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A Complete Overview of Nanocrystals in Pharmaceuticals

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ABSTRACT

Nanocrystals are nanoparticles that are fully composed of drugs without any carriers. In Nanocrystals, the drug molecules are wrapped within a thin coating of surfactant. It is an excellent drug delivery system for BCS Class II and Class IV drugs. Nanocrystals provide numerous benefits, such as enhanced solubility and bioavailability; they overcome toxicity problems and inappropriate absorption patterns. In addition, Nanocrystals facilitate dose reduction, sustained drug release, and tissue targeting. Nanocrystals are an industrially feasible drug delivery system, and they have great potential for use in various routes such as oral, ophthalmic, dermal, parenteral, pulmonary, etc. In the future, Nanocrystals will be a one-stop solution for poorly soluble drugs and for drugs with the least permeability .This article reviews in briefly about significance of Nanocrystals ,various Nanocrystalline technologies, characterization of Nanocrystals and the future aspects of Nanocrystals.

INTRODUCTION

Nano crystallization is an excellent technique used for improving the bioavailability and solubility of poorly soluble drugs. Nanocrystals are completely drug-loaded, pure solid particles having a mean diameter of less than 1 µm. They have no carriers and are crystalline in nature[1].According to the US Food and Drug Administration, nanotechnology is an emerging technology with potential applications in a variety of fields, including medical items, foods and cosmetics (e.g., modifying the texture and appearance of cosmetics). A substance or finished product intended to display physical, chemical, or biological qualities attributable to its nano-size dimensions (up to 1,000 nm) is referred to as a nanomaterial.[2]Macromolecular polymers which stabilize submicron colloidal dispersions, are known as Nanocrystals (NCs). Low costs, fewer side effects, and high drug loading are the characteristics of colloidal systems. Because of their higher specific surface area, they can also increase the saturation solubility and rate of dissolution for compounds that are insoluble in water[3,4,]Nanocrystals can be administered by several routes such as Oral, dermal, intranasal(Local and Systemic),parenteral, pulmonary and ocular route. In terms of polymeric stabilizers, the most commonly utilized poloxamers for Nanocrystals are Pluronic F68 and F127, and the polymers are polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), hydroxyl propyl methylcellulose (HPMC), and hydroxy propyl cellulose (HPC). Among surfactants, lecithin, Brij 78, Tween® 80 (non-ionic), sodium lauryl sulphate (SLS), sodium dodecyl sulphate (SDS), and dioctyl sodium sulphosuccinate (DOSS) have been used[5,6]. As they are more suitable for scale-up methods, need fewer excipients, and improve apparent solubility because of their small particle size, Nanosuspensions or Nanocrystals among nanoparticulate systems have gained more popularity in the field of pharmaceuticals.[7]

SIGNIFICANCE OF NANOCRYSTALS

When administering poorly soluble medications orally, drug Nanocrystals exhibit a number of advantages, such as enhanced oral absorption, increased bioavailability, quick start of action, decreased fed/fasted state variability, and decreased inter subject variability. Increased saturation solubility and dissolution velocity in drug formulations delivered as Nanocrystals result in a high drug concentration gradient between the gastrointestinal tract and blood vessel, which in turn promotes better absorption and high bioavailability[8,9].Drug Nanocrystals can also improve the topical availability of drugs which is poorly soluble, Curcumin is formulated as Nanocrystals and is incorporated in Carbopol gel to heal the dermal wounds

rapidly and it is more effective than other commercially available gels[10]. Moreover, by building up in hair follicles, Nanocrystals can improve skin penetration and greatly increase cutaneous absorption[11].Nanocrystals are used to treat various diseases such as ophthalmic diseases, cardiovascular diseases, cancer, inflammatory diseases, anthelmintic, antiviral and liver diseases[12].The blood–brain barrier, where endothelial cells block the diffusion of large hydrophilic drug molecules into the cerebrospinal fluid, is a barrier that many medications designed to treat neurological illnesses have low permeability across . With Nanocrystals, one can take advantage of surface functionalization and other cellular absorption mechanisms like endocytosis to potentially distribute drugs in a tailored manner[13,14]. Selection of stabilizers is a challenging part in formulation of Nanocrystals, while choosing stabilizers, it's crucial to consider their role in subsequent formulation and impact on drug bioavailability in addition to stabilizing newly generated drug Nanocrystals. Sedimentation or creaming, agglomeration, growth, change of crystalline state and chemical instability are the major issues associated with Nanocrystals.[15]

NANOCRYSTALLINE TECHNOLOGIES

Nanocrystalline technologies can be categorised into Top down techniques and Bottom up techniques. Top down techniques includes milling and high pressure homogenization and the bottom up techniques includes self-assembly and precipitation. Of all these techniques one of the simplest and economical techniques is the precipitation method[16]Most of the drugs in market and the patented drugs are formulated by top down techniques as it is industrially feasible than other approaches. Bottom up technique is a kind of precipitation technique it have been mainly used for the preparation of inorganic particles in nanometre size for long time. Sucker have developed a Hydrosol technique which is a first-ever bottom-up process for formulation of Nanocrystals.[17]

