REVIEW

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Progress in the study of drug nanocrystals

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The poor water solubility of many candidate drugs remains a major obstacle to their development and clinical use, especially for oral drug delivery. Nanocrystal technology can improve the solubility and dissolution rates of many poorly water-soluble drugs very effectively, significantly improving their oral bioavailability and decreasing the food effect. For this reason, this technology is becoming a key area of drug delivery research. This review presents much of the recent progress in nanocrystal drug pharmaceuticals, including the characteristics, composition, preparation technology, and clinical applications of these drugs. Finally, the effect of nanocrystal technology on insoluble drugs is quantified and described.

1. Introduction

According to existing literature, about 40% of all candidate drugs have poor utility due to their low solubility in water (Stegemann et al. 2007). When taken orally, their low bioavailability makes them less likely to reach effective plasma concentrations. There is a notable food effect and considerable individual variability. Finding suitable solvents for delivery *via* injection can also be difficult. For these reasons, the improvement of drug solubility is key to the study and development of many types of drugs. In 1995, Amidon proposed the first biopharmaceutics classification system (BCS) (Amidon et al. 1995). In this system, drugs are divided into four classes based on their solubility and membrane permeability: BCS Class I (high solubility, high permeability), BCS Class II (low solubility, high permeability), BCS Class III (high solubility, low permeability), and BCS Class IV (low solubility, low permeability). Insoluble drugs are placed in BCS Classes II and IV, most of them in Class II. With oral administration, the low bioavailability of insoluble drugs can be improved by salification, structural transformation, the use of prodrugs, and pharmaceutical methods (Serajuddin 2007, Stella and Nti-Addae 2007, Pouton and Tens 2008).

Nanotechnology can improve the solubility of insoluble drugs, promoting dissolution and increasing bioavailability. The nano-drug particles range in size from 1–1000 nm. Depending on the form in which nanoparticles exist, nano-drugs can be divided into two general categories: drug nanocrystals (nano-crystallized versions of the drugs themselves) and drug nanocarriers (drugs dispersed and nano-crystallized in the carrier). Due to the quantum-size effect of nanoparticles, nano-drugs have a large amount surface energy, making them thermodynamically unstable but kinetically stable. Early studies on nano-drugs focused mainly on nanocarrier preparations, such as liposomes, nanoparticles, micelles, and nanocapsules. In-depth basic and applied studies have reported preparations of nano-drug carriers, physical and chemical characterizations, absorption and targeting mechanisms. Related nano-preparations have been made (Harilall et al. 2013, Jin and Kim 2012, Parveen et al. 2012, Kumari et al. 2010, Gaucher et al. 2010, Einat et al. 2009). However, carrier-type nano-preparations in general have low encapsulation rates and are leaky, unstable, and subject to constraining factors such as toxicity. At present, out of all synthetic polyester-based carrier materials, only PLGA and PLA are indexed in the *United States Pharmacopeia*. In addition, the materials and methods of preparing the carrier and the model drug are different. Some methods require the addition of organic solvents, which can be difficult to remove from the final drug product. This increases the risk of side effects in patients.

In recent decades, the study of drug nanocrystals has gradually become a hotspot in nano-preparation research. The preparation of nanocrystals does not require carrier materials. Rather, nanocrystals are a colloidal dispersion system made of the submicron-scale particles of the pure drug. The stability of the system depends on charged protective agents and protective agents that maintain the three-dimensional structure. The solubility and bioavailability of water-insoluble and oil-insoluble drugs can be increased by nanocrystal technology. This paper reviews and discusses the characteristics, composition, preparation, clinical applications, and mechanisms of drug nanocrystals.

2. Advantages of drug nanocrystals

The special features of drug nanocrystals, and their differences from drug nanocarriers, include the following: 1. Drug nanocrystals are not limited by an encapsulation rate, and they have a wide and adjustable dosage range, unlike nanocarriers, which are subject to drug-loading capacity. Clinical requirements can thus be easily met. Even large doses (therapeutic dose > 500 mg) can be administered as nano-preparations. 2. Nanocrystals can be made into many types of usable forms. Through spray drying, freeze drying, and fluidized bed drying, nanocrystal suspensions can be solidified and made into solid agents such as capsules, tablets, or injectable forms such as lyophilized powder. 3. The size of the nanoparticles can be accurately controlled. Particle size is an important parameter for nano-preparations; it is closely related

to solubilizing effects and to bioavailability in orally administered drugs. Because the drug itself is nano-crystallized, the measured size reflects the actual particle size. 4. The methods of preparing nanocrystals are versatile, simple to perform, and easily scaled-up for industrial applications and mass production. Conventional equipment, such as high-pressure homogenizers, high-pressure micro jets, and wet-grinding machines, can be used to make drug nanocrystals.

