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REVIEW ARTICLE

Nanocrystal Technology as a Tool for Improving Dissolution of Poorly Soluble Drugs

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Abstract

Many approaches have been developed over time to counter the bioavailability limitations of poorly soluble drugs. With advances in nanotechnology in recent decades, this issue has been approached through the formulation of drugs as nanocrystals. Nanocrystals consist of pure drug(s) and a minimum of surface active agent(s) required for stabilization. They are carrier-free submicron colloidal drug delivery systems with a mean particle size typically in the range of 200 - 500 nm. By reducing particle size to nanoscale, the surface area available for dissolution is increased, and thus bioavailability is enhanced. Drug nanocrystals constitute a versatile formulation approach to enhance the pharmacokinetic and pharmacodynamic properties of poorly soluble drugs. This enhancement is achieved by increasing the dissolution velocity, saturation solubility and mucoadhesion. However, stabilization of nanocrystals remains a major challenge in the development of nanocrystals. Main stability issues include increase in particle size, agglomeration, crystal transformation, and chemical instabilities. as such, combination of steric and ionic stabilizers are required for optimal stabilization. Nanocrystals can be administered by various routes including oral, parenteral, ocular, pulmonary and dermal routes with enhanced pharmacodynamic activity and safety. Functionalization of nanocrystals with radionuclide, imaging moieties and ligands further increases the versatility of nanocrystals. Nanocrystals has been proven successful, as demonstrated by the number of marketed drug products utilizing this technology. The present work provides an overview of the more recent achievements in improving the bioavailability of poorly soluble drugs according to their administration route, and describes the methods developed to overcome physicochemical and stability related problems.

Keywords: *Nanocrystals, Poorly soluble drug, Nanotechnology.*

Introduction

Nanocrystals are crystalline nanoparticles (200 to 500 nm) composed of large concentration of drug stabilized with surface stabilizers [1].Drug nanocrystals constitute a versatile formulation approach to enhance the pharmacokinetic and pharmacodynamic properties of poorly soluble drugs. Contrary to micronized drugs, nanocrystals can be administered via several routes. Oral administration is possible in the form of tablets, capsules, sachets or powder, preferably in the form of a tablet.

Nano suspensions of nanocrystals can also be administered via the intravenous route due to very small particle size, and in this way, bioavailability can reach up to 100%. Nanocrystal technology leads to an increase in dissolution rate driven by the increase in surface area obtained through reduction of particle size of the active drug substance down to the nano size range and yet preserving the crystal morphology of the drug [2].

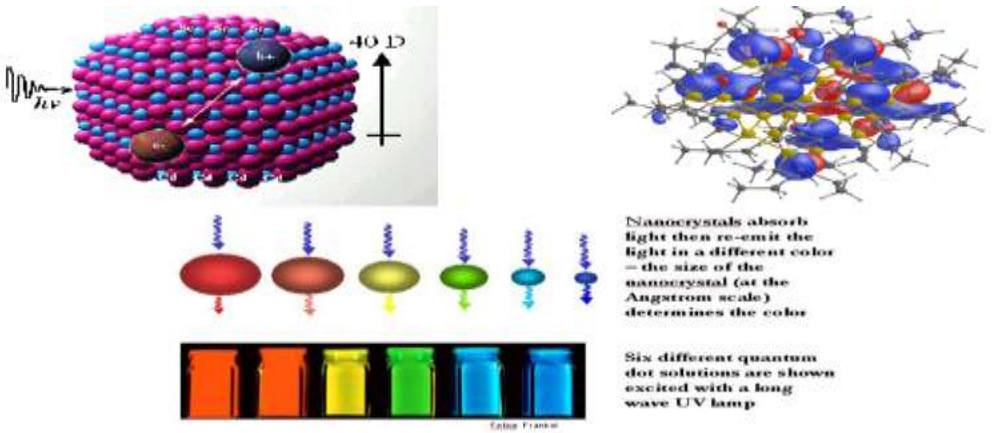

Fig.1: Images for Nanocrystals

Advantages: Nanocrystal technology offers many advantages some of which are listed below

- It can be given by any route of administration.
- Reduced tissue irritation in case of subcutaneous/intramuscular administration.
- Rapid dissolution & tissue targeting can be achieved by IV route of administration.
- Oral administration of nanosuspension provide rapid onset, reduced fed/fasted ratio & improved bioavailability.
- The absorption form absorption window can be increased, due to reduction in the particle size.
- Drug with higher log P value can be formulated as nanocrystals to increase the bioavailability of such drugs.
- Nanocrystals can be incorporated in tablets, pellets, hydrogel & suppositories are suitable for various routes of administration.
- Increasing the amorphous fraction in the particles leading to a potential change in the crystalline structure & higher solubility.
- Possibility of surface-modification of nanosuspension for site specific delivery.
- Possibility of large-scale production, the prerequisite for the introduction of delivery system to the market.
- Enhanced solubility and bioavailability of drug.
- Higher drug loading can be achieved.
- Long term physical and chemical stability (due to absence of Ostwald ripening) [3, 4].

