Recent advances in Nanocrystal

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Article History:
Received on: 30 Jun 2020
Revised on: 25 Jul 2020
Accepted on: 06 Aug 2020

Keywords:
Poor water solubility, Pharmacokinetic, Pharmacodynamic, Nanocrystals

ABSTRACT
The biggest challenge in the discovery and fabrication of drugs nowadays is low solubility. Many new chemical entities have major therapeutic effects, increased performance, but due to poor water solubility their clinical applications are limited. This is why Nanocrystal technology to solve the issue of low aqueous solubility was established. Nanocrystal technology improves the rate of dissolution according to the surface area of the active medicinal substance by reducing its particulate size to the nano size level, maintaining the pharmaceutical crystal morphology and enhancing pharmacokinetic and pharmacodynamic properties of different types of pharmaceuticals. Nanocrystals are prepared using the method down, up and down, spray drying and thus new techniques. Nanocrystals loaded as tablet or capsule. The obtained nanocrystal can be managed in different ways. Using freeze-drying or spray-drying to produce powder, which then is used for tabletting or other oral product, may usually be dried with nanocrystal.

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ISSN: 0975-7538
DOI: https://doi.org/10.26452/ijrps.v11i4.3227

INTRODUCTION
The biggest challenge in the discovery and production of medicines nowadays is its low solubility. Many new chemical entities have significant therapeutic effects, increased performance, but due to poor water solubility, their clinical applications are limited. Such forms of new chemical substances belong to class II or IV of the BCS in the Biopharmaceuticals Classification system (BCS). Numerous approaches to solving the problem of low aqueous solubility have, therefore, been established. Those are: salt-forming, co-solvent, complexing and solid-state manipulation, emulsion, active surface agents, micronising. (Dandagi and Kaushik, 2011; Drug nanocrystals, 2009)

Nanocrystals are crystalline nanoparticles with surface stabilisers of a size ranging from 200 to 500 nm. They increase the solubility of saturation, dissolution rate and probably the mucoadhesive property of the drug dissolution-dependent bioavailability in oral improvements. (Drug nanocrystals, 2009)

Nanocrystal formulations for oral administration have many advantages and are as follows. (Möschwitzer, 2007)

1. Higher absorption rate,
2. Enhanced oral bioavailability,
3. Effect quickly,
4. Enhanced ratio of dose,
5. Necessary dose reduction,
6. Applicability for all dosage routes Application.
Nanocrystals may be distributed over different routes as opposed to micronised products. Oral administration is possible in the form of pills, capsules, sachets or powder. Since they are of tiny particle sizes, the intravenous device may also deliver nanosuspensions, which can thus achieve 100 per cent bioavailability (Neslihan, 2009).

Figure 1 Shows how nanocrystals are derived from drugs.

1. decline in fed/fasted variability,
2. quick, easy and economical formulation development
3. Ability to carry high amounts of drugs (30-40%).
4. Reliability improved.

The nanocrystal technology improves the dissolution rate reducing the surface area of the drug's particles to nanoscale conserving the morphology for medication. (Waard, 2011; Möschwitzer, 2004a)

Strong stability. Greater stability. These are stable structures by using a stabiliser that prevents successful drug reaggregation during preparation. Suspension by the application of the active surfaces or polymers to drug nanocrystals in liquids may be stabilised. Applicability to all poorly soluble drugs because all these drugs could be directly disintegrated into nanometer-sized particles.

Preparation of nanocrystals
The development of nanocrystals, bottom-up (controlled precipitation/crystallisation) technologies and the up-to-date nanoionising technologies (great drug powder to decrease in size, e.g. through mechanical attrition) are two basic strategies. Nevertheless, hybrid techniques are often employed in conjunction with pre-treatment and a subsequent size reduction stage. (Emons and Boenicke, 2010)

Figure 2 gives methods of preparation of nanocrystals.

Bottom-up technology
The theory for the process is that the active material is dissolved in an organic solvent that is then added in a non-solvent (miscible with an organic solvent). The nanocrystals then precipitate in the presence of stabilisers. This is quick and has a low cost as a primary benefit of the precipitate technique. In this process, scale-up is also simple. We must note that several parameters should be tested to obtain homogenous nanocrystals, such as stirring rate, temperature, solvent / non-solvent rate, medicine concentration, viscosity, a form of solvent and stabilizer. (Kobierski, 2008)

Top-down technology
“Top-down” technology employs various types of
grinding and homogenisation techniques for dispersion methods. "Top-down" technology is more common than technology called "Bottom-up." This is a mechanism that splits large crystal particles into tiny pieces, in other words. Both approaches are used together in "top-down and bottom-up" research. Homogenisation or framing can apply top-down technology. (Dandagi, 2011)

**Homogenisation methods**

The Micro Fluidizer is a jet stream homogeniser that collides on the front with high-speed underpressures up to 4000 bar (up to 1000 m / sec). Turbulent flow, large shear forces and particulate matter collide into the nanometer range for particles reduction. Hypertension added, and the high-streaming velocity of the lipid can also lead to cavitations. Stabilisation of phospholipids and other surfactants and stabilisers is necessary to prevent particle size. 50 to 100 passes are often required to reduce the particle size (Muller, 2001).