3. Composition of nanocrystal suspensions

In the preparation of nano-crystallized drugs, drugs are first dispersed into media (water) to make a nanocrystal suspension. Next, after different solidification methods, such as spray drying, freeze drying and fluidized bed drying, they can be processed further into different forms, such as capsules, tablets, and lyophilized powder. They can then be delivered by oral administration, injection, or other routes of administration.

Nanocrystal suspensions are mainly composed of water, drugs, and stabilizers. Accessory components, such as buffers, salts, and sugar may also be added into the dispersion system based on the need. Nanocrystals are a colloidal dispersion system, and such systems are thermodynamically unstable but kinetically stable. These nanocrystals have relatively large surface areas and aggregate readily. The selection of proper stabilizer is crucial to producing a physically stable nanocrystal suspension. The stabilizer must be able to wet the surface of the drug crystals, provide space or create a charge barrier, inhibit crystal growth by facilitating steric hindrances or electrostatic repulsion, and prevent the effects of Ostwald ripening (Panyam and Labhasetwar J 2012). If no proper stabilizer is present, nanoparticles with relatively high surface energy tend to agglomerate or aggregate. Physically stable nano-preparations are produced when the weight ratio of drug to stabilizer falls to within 20:1 and 2:1 (Yokoyama 2011). Too little stabilizer can cause agglomeration and aggregation of the particles, but too much stabilizer can promote Ostwald ripening. Stabilizers can be divided into two types: ionic and non-ionic. Ionic stabilizers include sodium dodecyl sulfate, docusate, arginine, and similar materials. They serve as charged protective agents and maintain the stability of the nano-system through ion-ion repulsion. Non-ionic stabilizers include cellulose, pluronics, polyethylene sorbitol esters, and povidone, etc. They surround the drug particles and provide a three-dimensional barrier. Typically, combined use of ionic and non-ionic stabilizers leads to better results than the use of either alone, and stable nanocrystal suspensions can be formed.

4. Preparation of drug nanocrystals

There are two main methods of nanocrystal preparation: top-down and bottom-up. Top-down methods are also called dispersion methods. They involve the division of large drug particles into small particles. Top-down methods mainly include media grinding and high-pressure homogenization. This type of method does not require the use of organic solvent and is particularly suitable for drugs that are insoluble in both aqueous and organic phases. Bottom-up methods are also called precipitation methods. The first step is to dissolve the drug in a good solvent. The solvent must then be changed so that fine precipitations or crystals can be formed. The bottom-up methods mainly include nano-deposition methods, emulsion methods, and supercritical fluid crystallization methods.

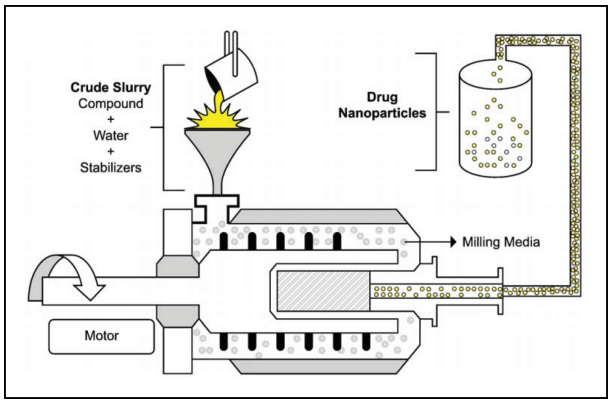

Fig. 1: Medium grinding process.

4.1. Medium grinding method

The medium grinding method is currently the most effective and economically efficient method. It involves using mechanical grinding to produce nanoscale particles. In this method, water, drug, and stabilizer are mixed at specific ratios and poured into a grinding chamber containing grinding medium (glass beads, ceramic beads, steel beads, etc.). The shear force generated between solid material and the grinding medium provides energy that breaks down the drug crystal into nanoscale particles. When the size of the particles is smaller than the gaps in the separator filter of the grinding chamber, the mixed material is pushed out of the grinding chamber and into the material cylinder by centrifugal forces. If this does not occur, the grinding process is repeated (Fig. 1). The minimum achievable particle size is 30 nm, and the particle size distribution is narrow. In general, in industrialized production, the time needed to produce a dispersion system with unimodal distribution and an average diameter less than 200 nm is typically 30–60 min. Media wet grinding technology can easily break down micron-scale particles into single-nanoparticle dispersion systems. Liversidge evaluated the particle size of the insoluble drug naproxen before and after media wet grinding: The initial size was 24.2 μm. After 30 min of grinding, the average diameter of the naproxen nanocrystals was 0.147 μm (Barzegar-Jalali et al. 2012). The media grinding method is a stable process. Once the formula and the production processes are optimized, variations between batches are rather small. However, the quality and durability of the grinding medium are a significant concern. The product can be contaminated by grinding media wear during preparation. Common grinding media include glass beads, ceramic beads, stainless steel beads, and highly cross-linked polystyrene resin beads. Polystyrene resin beads, for example, involve a risk that impurities produced during the development and validation processes may contaminate the product. The process should be monitored so that the concentration of the residual monomers remains below 50 ppb and the amount of insoluble substances remains below 0.005%w/w of the mass of the drug. Elan Chemical Company, Inc. owns a patent in nanocrystal technology, and this technology has been used to develop 5 new drugs that have entered the U.S. market (Table).