Disadvantages

- Physical stability, sedimentation & compaction can cause problems.
- Products are bulky thus require sufficient care during handling & transportation.
- Uniform & accurate dose cannot be achieved [4, 5].

Mechanism of Solubility Enhancement

Decrease in particle size to nano range via nanocrystallization results in improved saturation solubility as well as dissolution velocity as explained by Ostwald–Freundlich and Noyes-Whitney equations respectively.

Increased Saturation Solubility

The relation between the saturation solubility of a drug and its particle size is best described by Ostwald–Freundlich equation (Eqn. 1), according to which decrease in particle size (r) results in increase in saturation solubility (CS) of the drug [6].

$$log\frac{C_s}{C_\infty} = \frac{2\delta V}{2.303RTpr}$$

Eqn (1)

Where:

C_S = saturation solubility,

C_α= solubility of the solid consisting of large particles,

δ = interfacial tension of substance,

V = molar volume of the particle material,

R = gas constant,

T = absolute temperature

R = radius of particle

Increased Dissolution Velocity

The surface area of a particle enhances drastically upon size reduction Fig. (1), there by a tremendous rise in dissolution velocity is observed as given by Noyes-Whitney equation (Eqn. 2) [6, 7] describing the dissolution velocity (dc/dt) as:

$$\frac{dc}{dt} = \frac{D.A}{h}(C_s - C_x)$$

Eqn (2)

Where:

D = diffusion coefficient,

A = surface area,

C_S = saturation solubility,

C_x= bulk concentration

H= diffusion distance over which the concentration gradient occurs.

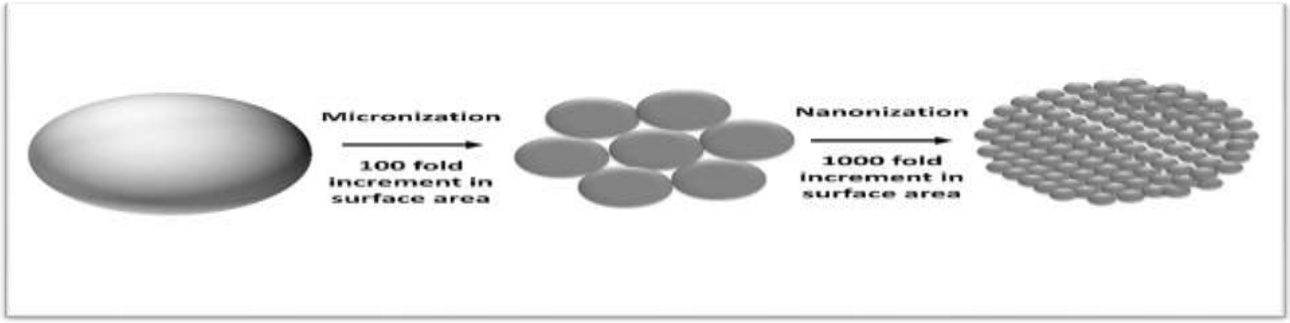

Fig. 2: A diagrammatic representation of nanonization mechanism

According to Noyes-Whitney, increase in Cs in addition to the enlarged surface area further increases the dissolution velocity. The dissolution velocity is inversely proportional to the diffusional distance h, which means that reducing h leads to a further increase in dissolution velocity represented by eqn. (2) [8].

Nanocrystal Based Formulations

Suspension

The most common approach to formulate a poorly soluble drug is a 'nanosuspension' with the advantage of multiple routes of administration including oral, parenteral, pulmonary etc. It is highly preferred for intravenous (IV) administration due to omission of toxic chemicals and solvents in the formulation hence, shows high safety profile [9]. Hydrosols are colloidal aqueous suspensions containing drug particles with size approximately 200 nm, suitable for IV administration.

They are prepared by precipitation method where the drug powder is dispersed in excess of water (about 98%) containing stabilizers. For long-term use, hydrosols are spray-dried and are reconstituted with water before use. Stability is the primary concerns for nanosuspension and due to their high susceptibility to crystal growth, suitable stabilizers are commonly used. Selection of stabilizers is an essential criterion for formulation development and the stabilizer should meet some important requisites: (a) high affinity for particle surface (like lecithin, Pluronic F68®), (b) sufficiently high diffusion velocity to shield nanocrystal surface instantly and lastly (c) the indispensable issue is their safety and acceptability by the body [10].

Tablets

Nanocrystals could conveniently be formulated into tablets. Generally, direct compression method is considered as a suitable process for tablet production. Tablets can be produced by two different ways: (a) Using Solid PEG (polyethylene glycol) as an excipient for tableting. In this case, the drug powder is dispersed in the molten PEG and the suspension is homogenized at high temperature resulting in a hot Nano dispersion, which finally solidifies. Subsequent milling yields a flowable powder, which undergoes direct compression to produce tablets containing nanocrystals; (b) in an aqueous nanosuspension, excipients and polymer(s) required for tablet production are dispersed.