HIGH PRESSURE HOMOGENIZATION

In this technique the appropriate quantities of drug and the stabilizers are weighed and the mixture is suspended then the suspension is sonicated for half an hour to break any agglomerated powder, then it is exposed to the high pressure homogenization and finally the suspension is lyophilized to obtain dry powder.[18]

HOMOGENIZATION METHODS

Dissocubes® technology employs the technique of piston gap homogenization in water. Nanopure® technology, which is a piston gap homogenization in water mixtures or in nonaqueous media, where the dimunition occurs because of cavitation and collision of crystals with each other. This was developed by Muller and his coworkers. IDD-PTM-TM technology, which is a micro fluidization technology, is one of the different methods of homogenization used in the production of Nanocrystals. Collision is a principle associated with micro fluidizer technology.[19,20]

ANTISOLVENT PRECIPITATION METHOD

The drug is dissolved in a solvent and the stabilizing agent is dissolved in double distilled water. The latter is placed in a magnetic stirrer at a constant speed of 1400 rpm. The drug solution is being injected into solution containing stabilizing agent with the help of a syringe. It is stirred, centrifuged and then suspended in distilled water and sonicated for 10min.After sonication it is filtered and dried to obtain Nanocrystals.[21]

WET MEDIA MILLING

Milling is one of the most commonly used physical unit operations for size reduction in pharmaceutical formulations. Wet media milling equipment used to produce Nanosuspensions are of two types: planetary ball mills and wet stirred media mills. Particles smaller than a micron are created when centrifugal force or Coriolis force accelerate the milling media quickly. Planetary ball mills are employed in laboratory settings because of their ease of use and adaptability. There are three distinct modes of operation for wet stirred media milling: batch, recirculation, and continuous. Among these three forms, the continuous mode is deemed appropriate for the pharmaceutical business.[22,23]

WET BALL MILLING

After the medication has been dissolved in an aqueous stabilizer, the suspension is moved to a milling vessel filled with beads, which is then placed in a planetary ball mill and ground at 1400 rpm for three minutes. The milling machine is then allowed to cool down by pausing it for fifteen minutes following each milling cycle, and the Nanosuspension is collected and separated using a pipette.[24]

COMBINATION TECHNOLOGIES

Nanoedge^{TM} technology is a combination technology which is developed by baxter, it utilizes the combination of both precipitation technique and homogenization techniques to produce a Nanocrystals. Smart crystal technology which is developed by pharmasol berlin is another combination technologies used for the development of Nanocrystals with optimized properties for different applications[25,26].It is a toolbox of several combination procedures where variations in the process can be selected based on the physical properties (like hardness) of the medicine. HPH and spray-drying are both used in the H42 process. One to a few homogenization rounds can yield drug Nanocrystals considerably more quickly.[27]

CHARACTERIZATION OF NANOCRYSTALS

DETERMINATION OF PARTICLE SIZE

Zetasizer is used for determining the particle size of Nanocrystals. For avoiding the multi scaterring phenomenon during measurement all the samples are diluted with distilled water. The measurement is carried out at room temperature.[28]

SCANNING ELECTRON MICROSCOPY AND TRANSMISSION ELECTRON MICROSCOPY

High power scanning electron microscopy is used for determining the morphological features of Nanocrystals. On a metal stub the crystal sample is placed and is plated with 200-300Å thick film of gold-palladium at low pressure and the SEM analysis is carried out at different magnifications. High spatial and temporal resolution images of nanoparticles are produced by Transmission electron microscopy.[29]

SATURATION SOLUBILITY

Shaker bath is used for performing the solubility study of drug, physical mixture of pure drug, surfactants and optimized nanocrystal formulation. During the entire experiment 50 RPM and the temperature of 37±0.5˚C is maintained. The nanocrystal formulation, pure drug and its physical mixture is added into water and phosphate buffer and the sample is collected at different intervals and it is subjected to ultracentrifugation. Then the supernatant is diluted and subjected to HPLC analysis for the determination of saturation solubility.[30]

In - vitro DRUG RELEASE STUDY

Franz diffusion cell is used to carry out the *in-vitro* drug release study of the formulation. Temperature of the apparatus is maintained at 37±0.5˚C and the RPM is set as 100.900 ml of phosphate buffer solution is used as a buffer solution in which the Nanocrystals are submerged. The samples are withdrawn at regular intervals and the drug content is measured by using UV -Visible spectrophotometer at appropriate wavelength[31].