One of the limitation of this method is that the process of grinding media wearing will lead to product contamination. Meanwhile the grinding media occupies two-thirds of the volume of the total grinding material which greatly increases the weight of the machine. Thus this situation limits its batch production. The other limitation is that the production cycle is long. Even after several days of grinding, the particle size distribution of the products is still wide (0.1 $\sim$ 25 μm). There are a number of particle diameters in the nanometer range. This makes the process especially not suitable for the preparation of nanoparti-

Table: Commercially available brands of drug nanocrystals

Nanotechnology	Brand name®	Drug	Inactive components	Targeted disease	Form	Year of release
High pressure homogenization	Triglide	Fenofibrate	Sodium carboxymethyl cellulose, crosslinked methyl cellulose sodium, lecithin, sodium dodecyl sulfate	Hypercholesterolemia	Oral tablets	2005
Medium grinding	Sirolimus	Rapamycin	Povidone, poloxamer 188	Immunosuppression	Oral tablets	2000
	Emend	Aprepitant	Hydroxypropyl cellulose, Sodium dodecyl sulfate	Antiemetic	Oral capsules	2003
	Tricor	Fenofibrate	Hydroxypropylmethylcellulose, sodium dodecyl sulfate, crosslinked povidone	Hypercholesterolemia	Oral tablets	2004
	Megace ES	Megestrol	Hydroxypropylmethylcellulose, docusate	Anti-anorexia, cachexia disease	Oral suspension	2005
	Invega, Sustenna	Paliperidone, Palmitate	Polysorbate 20, Polyethylene glycol 4000	Schizophrenia	Intramuscular suspension	2009

Fig. 2: Schematic representation of high-pressure homogenization process.

cles suspensions for intravenous injection. Furthermore the long cycle leads to the low production efficiency and increases the risk of microbial pollution (Huang et al. 2013).

4.2. High-pressure homogenization

The first generation of nano-homogenization methods used bead grinding equipment to fully grind the drug-surfactant solution. This typically requires several hours or even several days. The second generation of nano-homogenization techniques uses high-pressure homogenization equipment to squeeze micronized drug-surfactant solution through pores ≈25 μm in diameter under high pressure (above 1.5×10^5 kPa). If the dynamic pressure of the squeezed fluid drastically increases and the static pressure rapidly decreases just as the fluid is squeezed out of the pores, then water can be made to boil violently at room temperature, and cavitations and bursts are generated. This bursting force can further break down the micronized drug. After 10–20 cycles, a nano-suspension with particle sizes 100–1,000 nm and solid content 10–20% can be produced (Ghosh et al. 2011, Georgea and Ghosh 2013). The key process parameters during preparation are pressure and number of cycles (Fig. 2). Kocbek et al. used high-pressure homogenization to make nano-suspensions of the BCSII drug Ibuprofen, which showed a substantially increased dissolution rate (Liversidge and Liversidge 2011). The *in vitro* dissolution rate of regular preparation at 10 min was only about 6%. After it was made into a nano-suspension, the dissolution rate at 10 min increased to 79% (Fig. 3).

However, the materials must be shattered before using this method, because the piston clearance is liable to be blocked by the drug particles which are up to 50 μm. Otherwise the machine's implosion force can barely crush harder crystals (Junghanns and Miller2008).