This suspension is then spray dried yielding a free-flowing powder, which is directly compressed into tablets. Nanocrystal technology could be incorporated into tablets of immediate-release, delayed-release, extended release and fast-melt (waterless) tablets. Based on NanoCrystal® Technology, Elan has developed an orally disintegrating tablet ingested without water for a more convenient mean of taking medication and freeing patients from the problem of swallowing cumbersome dosage forms [11].

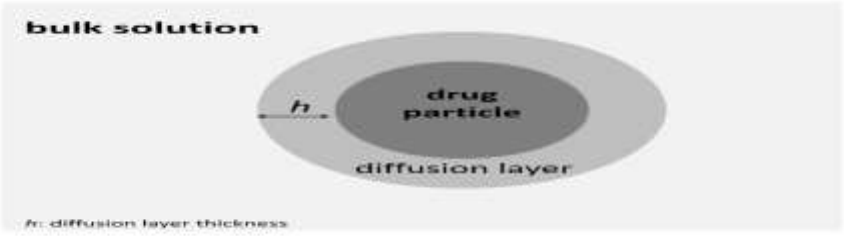

Fig.3: Diffusion layer model showing dissolution of a drug particle Tablet

Capsules

Usually, PEGs (liquid, semi-solid and solid) are used for capsule filling. Drug powder is dispersed into the hot liquid PEG and homogenized. After homogenization, the resulting suspension is allowed to cool down where PEG recrystallizes entrapping drug nanocrystals within its matrix preventing crystal growth. The liquid PEG nanosuspension is finally filled into capsules.

In case of solid PEG, the melted PEG nanosuspension is either directly filled into hard gelatin capsules (where the suspension solidifies within the capsule) or the liquid suspension is first solidified and ground with subsequent filling of the powder into hard gelatin capsules. Filling of solid material is easier than liquid nanosuspension as the latter requires sealing of gelatin capsules [12].

Powder for Inhalation

Nanocrystals are one of the alternatives for preferential pulmonary delivery of drugs for treatment of diseases such as asthma or deep lung delivery for systemic or local effect. Drug particles in nano-size range could be readily obtained by techniques like milling and high-pressure homogenization, which usually result in nanosuspensions. Such dispersions of nanocrystals are spray dried into powders suitable for pulmonary delivery. In order to achieve optimal drug delivery, the particles should be of appropriate size, shape and density which can be controlled by adjusting the spray drying parameters.

The greater tendency of the drug powder to adhere to each other to form aggregates can be reduced by the addition of carriers (usually lactose) which enhances flow property of the powder by decreasing drug powder cohesion and helps in better delivery. Carriers also act as fillers by adding bulk to the volume when the unit dose of the drug is very small. Dry powder inhalers are commonly used in devices that create aerosols by drawing air through a dose of dry powder medication for the appropriate deposition of drugs in the desired part of the respiratory tract [13].

Emulsion

Besides suspensions, emulsions are also preferred as IV formulation when a parenteral product is desired. For emulsion fabrication, the drug is first dissolved in an organic solvent containing lecithin (phospholipid), evaporated, and then the mixture is used to produce the emulsion where drug molecules are incorporated into the interfacial layer of the emulsion. However, this method is not applicable to large-scale production due to the complex nature of the process.

The Sol-Emuls technology is a novel alternative for the production of emulsion without solvents: hybrid dispersion is prepared by dispersing liquid oil droplets in water and drug nanocrystals dispersed in the water phase. The dispersion is then subjected to high-pressure homogenization (HPH) with a very high streaming velocity resulting in the complete dissolution of drug nanocrystals to obtain the emulsion finally. One of the most significant features of this Sol-Emuls technology is that drugs possessing poor solubility in both water and oils could efficiently be localized in the interfacial layer of the formulation [12].

Methods for Production of Drug Nanocrystals

Several preparation methods for drug nanocrystals have been investigated. Today, implemented preparation methods of nanocrystal formulations can be classified as “bottom up”, “top-down”, “top down and bottom up” and other methods. “Bottom up” technology begins with the molecule; active drug substance is dissolved by adding an organic solvent, and then, solvent is removed by precipitation.

“Top-down” technology applies dispersing methods by using different types of milling and homogenization techniques. “Top-down” technology is more popular than “Bottom up” technology; it is known as “nanosizing”. In other words, it is a process which breaks down large crystalline particles into small pieces. In “top down and bottom up” technology, both methods are utilized together [14].