**Top-down and bottom-up technology**

Both approaches are used together in "top-down and bottom-up" research. Nano-Edge® is a combination-technology product. The formulation technique for poorly water-soluble drugs was defined by nano-edge technology. It is a useful technology with high melting points and high octanol-water partition coefficients for active ingredients. It is based on direct harmonisation, micro precipitation and emulsions of lipids. The substance is dissolved into a water-miscible solvent in micro precipitations and is a solution. (Nanjwade, 2011)

**Characterisation parameters**

Table 1 represents various characterisation parameter for Nanocrystals. (Emons and Boenicke, 2010)

**Applications**

Figure 3 shows different applications of these
nanocrystals. Each of them is explained briefly one by one.

**Parenteral administration**

The parenteral application of poorly soluble drugs with the use of co-solvents, surfactants, liposomes or cyclodextrins, especially intravenously (IV), often involves significant amounts of injection and side effects. Carrier-free nanosuspensions allow a higher capacity of the load than other parenteral applications. The application volume can be reduced dramatically compared to solutions with nanosuspensions. The nanocrystals in drugs must be manufactured in an aseptic method to meet the significantly higher regulatory barriers. Additionally, autoclav- ing or gamma irradiation and sterile filtration will sterilise nanosuspensions. The quick resolution of nanocrystals imitates the plasma concentration profile of a solution when a medication is given as a nanosuspension. Medicinal surfactants and poly- meric stabilisers can be formulated for IV injection using nanosuspension.

**Figure 3: Applications of Nanocrystal**

The emphasis was close to the liposomal formulation on the reticuloendothelial system, the lung, liver and spleen. (Nanjwade, 2011)

**Peroral administration**

Nanosizing of the drug dramatically improves oral absorption and bioavailability afterwards. Aqueous nanosuspension can also be used as a liquid medication such as tablets and pellets of hard gelatin. (Nanjwade, 2011)

**Pulmonary drug delivery**

Mechanical and ultrasonic nebulisers for lung delivery can be used with the use of aqueous nanocrystals. The dispersion can be large since more tiny particles are present instead of several micro-particles; all aerosol droplets contain nanocrystals. Budes- onide has been successfully prepared, a poorly soluble corticosteroid because nanosuspension is developed through nebulisation to treat lung infections. (Sawant, 2011)

**Target drug delivery**

Nanocrystals are ideal for targeted distribution because their surface properties can easily alter in vivo behaviour and stabiliser transition. The flexibility, scale-up and industrial production enable the economically viable application for the targeted distribution of drugs. If macrophages are not the desired targets, a usual targeting method can pose obstacles. Thus, the surface potentials must be modi- ied to avoid the phagocytic use of drugs. To boost the drug targeting effect on macrophages infected with Leishmania, Kayser developed aphidicolin formulation as a nanosuspension. He said aphidicolin is highly active in the microgram range at a concentration. It offers a source for administrative drugs with poorly soluble side effects in the brain. Microparticulate busulfan in mouse administered intrathecally has been associated with substantial performance. Another example is successful target- ing of the peptide Dalargin to the brain by employ- ing surface-modified polyisobutylene cyanoacrylate nanoparticles. (Malamatari, 2018; Gao, 2008)

**Dermal Drug Delivery**

Dermal nanosuspension is of primary interest, provided the usage of drug nanocrystals does not lead to an increased gradient of concentration between formulation and skin. The increased solubility of the saturation leads to over-saturated formulations, which increase the medication absorption by the skin. The use of positively charged poly- mers as stabilisers for nanocrystals will further improve this effect. The opposite charge leads to the drug nanocrystals being more closely related to the negative conium in the stratum. (Gao, 2008;
Table 1: Characterization Parameters

| Characterization Parameters                  | Methods                                      |
|---------------------------------------------|----------------------------------------------|
| Mean Particle size & size distribution      | SEM, TEM                                     |
| Structure & Morphology                      | Light Microscopy, SEM                        |
| Surface Charge                              | Zeta potential                               |
| Solid state analysis                        | Powder X-ray diffraction, DSC                |
| Solubility                                  | UV Spectrometer                              |