4.3. Nanoprecipitation

The basic principle underlying nanoprecipitation methods is to precipitate drugs from good solvents. A good solvent containing the drugs is added to miscible poor solvent, and the

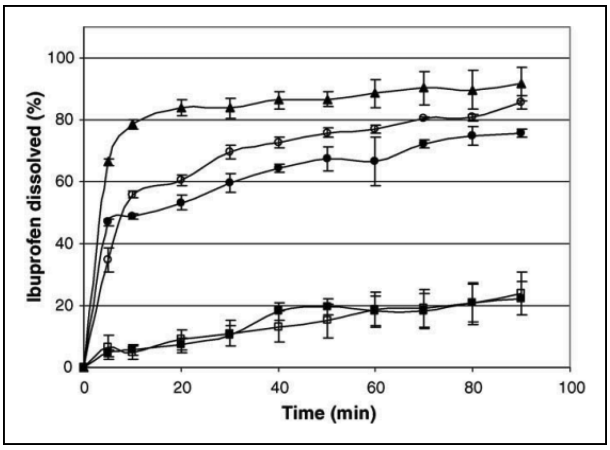

Fig. 3: Dissolution profiles of micronized ibuprofen (□), physical mixture of ibuprofen and poloxamer 188 (1:1) (■), granules composed of micronized ibuprofen and powder mixture granulated with poloxamer 188 solution in the mixer (●), and granules prepared in a top-spray chamber either with dispersion of micronized ibuprofen in poloxamer 188 solution (◯) or nanosuspension (▲) as granulating liquid.

drugs become oversaturated and precipitate. By properly controlling the formation and speed of growth of the crystal nuclei, nanoscale drug crystals can be produced. This method is simple to perform and easy to scale up for mass production. Its main drawback is that the use of organic solvent involves environmental pollution, and the residual organic solvent in the drug may be toxic. Douroumis et al. used nanoprecipitation to prepare carbamazepine nano-drug crystals (Wang et al. 2012). Chen et al. used hypergravity anti-solvent precipitation to prepare nanoscale cefuroxime axetil with an average particle diameter of 305 nm and a particle diameter ranging from 100–400 nm (Dhumal et al. 2008). But the drug needs to be soluble in at least one solvent, which creates problems for newly developed drugs that are insoluble in both aqueous and organic media. These are some reasons why, to our knowledge, this technology has not been applied to a product as yet. One needs to bear in mind that these nanocrystals need to be stabilized in order not to grow to the micrometer range (Junghanns and Miller 2008).

4.4. Emulsion

In emulsion methods, drugs are dissolved in organic solvents such as dichloromethane, chloroform, or ethyl acetate, and then the organic solvent is added dropwise into the water phase and emulsified to form an O/W type emulsion. Suitable surfactants and emulsifying agents include gelatin, polyvinyl alcohols, polysorbate 80, and Poloxamer 188. After a stable emulsion is formed, the organic solvent can be made to evaporate by increasing the temperature, reducing the pressure, or continuous stirring. Factors that affect particle size include the emulsifying agent, phase ratio, stirring speed, and evaporation speed (Sinha et al. 2013). This method requires high-speed homogenization or ultrasound, which is feasible in laboratories but not suitable for large-scale production. For large-scale production, emulsifying methods that have lower energy costs, such as the emulsion-solvent diffusion method, can be used.

In the emulsion-solvent diffusion method, acetone or methanol serves as the water phase and a water-insoluble organic solvent such as dichloromethane or chloroform serves as the oil phase. In the presence of emulsifying agent, rapid automatic diffusion of the water phase disperses the oil phase into fine droplets, and interfacial turbulence forms between the two phases. The decrease in the interfacial energy and interfacial disturbance causes the formation of even smaller emulsion droplets, at the nanoscale. These are then solidified and isolated to produce nanoparticles. As the concentration of the water phase (acetone) increases, particle size is substantially reduced. After the solvent evaporates, solid nanoparticles are formed. This method does not require homogenization or ultrasound, so it is called low-energy emulsion. In 1993 Niwa first proposed a self-emulsion–solvent diffusion method for the preparation of nanoparticles (Niwa et al. 1993).

4.5. Supercritical fluid technology

After drugs are dissolved in supercritical fluids, such as CO_2, the fluid is subjected to vacuum atomization through a nozzle with a tiny aperture. The supercritical fluid undergoes rapid vaporization, and solid nanoparticles are precipitated. Because most drugs do not dissolve in supercritical fluid, the so-called supercritical anti-solvent technique can also be used. Drugs are dissolved in an anti-solvent that is miscible with the supercritical fluid. They are atomized at the same time. At high pressure, the supercritical fluid completely absorbs the anti-solvent, and the nanoparticles are precipitated. Supercritical fluid technology has attracted a great deal of interest, because environmentally friendly solvents can be used during preparation. It can also produce very pure particles without any residual organic solvent. The solutes precipitated with this technology are extremely pure, completely free of solvent. However, because many drugs are completely insoluble or barely soluble in supercritical fluids, this technique is of relatively small practical value.