Techniques for Manufacturing of Nanocrystals

Bottom up Technology

Anti-solvent precipitation

Supercritical fluids

Spray-drying

Top down Technology

Media milling

Bead milling

Dry co-grind

High pressure homogenizations

Homogenization in Aqueous media (Dissocubes)

Homogenization in Non-Aqueous Media (Nanopure)

Nanojet technology

Emulsion solvent diffusion method

Combination Technology

NANOEDGE® Technology

SmartCrystal® Technology

Other Methods

Solvent evaporation

Sonocrystalisation

Melt emulsification

Bottom-Up NanoCrySP Technology

Bottom up Technology

Bottom up technology starts with molecule .Principal of this technology is based on precipitation by dissolving the drug in a solvent and adding the solvent to a non-solvent that cause precipitation of the fine drug particle. Example of product which is manufacturing by using this technology is Hydrosols and NanomorphTM, which are developed by Sucker and Soliqs/Abbott respectively. This has the basic advantage of using relatively simple and low-cost equipment. However, this created problems in stirring and mixing when taken up for large-scale production. The major challenge of this technique is to avoid crystal growth that occurs on storage due to Ostwald ripening [11].

Precipitation Technology

It is also known as hydrosol technology, and the IP is owned by Sandoz (now Novartis). A poor water-soluble drug is dissolved in an organic medium, which is water miscible. A pouring of this solution into a non-solvent, such as water, will cause a precipitation of finely dispersed drug nanocrystals. A problem associated with this technology is that the formed nanoparticles need to be stabilized to avoid growth in micrometer crystals. In addition, the drug needs to be soluble at least in one solvent; this creates problems for the newly synthesized or discovered drugs, being poorly soluble in water and simultaneously in organic media. Lyophilization is recommended to preserve the particle size [15].

Supercritical Fluid Method

Nanoparticles are produced by various methods like rapid expansion of supercritical solution (RESS) process, supercritical antisolvent process, and precipitation with compressed antisolvent (PCA) process. In RESS technique, drug solution is expanded through a nozzle into supercritical fluid, resulting in precipitation of the drug as fine particles by loss of solvent of the supercritical fluid. Young et al. prepared cyclosporine nanoparticles having diameter of 400 to 700 nm by using this technique.

In the PCA method, the drug solution is atomized into the CO2 compressed chamber. As the removal of solvent occurs, the solution gets supersaturated and finally precipitation occurs. In supercritical antisolvent process, drug solution is injected into the supercritical fluid and the solvent gets extracted as well as the drug solution becomes supersaturated [9]. The basic disadvantages of the above reported methods are use of hazardous solvents and use of high proportions of surfactants and stabilizers as compared with other techniques [16].

Spray Drying

One of the preparation methods of nanocrystals is spray drying. This method is usually used for drying of solutions and suspensions. In a conical or cylindrical cyclone, solution droplets are sprayed from top to bottom, dried in the same direction by hot air and spherical particles are obtained. Spraying is made with an atomizer which rapidly rotates and provides scattering of the solution due to centrifugal effect.

The solution, at a certain flow rate, is sent to the inner tube with a peristaltic pump, nitrogen or air at a constant pressure is sent to the outer tube. Spraying is provided by a nozzle. Droplets of solution become very small due to spraying; therefore, surface area

of the drying matter increases leading to fast drying. Concentration, viscosity, temperature and spray rate of the solution can be adjusted and particle size, fluidity and drying speed can be optimized. The dissolution rate and bioavailability of several drugs, including hydrocortisone, COX-2 Inhibitor were improved utilizing this method [17, 18].

Top down Technology

The 'Top down Technologies' are the disintegration methods and are preferred over the precipitation methods .This includes:

Media Milling (Nanocrystals or Nanosystems)

Bead Milling

The method is first developed by liversidge *et. al*. In this method the nanosusensions are produced using high- shear media mills or pearl mills [19]. The media mill consists of a milling chamber, a milling shaft and a recirculation chamber. The milling medium is made up of glass, zirconium oxide or highly cross- linked polystyrene resin. The milling chamber is fed with the milling media, water, drug and stabilizer and then milling media or pearls are then rotated at a very high shear rate. The milling process is performed under controlled temperatures.

The Nano suspension or nanoparticles are form as result of high energy and shear forces generated due to the impaction of the milling media with the drug which provide the energy input to break the micro particulate drug into Nano sized particles. The unimodal distribution profile and mean diameter of <200, require a time profile of 30- 60 min. The media milling procedure can successfully process micronized and non- micronized drug crystals. A nanosuspension of Naproxen with a mean particle size of 300- 600 nm was prepared using pearl milling technique [20].

Co-grinding

Now a day, nanosuspensions can be also prepared by dry milling techniques. Successful work has been reported in preparing stable nanosuspensions using dry grinding of poorly soluble drugs with soluble polymers and copolymers after dispersing in a liquid media. It is the colloidal particles formation of many poorly water soluble drugs; griseofulvin glibenclamide and nifedipine obtained by grinding with polyvinyl pyrrolidone (PVP) and sodium dodecylsulfate (SDS). Various soluble polymers and co-polymers such as PVP, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC) and cyclodextrin derivatives have been used. By using this method the physicochemical properties and dissolution of poorly water soluble drugs were improved because of an improvement in the surface polarity and transformation from a crystalline to an amorphous drug. Dry co grinding can be carried out easily and economically and can be conducted without need of organic solvents [21].