ENTRAPMENT EFFICIENCY

The entrapment efficiency of the formulated nanocrystal is determined by using the formula:

$$\text{Entrapment efficiency}\% = \frac{\text{Amount of drug determined in the formulation}}{\text{Total drug added in the formulation}} \text{ X } 100$$

The amount of drug in formulation is determined by UV- Visible spectrophotometer.[32]

TABLE-1. NANOCRYSTALLINE DRUG PRODUCTS IN MARKET[33,34]

TRADE NAME	DRUG	USES
Rapamune®	Rapamycin	Immunosuppressive agent
Tricor®	Fenofibrate	Hypercholesterolemia
Triglide®	Fenofibrate	Hypercholesterolemia
cesamet®	Nabilone	Antiemetic
Invega sustenna®	Palperidone palmitate	Antidepressant
Emend	Aprepitant	Anti-emetic
Megace ES®	Megestrol	Anti-anorexic
Paxceed®	paclitaxel	Anti-inflammatory
Avinza®	Morphine sulfate	Anti-chronic pain

Herbs and Nanocrystals

Herbal medicines are formulated as Nanocrystals to enhance the solubility, bioavailability and to reduce the toxicity and to increase the encapsulation efficiency. Nowadays Herbal medicines are used in the treatment of various diseases such as Cancer, Neurological diseases, Cardiovascular diseases, Inflammatory diseases, Antimicrobial treatment etc[35],.Some of the well-known medicinal herbs are Vincristine, Vinblastine, Ginkgo biloba,

Digitalis, Brahmi, Curcmin, Belladona, Paclitaxel, Senna and so on. Curcumin Nanocrystals are prepared by Henirachmawati, et al., to enhance the solubility and bioavailability as it is insoluble in water at acidic and neutral condition but is soluble in alkaline condition where it is highly unstable. Nanocrystal is reported as an efficient formulation to deliver the curcumin[36].Paclitaxel Nanocrystal formulated by Yang Liu et al, is used to overcome the multidrug resistance which is a major problem associated with cancer treatment. Thus Nanocrystals are an efficient way to overcome the Multi Drug Resistance[37].To enhance the solubility, penetration ability and retention time of the tretinoin which is a Vitamin A derivative used for Anti-acne treatment is formulated as Nanocrystals by Pottathilshinu et al, .[38]

STABILIZATION OF NANOCRYSTALS

Hydrophilic polymers and/or surfactants are commonly added to the Nanosuspensions in order to stabilize the formulations of Nanocrystals. The process of stabilization involves the repulsion of polymers or surfactants that adsorb onto the surface of the Nanocrystals and/or change the dielectric constant of the aqueous environment through either steric or electrostatic hindrance. Using proteins as stabilizers is a further approach that might be taken. Serum proteins, in particular, are naturally occurring proteins that offer an alluring substitute for the conventional stabilizers[39]. The accumulation of Nanocrystals must be stopped by stabilizers. Drug particles often aggregate because of the surface tension of drug Nanocrystals, which is frequently quite high. Surface tension can be lowered and Nanocrystal aggregation can be avoided by using an appropriate stabilizer.[40]

FUTURE OF NANOCRYSTALS

Nanocrystals will be a promising drug delivery system in future owing to the ongoing discovery of more number of insoluble drugs. As the majority of drugs in cancer treatment are water insoluble, injectable Nanocrystals will be a better alternative for cancer therapy. While Nanocrystals have been demonstrated to improve transdermal, ocular and pulmonary delivery systems, there are no comparable formulations available. Only a few dermal Nanocrystals, such as Platinum Rare® and Juvedical® that contain rutin Nanocrystals are currently available on the cosmetic market. The development of Nanocrystals through pulmonary, ocular and skin channels is essential because parenteral preparations have a good life expectancy[41].Nanosizing becomes the versatile approach in the recent pharmaceutical era and in future the performance of drug Nanocrystals will enhance in many aspects such as

tissue targeting, sustainability in drug release and so on[42].Topical drug delivery can also be improved by the pharmaceutical Nanocrystals, by enhancing a number of mechanisms, such as the production of a diffusional corona, hair follicle targeting, adherence to skin, and a greater concentration gradient across the skin, Nanocrystals can boost delivery through the skin. Nanocrystals will be an excellent option for delivering a drug molecules which have a non optimal physicochemical properties for conventional delivery in a topical manner.[43]

CONCLUSION

Enhancing the solubility of poorly soluble drug can be done easily and simply with Nano sizing; in many cases, minimal alterations in particle size is sufficient to achieve satisfactory product performance. Nanocrystals in enhancing the solubility and bioavailability of pharmaceutical, Nutraceutical as well as the cosmeceutical products. It will be a better alternative for the drugs to cross the BBB to treat the neurological diseases as it facilitates crossing BBB by cellular uptake processes such as endocytosis and surface functionalization for targeted delivery. Due to 100 fold size reduction and crystalline morphology, Nanocrystals will increase the saturation solubility and bioavailability of BCS class II as well as the Class IV drugs.

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