5. Applications of drug nanocrystals

5.1. Oral administration

After oral administration, the rate-limiting step of the absorption of insoluble drugs is dissolution control. Increases in the dissolution rate can substantially increase the bioavailability of insoluble drugs. The dissolution rate of a drug is related to the inherent solubility of that drug and to particle size. As early as 1897, Noyes and Whitney conducted a drug dissolution experiment (Noyes and Whitney 1897). They deduced the equation $dX/dt = k(Cs-C)$. Here, k is the dissolution constant, Cs is the saturation solubility of the compound, and C is the bulk concentration. The Noyes-Whitney equation shows that the dissolution rate of a drug is positively correlated with its solubility. Since then, this equation has been modified by many other scholars. In 1904, Nernst and Brunner introduced the concept of the diffusion layer and Fick's second law into the dissolution rate equation and deduced the famous Nernst-Brunner equation: $dC/dt = (D \times S/V \times h) \times (Cs-C)$; here D is the diffusion coefficient, S is the surface area, V is the volume of dissolution medium, h is the thickness of the diffusion layer, Cs is the saturation solubility, and C is the concentration of the solution. This equation quantitatively defines the relationship between the dissolution rate of the drug, surface area, and solubility. As the collective surface area of the drug particles increases and the saturation solubility increases, the drugs dissolve faster *in vivo* and show higher bioavailability. In preparation of drug nanocrystals, the sizes of drug particles drop to nanoscale. This not only dramatically increases the total surface area of the insoluble drugs but also substantially increases their saturation solubility (Mauludin et al. 2009). In this way it can notably increase their bioavailability.

The advantages of oral administration of nanocrystals in clinical applications mainly involve three factors: 1. Increases in the bioavailability of the insoluble drugs. The surface area of insoluble drugs is closely correlated with their bioavailability, and reducing particle size can increase surface area. For

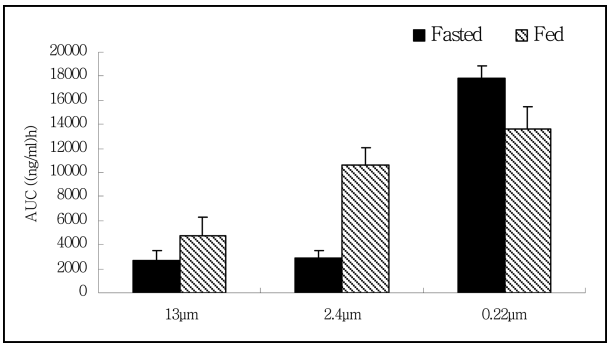

Fig. 4: AUC of cilostazol following oral administration in Beagle dogs given a hammer-milled, jet-milled, and NanoCrystal® suspension of cilostazol at a dose of 100 mg/dog.

example, reducing the particle diameter from 10 μm to 200 nm can increase the surface area 50 times. Reducing particle size can substantially increase the bioavailability of insoluble drugs whose bioavailability is limited by the dissolution rate. Jinno studied the effects of the particles size of the insoluble drug cilostazol and its bioavailability and found that when the particle diameter was reduced from 13 μm to 0.22 μm, bioavailability increased 6.55 times (Fig. 4) (Willmann 2010). 2. Elimination of the food effect. The absorption of insoluble drugs taken orally is influenced by food effects. Eating triggers the secretion of bile into the digestive tract. This bile increases the concentration of surfactants. This increases the solubility of drug, and the physiological conditions in these states tends to improve the drug's bioavailability. In the fasting state, the bioavailability of drug typically decreases, at least in part because there less bile is present. This leads to pronounced variability in drug absorption after oral administration. Nano-preparations can decrease this variability in the gastrointestinal tract and substantially reduce the food effect. Liversidge et al. examined the decrease in the food effect associated with danazol nanocrystals (Eerdenbrugh et al. 2008). They reported that when the size of the drug particles was reduced from microscale to nanoscale, the ratio of bioavailability of danazol during the fed state to that during the fasting state dropped from 6.32 to 1.26. Decreases in the variability of drug absorption associated with oral administration and increases in controllability both reduce risks in clinical settings. They also help clinicians design clinical treatment programs. 3. Absorption and effects both take place quickly. The rapid onset associated with some medicines can improve the effects of treatment. For example, the nanocrystals of the analgesic drug naproxen showed a T_{max} of about 50% that of suspensions and tablets. One hour after nanocrystal administration, AUC was 2.5 times that of suspensions and 4.5 times that of tablets.