High Pressure Homogenization

Homogenization in Aqueous media (Dissocubes)

This technology was developed by R.H. Muller in 1999 and first patent was taken by DDS Gmbh and later ward the patent was transferred to Skyp pharmaceuticals. Commonly used homogenizers are the APV Micron Lab 40 (APV Deutschland Gmbh, Lubeck, Germany) and piston-gap homogenizers. In this method, the suspension containing a drug and surfactant is forced under pressure through a Nanosized aperture valve of a high pressure homogenizer. In this method the particle size reduction depend on cavitation principle.

The dispersion present in 3cm diameter cylinder is suddenly passed through a very narrow gap of 25µm. According to Bernoulli's law the flow volume of liquid in a closed system per cross section is constant. It leads to increase in dynamic pressure and decrease of static pressure below the boiling point of water at diameter from 3cm to 25µm.Then water starts boiling at room temperature and forms gas bubbles, which implode when the suspension leaves the gap (called cavitation) and normal air pressure is reached. The particles cavitation forces are sufficiently high to convert the drug micro particles into nanoparticles. In this the final particle size of drug nanocrystal is based on power density of homogenizer, number of homogenization cycles, temperature and homogenization pressure [22].

Homogenization in Non-Aqueous Media (Nanopure)

Nanopure is one the technology in which suspension is homogenized in water-free media or water mixtures.

In the Disso cubes technology the cavitation is the principle determining factor of the process. Oils and oily fatty acids have very low vapour pressure and a high boiling point as compare to water. Hence, the drop of static pressure will not be sufficient enough to initiate cavitation. Patents covering disintegration of polymeric material by high-pressure homogenization mention that higher temperatures of about 80 °C promoted disintegration, which cannot be used for thermo labile compounds.

In Nano pure technology, the drug suspensions in the non-aqueous media were homogenized at 0°C or even below the freezing point and hence are called "deep-freeze" homogenization. The results obtained were comparable to Disso cubes and hence can be used effectively for thermo labile substances at milder conditions [23].

Nanojet Technology

This technology called opposite stream or nanojet technology. This method consists of micro fluidizer which uses a chamber where a stream of suspension is divided into two or more parts, which colloid with each other at high pressure. The high shear force produced during the process due particle collision and high pressure results in particle size reduction. Equipment using this principle includes the M110L and M110S micro fluidizers. Dearn prepared Nano suspensions of atovaquone using the micro fluidization process [21].The major disadvantage of this technique is the high number of passes through the micro fluidizer and that the product obtained contains a relatively larger fraction of microparticles [24].

Emulsion Solvent Diffusion Method

Apart from the use of emulsion as drug delivering vehicle they can also be used as to produce Nano suspension. The use of emulsions as templates is applicable for those drugs that are soluble in either volatile organic solvent or partially water- miscible solvent. Such solvents can be used as the dispersed phase of the emulsion. An organic solvent or mixture of solvents loaded with the drug is dispersed in the aqueous phase containing suitable surfactants with stirring to form an emulsion. The obtained emulsion was further homogenized by high pressure homogenization. After homogenization cycles the emulsion was diluted with water, homogenized by homogenizer to diffuse the organic solvent and convert the droplets into solid particles. Since one particle is formed in each emulsion droplet, it is possible to control the particle size of the nanosuspension by controlling the size of the emulsion.

Optimizing the surfactant composition increases the intake of organic phase and ultimately the drug loading in the emulsion. Originally methanol, ethanol, ethyl acetate, chloroform are used as organic solvents. However, environmental hazards and human safety concerns about residual solvents have limited their use in routine manufacturing processes. Nanosuspension of ibuprofen, diclofenac, and acyclovir were prepared by this method [25].

Patented Technologies of Nanosuspension

Nanoedge™

The basic principles of Nanoedge are the same as that of precipitation and homogenization. A combination of these techniques results in smaller particle size and better stability in a shorter time. The major drawback of the precipitation technique, such as crystal growth and long-term stability, can be resolved using the Nanoedge technology.

In this technique, the precipitated suspension is further homogenized, leading to reduction in particle size and avoiding crystal growth. Precipitation is performed in water using water-miscible solvents such as methanol, ethanol and isopropanol. It is desirable to remove those solvents completely, although they can be tolerated to a certain extent in the formulation. For an effective production of nanosuspensions using the Nanoedge technology, an evaporation step can be included to provide a solvent-free modified starting material followed by high-pressure homogenization [9].

Smart Crystal® Technology

Recently Smart Crystal® technology was first developed by PharmaSol GmbH and was later acquired by Abbott. It is a tool-box of different combination processes in which process variations can be chosen depending upon the physical characteristics of the drug (such as hardness). The process H42 involves a combination of spray-drying and HPH.