Möschwitzer, 2013)

**Ophthalmic Drug Delivery**

Nanoparticles can be seen to have a long retention period in the eye, mainly because of their adhesive characteristics. This can be used as a nanosuspension for poorly soluble pharmaceuticals. The production of these ophthalmic colloidal delivery systems is intended to include dropable types of dosage with a high drug loading and enduring drug action. Nanosuspensions were formed using varied formulation parameters (a drug to polymer ratio, total drug amount and polymer number, vibrant speed) by modifying the quasi-emulsion dissolvent diffusion technique. This makes nanosuspensions suitable for ophthalmic applications with mean widths of about 100 nm and a positive charging (Zeta-Potential of +40/+60 mV) To improve a suitable pharmaceutical preparation, and stability tests were performed (up to 24 months storage at 4°C or room temperature) or freeze-drying. A controlled release profile of nanoparticles from IBU was shown during in vitro dissolution testing. After inducing an ocular trauma (paracentesis), in vivo efficacy was evaluated on the rabbit’s eye. An inhibition in miotic reaction to the operative trauma was reported, which compares to an aqueous acidic formulation of the eye drop. However, the nanoparticle method produced a lower free drug concentration in the conjunctival sac. After the application of the nanosuspension drug levels in aqueous humour were also higher; moreover, IBU-infected nanosuspensions were not toxic to eye tissues. (Gao, 2008; Möschwitzer, 2004b)

**Nanocrystals loaded in the carrier**

Drug nanosuspensions can also be incorporated in carriers such as human erythrocytes or be combined with fluorescent dyes with the advancement of modern pharmaceutical systems. They can be transformed not only into pills, capsules, creams, injectors, or other traditional products.

**For Oral**

Nanocrystals, such as the may tablet, or capsule may be filled in oral dosage. The nanosuspensions obtained can be managed in different ways. Designed to make powder with freeze-drying, or spray drying, which can then be used for tableting or other oral formulations, medicament nanosuspension may usually be dried up. Alternatively, nanosuspension may also be used directly for downstream formulation. Nanosuspension could be used as a wet agent to blend for granulation with other excipients, for example, starch, and was then applied for the tablet. In one study, lactose monohydrate and microcrystalline cellulose were loaded with glyburide nanocrystals, which in vivo AUC compared to tablets were ultimately highly improved. (Gruverman et al., 1998)

**For Inhalation**

Nanocrystals represent homogeneous smaller medicinal particles which, thank their extended pharmacology surface, are suitable for charging them in microparticle by use of tools such as the pulverisation of the inhalation and improve their similar bioavailability. The microparticle may be mannitol or other medicinal excipients as a carrier of nanocrystals. (Bushrab, 2003)

**For Transdermal**

Medicament nanocrystals could be loaded to commonly used transdermal gels which would result, compared to the micro formulation or drug solution in vitro and in vivo, in an improvement in performance. For example, for an average particle size of 369 nm, silver sulfadiazine nanosuspension was produced from the product HPH and then loaded into hydrogel thermosensitive. The drug release tests showed apparent changes of the sample loaded in comparison with the consumer product, and the nanosilver sulfadiazine formulation was also found to be superior for in vitro antibacterial experiments. Some nanocrystal combinations have been documented with different built carriers. (Keck, 2004)

**Cell Targeting**

Human cells are considered biocompatible and have been applied to drug carriers, as opposed to synthetic chemical carriers. The use of red blood cells, leucocytes or stem cells as carriers for the nanopar-
article to achieve the appropriate target for drugs has been documented. (Möschwitzer, 2013)

Some of the nanocrystals based formulations are given in Figure 4.

CONCLUSIONS

The Problem of Poor solubility is a hurdle for formulation scientists. In any route of administration, the therapeutic performance of poorly soluble drugs is improved by drug nanocrystal approach. Size of the drug is reduced to nanometer size. The excellent advantage that can be illustrated that the drug nanocrystal can be applied to different administration routes. To create a supersaturated activity with high thermodynamic activity, Dermal delivery of these nanocrystals is very beneficial as well as these can be administered with oral and parenteral administration. The drug nanocrystal technology is a successful emerging technology.

ACKNOWLEDGEMENT

The author thanks, Department of Pharmaceutical Chemistry and Analysis, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Pallavaram, Chennai, Tamil Nadu for providing required facilities and support to carry out this review.

Funding Support

All authors declare they have no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Conflicts of Interest

The authors declare that they have no conflict of interest for this study.

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