5.2. Parenteral route of administration

For drugs delivered at high doses, administration of nanocrystals by injection has notable advantages. First, injected drug nanocrystals do not need carrier material and are not limited by encapsulation rate or loading capacity, and thus can satisfy the need of high-dosage, high-concentration preparations. In addition, unlike traditional injections, nanocrystal injections do not involve excipient toxicity. The traditional injection of insoluble drugs requires large amounts of surfactants or co-solvent to increase drug solubility. Injection with surfactants such as Tween 80 and polyoxyethylene castor oil can easily lead to toxic side effects, including hemolysis and allergic reactions, but injection with the organic solvent propylene glycol can cause intense pain and poor patient compliance. In addition, due to the toxicity of the excipient, the drug dose is usually limited, and ideal effects cannot be achieved. Nanocrystal preparations are typically aqueous dispersions, free of organic solvent. There is only a very small amount of stabilizer in the mixture. Stabilizers are selected based on the safety of the injection product. For this reason, the toxicity of nanocrystal preparations administered by injection is very low. For example, the anti-cancer drug Taxol is a water-insoluble drug. The commercially available Taxol preparation contains a castor oil EL/ethanol mixture to dissolve the drug. Due to the toxicity of the solvent, the dose must be rather low, which limits the effects of treatment. A study performed on MV522 tumor-bearing mice showed that the maximum tolerable dose of market Taxol was 30 mg/kg, but that of taxol nanocrystals was 90 mg/kg, When both were administered at their respective tolerable doses, 22% of the mice in the market Taxol group died, but none of the mice in the Taxol nanocrystal group died, and the average tumor weight was significantly lower than in the market group (Eerdenbrugh et al. 2008).
In nano-preparations administered by injection, nanosize has been shown to affect the pharmacokinetic characteristics of the drug. After intravenous administration, drug particles are captured by the mononuclear phagocytic system and concentrated in the liver and spleen. The post-injection tissue distribution of nanoparticles is influenced by many factors, including the physical characteristics of the particle itself, the dose, infusion time, and the dissolution behavior of the drug particles in the blood. If the solubility of the drug can reach the level of mg/ml, or if the drug can be ionized, then it will dissolve completely after it enters the body. In this case, the tissue distributions of nano-preparations and regular preparations are not different from each other. However, if the inherent solubility of the drug is only at the level of μg/ml, then the drug does not dissolve completely, even as the dose increases. In this case, the tissue distributions of nano-preparations will differ from those of regular preparations. The drug clearance rate and tissue distribution volume of nano-preparations of Taxol, for example, are lower than those of regular injections of Taxol. This is mainly because the nanoparticles are retained by the Kupper cells in the liver. From the point of safety, this conclusion further demonstrates that that capture of the nanoparticles by the Kupper cells is not a side effect. Rather, such capture augments drug tolerance and can increase the maximum tolerable dose 5–10 times (Liu et al. 2010).

5.3. Administration by inhalation

The pulmonary drug delivery system delivers drugs directly to the lungs. This is suitable for the treatment of tuberculosis, asthma, and other local diseases. The drug particles must fall in the aerodynamically respirable range 0.5–5 μm, and the nano-drug particles must be within the range of 10–100 nm. Budesonide is a corticosteroid used to treat chronic asthma. Its time of residence in the lungs is relatively long. Researchers have made budesonide nanosuspensions and compared their pharmacokinetic parameters to that of the commercially available dry powder inhalant (Busse et al. 2008). The peak time of budesonide nanosuspension aerosols was found to be 8.4 min, which was significantly shorter than that of dry powder inhalant (14.4 min). The half time of nanosuspension was 6.62 h, and that of dry powder inhalant was 5.42 h. The peak plasma concentration of the nanosuspension was 1.83 greater than that of dry powder inhalant.

5.4. Transdermal administration

Studies on nanocrystals related to the transdermal drug delivery system have been carried out. Nanocrystals are good for topical and transdermal applications. The use of nanocrystals instead

of regular preparations can increase the solubility of the drug, substantially increase its bioavailability, promote its transdermal absorption, increase the effects of treatment, and reduce the severity of side effects. Zhao et al. (2009) studied the *in vitro* skin permeability of nano-silver hydrogel glue, and the results showed the skin permeability of nano-silver hydrogel glue to be good. Adding a proper amount of urea to the cellulose nano-silver gel was found to further promote penetration of the drug into the skin, and the duration of its effects increased.

5.5. Administration through commercially available drug nanocrystals

Since 2000, there has been rapid development of drug nanocrystals. There are currently 6 commercially available brands (Table).