Within few homogenization cycles the nanocrystals is prepared. Process H69 (Precipitation and HPH) and H96 (lyophilization and HPH) yield nanocrystals of amphotericin B within a size range of about 50 nm. S. Kobierski et al. produced nanocrystals in a two-step process i.e. pre-milling followed by high pressure homogenization (HPH). Nanosuspensions of cosmetic active hesperidin were produced by ball-milling process and with combination process. Both the prepared nanosuspensions were kept for storage. Nanosuspension prepared using SmartCrystal® technology was found to be of a smaller size indicating better physical stability.

Also combination technique is faster and more economical as compared to HPH alone. Möschwitzer and Müller43 (2005) prepared spray dried hydrocortisone acetate powder from nanosuspension produced by HPH with a micron LAB 40 and planetary monomill "pulverisette".

The number of cycles required could be distinctly reduced. Additionally, a smaller particle size and better particle size distribution could be obtained. Another finding of the study was that the application of different homogenization pressures (e.g. 300 and 500 bar) was equally efficient. Therefore, during large scale production, low homogenization pressures (300 bars) may be preferred to reduce wearing of the machine [26].

Other Technologies

Solvent Evaporation

In the solvent evaporation method, the solutions of polymer are prepared in volatile solvents and emulsions. But from the past years dichloromethane and chloroform were used which was now replaced by ethyl acetate which has a better profile of toxicology.

The emulsion is converted into a nanoparticle suspension on evaporation of the solvent for the polymer, which is allowed to diffuse through the continuous phase of the emulsion. In the conventional methods, two main strategies are being used for the formation of emulsions, the preparation of singleemulsions, e.g., oil-in-water (o/w) or double-emulsions, e.g., (water-in-oil)-in-water, (w/o)/w.

These methods require high-speed homogenization or ultrasonication, followed by evaporation of the solvent, either by continuous magnetic stirring at room temperature or under reduced pressure. By ultracentrifugation the solidified nanoparticles are collected which was washed with distilled water to remove the additives like surfactants, and then it was lyophilized. The particle size was influenced by the concentration of polymer, stabilizer and the speed of homogenizer [27].

Sonocrystallization

Recrystallization of poorly soluble material using liquid solvents and antisolvents has also been employed successfully to reduce particle size. The novel approach for particle size reduction on the basis of crystallization by using ultrasound is sonocrystallization. Sonocrystallization utilizes ultrasound power characterized by a frequency range of 20-100 kHz for inducing crystallization. It not only enhances the nucleation rate but also an effective means of size reduction & controlling size distribution of the active pharmaceutical ingredient (API).

Most applications used ultrasound in the range 20 khz -5mhz. Sonocrystallization technique or technology has also been studied to modify the undesirables of NSAID'S i.e. poor solubility and dissolution rate and consequently the poor bioavailiability. Flubiprofen was poured in deionized water at 25°C and sonicated for 4 minutes at an amplituted of 60% and cycle is 40 sec on and 10 sec off.

The particle size of treated flubiprofen was significantly reduced and the increased solubility of treated flurbiprofen was about 35%. The intrinsic dissolution rate of treated flubiprofen increased by 2-fold. The dissolution studies obtained that 90% of the drug was released within 20 minutes for treated flubiprofen as compared to untreated flubiprofen obtained 60% release of the drug [28, 29].

Melt Emulsification Method

Solid lipid nanoparticles are mainly prepared by melt emulsification method. Kipp and coworkers firstly prepare nanosuspensions of ibuprofen by using melt emulsification method. It is a four-step procedure. Drug is first added to aqueous solution having stabilizer.

The solution is heated at temperature higher than the melting point of the drug and then homogenized by high-speed homogenizer for the formation of emulsion. The temperature is maintained above the melting point of the drug during overall process. Finally, the emulsion is cooled to precipitate the particles. The particle size of nanosuspension mainly depends on parameters like drug concentration, concentration and type of stabilizers used, cooling temperature, and homogenization process [30].

Bottom-Up Nano Cry SP Technology

G. Shete, Y. Pawar et al, National Institute of Pharmaceutical Education and Research (NIPER) introduced a newer method to generate nanocrystalline solid dispersion (NSD) of hesperetin using Nano Cry SP technology: a novel bottom-up process based on spray drying to generate solid particles containing drug nanocrystals dispersed in the matrix of small molecule excipients (WO2013132457 A2). The purpose of their study to improved oral bioavailability and pharmacodynamic activity of hesperetin nanocrystals generated using a novel bottom-up Nano Cry SP Technology.

Hesperetin and mannitol were used in 1:1 ratio and NSD was generated using spray drying. The process of NSD formation is based on classical nucleation theory wherein mannitol contributed to crystallization of hesperetin by acting as plasticizer, crystallization inducer and by providing heterogeneous nucleation sites. Hesperetin was found to exist as nanocrystals dispersed in the matrix of mannitol with average crystallite size of 137 nm in the NSD [31].

