technique is a combination of bead milling and high-pressure homogenization to fabricate drug nanocrystals. The ArtCrystal process combines rotor-stator high-speed stirring with a later HPH stage to produce nanocrystals more quickly and efficiently. It was created by PharmaSol Ltd at first but was later purchased by Abbott Ltd[49].

As a result, combining approaches is favorable for faster production, easier scalability, and increased stability, and it has become the industry's preferred method for producing nanocrystals.

Table 1. Advantages and disadvantages of nanocrystal production techniques[50-53]

	Technique	Advantages	Disadvantages
Bottom-up approach	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,
Top-down approach	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	4. Expensive manufacturing process 5. High shear forces and heat buildup could destabilize the drugs. 6. Unwanted drug loss. 7. Contamination risk from dispersion media 8. High energy requirement
	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.

APPLICATION OF NANOCRYSTAL BASED FORMULATION FOR TOPICAL DELIVERY

Skin inflammation, fungal diseases, skin infections, psoriasis and atopic dermatitis, anti-aging treatments, skin inflammation, and anti-acne effects have all been studied using topical nanocrystal-based formulations. Table 2 summarizes the most important findings and current advances in the application of nanocrystal-based formulations via topical routes.

Table 2: Nanocrystal-based formulation developed for topical delivery[60-63]

Sr.no	Drug	Stabilizer used	Dosage form	Manufacturing technology	Application	Inference
1	Luliconazole	Vit.E TPGS and HPMC	Hydrogel	Modified nanoprecipitation	Fungal infection	The gel was homogenous for human usage, trapping roughly 88 percent of the particles, and was non-irritant and safe. The hydrogel showed better drug retention and antifungal activity than the coarse suspension, nanosuspension , and coarse drug-loaded gels.
2.	Fusidic acid	PVA 4-88	Cream	Modified nanoprecipitation	antibacterial	The nanocrystal-based cream outperformed the commercialized Fucidin® cream in terms of antibacterial activity and wound healing capabilities.
3	Azelaic acid	Polysorbate 60	Hydrogel	Wet media milling	Acne rosacea	The produced hydrogel's stratum corneal penetration depth and amount of medication penetration were identical to those of the marketed product Skinoren®.
4.	Apremilast	Poloxamer 407	Nanosuspension, nanogel, nanocream	Wet media milling	Psoriasis	Nanocrystal-based formulations exhibited better drug penetration in viable skin layers than formulations containing micron-sized particles.

CONCLUSION:

Drug nanocrystals are an innovative and adaptable method for improving the solubility and bioavailability of poorly water-soluble active pharmaceutical ingredients. This technology uses basic production procedures that are easy to scale up. The creation of nanocrystals is based on size reduction concepts. The development of tailor-made nanocrystals for better passive diffusion and/or hair follicle targeting can be enabled by careful selection of the proper excipients and/or carriers in topical formulations. The fast and controlled release of medications from nanocrystal-based formulations can aid in the treatment of topical and deeper skin infections. Nanocrystal technology has been successfully utilized in sunscreens, antiaging, moisturizers, foundations, and other cosmeceutical products. Pharmaceutical nanocrystals have a lot of commercial significance since they offer a lot of potential for delivering new chemical entities and existing medications topically.

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