5.5.1. Fenofibrate tablets

The brand name of fenofibrate is Triglide. It is a BCS Class II drug, and poor solubility is the main factor that limits its clinical application. In 2005, Triglide was launched by Sciele Pharma Inc. It was designed to treat cases of adult hyperlipidemia (type IIa) that did not satisfactorily respond to diet and to treat simple and mixed endogenous hypertriglyceridemia (types IIb, III, and IV). It is particularly effective in cases in which blood cholesterol continues to rise even after a diet regimen is in place or when there are other concurrent risk factors. The inactive components include carboxymethyl cellulose, crosslinked methyl cellulose sodium, lecithin, and sodium dodecyl sulfate. High-pressure homogenization nanotechnology is used to produce this drug, solving the problems of poor drug solubility and the food effect and reducing individual variability.

5.5.2. Sirolimus tablets

The brand name of sirolimus (rapamycin)) is Rapamune. It is a BCS Class II drug. In 2000, it was the first drug prepared with nanocrystal technology to be approved by the FDA. It was launched by Wyeth, and is considered an immune agent. The inactive components include povidone and poloxamer 188. The original formulation of rapamycin is an oral solution that must be stored at low temperatures. To make sirolimus tablets, medium grinding is used to prepare nanocrystal suspension, which is then solidified into tablets, making them easy to carry and to store. Each tablet contains 1–2 mg rapamycin nanocrystals. The bioavailability of rapamycin nanocrystals is at least 21% higher than that of solution preparations, and the effects of treatment are significantly better (Bisht et al. 2008).

5.5.3. Aprepitant capsules

The brand name of aprepitant is Emend. It is a BCS Class IV drug (low solubility, low permeability). When taken orally, its bioavailability is only 9%. In April 2003, the U.S. FDA approved the launch of nano-crystallized aprepitant capsules produced by Merck Inc. under the brand name Emend. To make aprepitant capsules, NanoCrystal technology (media grinding method) patented by Elan Inc. was used. Emend (125 mg/80 mg regimen) was prescribed to prevent chemotherapy-induced acute and delayed nausea and vomiting. In March 2010, 40 mg aprepitant capsules were approved for the market. The inactive components included hydroxypropyl cellulose and sodium dodecyl sulfate. Hydroxypropyl cellulose serves as the protective agent for maintenance of the three-dimensional structure, and sodium dodecyl sulfate serves as a charged protective agent. Aprepitant capsules developed with nanotechnology substantially increase the bioavailability of the drug when administered orally. Bioavailability studies in humans have shown that the bioavailability of nano-crystallized drug is around 65%, while that of regular suspensions is only 9%. In addition, the food effect is notably reduced. The bioavailability of regular tablets in the fed state is about 4 times that of the fasting state. However, the food effect is not associated with nano-crystallized preparations. The level of bioavailability observed before eating is the same as that observed after eating (Wu et al. 2004) (Fig. 5). Compared to nano-crystallized aprepitant capsules, Nano-crystallized aprepitant capsules reduce differences in effect among patients of different sexes, races, and ages, and reduces individual variability as well, thus helping clinicians to design clinical treatment programs and improving treatment effects.

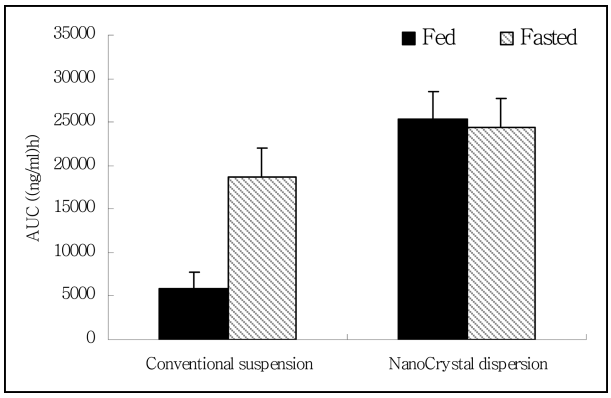

Fig. 5: AUC of aprepitant after oral administration to Beagle dogs(N = 5) of a conventional suspension and NanoCrystal dispersion formulation of aprepitant at a dose of 2 mg/kg.

5.5.4. Fenofibrate tablets

The brand name of fenofibrate is Tricor, which was launched by Abbott Inc. in 2004. The inactive components include hydroxypropylmethylcellulose, sodium dodecyl sulfate and crosslinked povidone. Like Triglide, this product is designed to reduce cholesterol levels. Both are nano-crystallized oral tablets produced with different nanotechnologies. Tricor also increases the solubility of the drug and reduces the effects of food on absorption.