Application for Oral Delivery

Oral Administration of Drug Nanocrystals

When drugs are administered as nanocrystal formulations, small size and increased surface area leads to an increased dissolution rate and saturation solubility. These result in high drug concentration gradient between Gastro Intestinal Tract and blood vessel, which markedly improves absorption and enhances bioavailability16. In addition, increased surface area and decreased particle size can lead to increased mucoadhesion, which can increase gastrointestinal transit time and lead to increased bioavailability [32].

Hence, a drug candidate that exhibits poor aqueous solubility and/or dissolution-rate limited absorption is believed to possess low and/or highly variable oral bioavailability. Owing to low oral bioavailability, such a drug candidate would have to be administered in a larger excess than actually required if it were completely bioavailable in order to achieve a therapeutically active concentration, thus making the therapy costly.

Orally administered antibiotics such as atovaquone and bupravaquone reflect this problem very well Nano sizing of such drug scan lead to a dramatic increase in their oral absorption and subsequently bioavailability. The amelioration in oral bioavailability can be attributed to the adhesiveness of the drug nanosuspension, increased surface area (due to reduction in particle size by 10–50- fold), and increased saturation solubility, leading to an increased concentration gradient between the gastrointestinal tract lumen and blood, and increased dissolution velocity. This enhancement in bioavailability will lead to a subsequent reduction in drug dose, rendering the therapy cost-effective and obliterating any undue drug dumping in the body [33].

Parenteral Administration of Drug Nanocrystals

Generally, parenteral delivery is the preferred alternative to the oral route in case where the drug is unstable in the gastric fluid or undergoes intensively high first pass metabolism. In addition, it shows high bioavailability in comparison to other routes with rapid onset of action, but is often associated patient non-compliance, allergic reactions, and limited use of excipients, as also uptake by macrophages.

Approaches like pH modification and salt formation lead to injection site reactions, while other approaches like liposomes and emulsions enhance solubility to some extent but suffer from poor drug loading [9, 34]. Implementation of nanocrystal technology enhances the performance of the parenterally injected poorly soluble drugs. It replaces organic solvents by aqueous-based solvents, reduces dose volume by improving drug loading, faster dissolution (due to nano size) and avoiding macrophage uptake. From a safety point of view, nanocrystals permit sterile filtering; also avoid use of any harsh excipients [35].

Drug Nanocrystals for Pulmonary Drug Delivery

Nanosuspension in case of pulmonary drug delivery is used for those drugs which are poorly soluble in pulmonary secretion. These drugs are delivered as suspension aerosols or as dry powders by means of dry powder inhalers.

Nebulized form of the aqueous nanosuspensions is used for the delivery of drugs to lung. Nebulization is generally done by using mechanical or ultrasonic nebulizers. Nanosuspensions could be used in all available types of nebulizer. The advantage is that increased adhesiveness of the drug to mucosal surfaces, prolonged residence time of the drugs at absorption site which prolongs the effect of the drug, and hence we get Initial quick onset of action. Lung infections can be treated by nanosuspensions. E.g. Bupravaquone nanosuspensions formulated by nebulization. Nanosuspension of Budesonide has also been prepared successfully for pulmonary delivery. It shows a good relationship between the drug concentration in the formulation and the number of micrograms of drug delivered per actuation [36].

Drug Nanocrystals for Dermal Drug Delivery

The increase in solubility of poorly soluble drug molecules in the skin secretions, leads to an increased concentration gradient across the skin leading to increased permeation. Hesperidin, rutin and lutein are some of the examples of antioxidants that have successfully been formulated as nanocrystals for dermal application. Lutein nanocrystals for example, were developed to enhance dissolution velocity and saturation solubility, the major factors limiting oral bioavailability and skin permeation. The nanocrystals exhibited increased localization after permeation, thus indicating their potential to exhibit anti-oxidative effect at the site of [37].

Drug Nanocrystals for targeted Drug Delivery

Nanosuspension can be used for targeted deliver as their surface properties & changing of the stabilizer can easily alter in vivo behaviour. Their versatility and ease of scale up and commercial production enables the development of commercially viable nanosuspensions for targeted drug delivery. The natural targeting process could pose obstacles when macrophages are not the desired targets. Hence, in order to bypass the phagocytic uptake of drugs, its surface potential needs to be altered. Kayser developed the formulation of aphidicolin as a nanosuspension to improve the drug targeting effect against Leishmania-infected macrophages.

He stated that aphidicolin was highly active at a concentration in the microgram range [38]. Nanosuspensions afford a means of administrating poorly soluble drugs to brain with decreased side effects. Significant efficiency has been associated with microparticulate busulfan in mice administered intrathecally. Another example is successful targeting of the peptide Dalargin to the brain by employing surface modified polyisobutyl cyanoacrylate nanoparticles [39].