5.5.5. Megestrol oral suspension

The brand name of megestrol is Megace ES. It is a BCS Class II drug. Megace ES is a nanocrystal oral suspension. It was approved by the FDA and launched by Par Pharmaceutical Inc. in 2005. This drug is used to treat unexplained weight loss and anorexia in cancer patients. Inactive components include hydroxypropylmethylcellulose and docusate; the former serves as the protective agent for maintenance of the three-dimensional structure and the latter serves as a charged protective agent. The original preparation was acetic acid megestrol regular oral suspension (Megace), with a concentration of 800 mg : 20 ml. The concentration of Megace ES nano-preparation is 625 mg : 5 ml. The nanocrystal drug release system for Megace ES not only improves the dissolution rate and bioavailability relative to the original acetic acid megestrol oral suspension but also reduces the volume of the oral suspension by 75%. In addition, the liquid viscosity is only 1/16 that of the original preparation. This is an important improvement for patients who have trouble swallowing fluids in large volumes and for patients with anorexia who have poor appetite.

5.5.6. Palmitic acid paliperidone injection

The brand name of paliperidone palmitate is Invega Sustenna. It is a BCS Class II drug. On July 31, 2009, Janssen Pharmaceuticals, Inc. announced that the FDA had approved the use of Invega Sustenna sustained-release oral suspension for the treatment of adult schizophrenia. The inactive components include Polysorbate 20 and polyethylene glycol 4000. Invega Sustenna is an injectable atypical antipsychotic with long-term effects. It is administered once a month. Nano-crystallized product showed significantly closer associations with delayed recurrence, improved compliance, and less frequent adverse reactions than regular preparations. Because it is administered only once a month, it can also facilitate monitoring of patient compliance with the medical regimen.

6. Quantitative expression of nano-effects

The composition of drug nanocrystals is simple because it does not involve carriers. The crystals are typically rigid in structure, and the sizes of the crystals faithfully reflect the sizes of the drug particles. Because the solubility and dissolution rates of the insoluble drugs are both closely correlated with the sizes of the particles, the nano-effects of nanocrystals in improving the solubility and dissolution rate of the insoluble drugs can be quantitatively determined using equations with non-dimensionless parameter dissolution numbers (Dn) and dose numbers (Do) in BCS (Oh et al.1993).

The expression of Dn is illustrated in Eq. (1)

$$Dn = \left(\frac{3D}{r^2}\right)\left(\frac{C_s}{\rho}\right)\langle T_{si}\rangle = \frac{\langle T_{si}\rangle}{T_{diss}} \quad (1)$$

Here, Dn is the ratio of retention time to dissolution time, and the relevant parameters include solubility (Cs), diffusion coefficient (D), density (ρ), and the initial particle radius (r). As shown in Eq. (1), Dn is negatively correlated with r2; the smaller the particle size, the faster the in vitro dissolution rate. Eq. (2) can be used to quantitatively calculate the ability of nanocrystals to promote the dissolution of insoluble drugs.

For insoluble drugs whose particle radius is at the micron level, radius has no effect on solubility. However, when the particle size is reduced to nanoscale, solubility increases as the particle radius decreases. The parameters do can directly show the effects of nanotechnology in increasing the solubility of insoluble drugs. The expression of Do is illustrated in Eq. (2).

$$Do = \frac{M/V_0}{C_s} \quad (2)$$

Do is the ratio of drug concentration to drug solubility. Here, Cs is solubility, M is the dose administered, and V_0 is the volume of water that is drunk when taking the medicine, typically 250 ml. Nanocrystal technology reduces the size of insoluble drug particles to nanoscale, and thus substantially increases its solubility.

Griseofulvin is an insoluble drug in BCS Class II. For its water solution, Do is 133, and Dn is 0.23. After it is made into nanomicelles, its solubility and dissolution rate are significantly increased. For griseofulvin micellar solution containing 2% SLS, Do was 0.9, and Dn was 0.23. In this way, the solubility was increased by 150 times and the dissolution rate by 33 times (Feng et al. 2008).

7. Conclusion

The study of drug nanocrystals has revealed some promising new directions in the development of preprations of drug preparations. In this type of preparation, because the drug itself is in the form of nanoparticles, it shows certain specific nano-effects and properties. This technology can substantially increase drug solubility, improve dissolution behavior and bioavailability, reduce toxicity, and enhance targeting and controllability. These features can solve key problems in the development of preparations of insoluble drugs. Currently, developing new chemical entities (NCE) with completely new structures is difficult, costly, and time-consuming. In many countries, including China, full realization of the potential of commercially available drugs through the development of new preparations and improvement of *in vivo* behavior of NCE is of great significance. In this way, studies on drug nanocrystals have a broad implication.

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