Drug Nanocrystals for Ophthalmic Drug Delivery

It could be shown that nanoparticles possess a prolonged retention time in the eye, most likely due to their adhesive properties. From this, poorly soluble drugs could be administered as a nanosuspension. The development of such colloidal delivery systems for ophthalmic use aims at dropable dosage forms with a high drug loading and a long-lasting drug action. The nanosuspensions were prepared by a modification of the quasi-emulsion solvent diffusion technique using variable formulation parameters (drug-to-polymer ratio, total drug and polymer amount, stirring speed). Nanosuspensions had mean sizes around 100 nm and a positive charge (zeta-potential of +40/+60 mV), this makes them suitable for ophthalmic applications. Stability tests (up to 24 months storage at 4 degrees C or at room temperature) or freeze-drying were carried out to optimize a suitable pharmaceutical preparation. In vitro dissolution tests indicated a controlled release profile of IBU from nanoparticles.

In vivo efficacy was assessed on the rabbit eye after induction of an ocular trauma (paracentesis). An inhibition of the miotic response to the surgical trauma was achieved, comparable to a control aqueous eye-drop formulation, even though a lower concentration of free drug in the conjunctival sac was reached from the nanoparticle

system. Drug levels in the aqueous humour were also higher after application of the nanosuspensions; moreover, IBU-loaded nanosuspensions did not show toxicity on ocular tissues [40].

Drug Nanocrystals for Topical Drug Delivery

Nanosuspension also incorporated into topical dosage form.

Drug nanoparticles can be incorporated into creams and water-free ointments. The nanocrystals form leads to an increased saturation solubility of the drug in the topical dosage form, thus enhancing the diffusion of the drug across the skin. Nanosuspensions in case of ocular drug delivery systems offer advantages includes Nanoparticle modified surface by appropriate bioerodible polymer results in prolonged residual time in cul-de-sac desired for effective treatment.

Commonly reported polymers in ocular nanosuspensions are poly (alkyl cyanoacrylates), polycaprolactone, and poly (lactic acid)/poly (lactic-coglycolic acid). Employing polymers in ocular drug delivery significantly prolongs drug ocular residence time and improves bioavailability [41].

Characterization of Nanocrystals

Nanocrystals are characterized in similar ways as those used for conventional suspensions such as appearance, color, odor, assay, related impurities, etc. Apart from the aforementioned parameters, the nanosuspensions should be evaluated for their particle size, zeta potential, crystalline status, dissolution studies and in vivo studies.

Particle Size Distribution

Particle size distribution determines the physiochemical behavior of the formulation, such as saturation solubility, dissolution velocity, physical stability, etc. The particle size distribution can be determined by photon correlation spectroscopy (PCS), laser diffraction (LD) and coulter counter multisizer. The PCS method can measure particles in the size range of 3 nm to 3 μm and the LD method has a measuring range of 0.05-80 μm.

The coulter counter multisizer gives the absolute number of particles, in contrast to the LD method, which gives only a relative size distribution. For IV use, particles should be less than 5 μm, considering that the smallest size of the capillaries is 5-6 μm and hence a higher particle size can lead to capillary blockade and embolism.

Zeta Potential

Zeta potential is an indication of the stability of the suspension.

For a stable suspension stabilized only by electrostatic repulsion, a minimum zeta potential of ±30 mV is required whereas in case of a combined electrostatic and steric stabilizer, a zeta potential of ±20 mV would be sufficient.

Crystal Morphology

To characterize the polymorphic changes due to the impact of high-pressure homogenization in the crystalline structure of the drug, techniques like X-ray diffraction analysis in combination with differential scanning calorimetry or differential thermal analysis can be utilized. Nanosuspensions can undergo a change in the crystalline structure, which may be to an amorphous form or to other polymorphic forms because of high-pressure homogenization [9].

Conclusion

When the size of the material is reduced to less than 100 nanometers, the realm of quantum physics takes over and materials begin to demonstrate entirely new properties. Hence nano-design of drugs by various techniques like milling, high pressure homogenization, controlled precipitation etc., are explored to produce, drug nanocrystals, nanoparticles, nanoprecipitates, nanosuspensions (which for ease of understanding commonly mentioned as nanocrystals).

As decreased size will increase the solubility of drugs hence, this technology is explored to increase oral bioavailability of sparingly water soluble drugs. On the other hand engineering of nanocrystals will avoid the use of toxic solvents and surfactants to develop injectable solutions of sparingly water soluble drugs. It is also possible to develop formulations for various routes of administration where size is the critical factor (injectables, ophthalmics and topical preparation).A nanocrystal is a nanoparticle with a crystalline structure.

Usually, nanocrystals are used in a "cluster" formation. Semiconductor nanocrystals that are less than 10 nanometers in diameter are called quantum dots. Due to the ability of such nanocrystals to change the wavelength of light, research and development currently is focusing on optical electronic applications.

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