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Review Article

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DissoCubes: A Novel Formulation to Enhance Solubility

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Abstract

Most of drugs are poorly soluble and have bioavailability problems. Therefore, there is an urgent need to find solutions for the formulation of these poorly soluble drugs. To achieve a broadly applicable technology, increasing interest has been focused on drug nanoparticles in the last few years. Going beyond micronization leads to a further increase in the dissolution velocity due to an even larger surface area. An additional effect can be achieved by a controlled structural change in drug nano particles, which means reducing the crystallinity and increasing the amorphous fraction eg Dissocubes. DissoCubes are crystalline nanoparticles of active substance obtained by a liquid state high energy process using a high pressure piston gap homogenizer to reduce the drug particle size in the presence of surface modifiers that associate at the freshly generated drug interface. A particle size reduction from approximately 50µm to about 0.5µm is achieved resulting in a very homogenous and stable formulation. The nanosuspensions could be formulated into various dosages forms. DissoCubes™ technology is a technology of choice for molecules with oral bioavailability issues and/or requiring rapid onset of absorption. However, there are two more interesting features of drug nano particles (i.e.,DissoCubes): (a) an increase in saturation solubility and (b) structural changes inside the particles.

Key words: DissoCubes, nanoparticles, nanosuspensions.

Introduction

Most of drugs are poorly soluble and have bioavailability problems. Therefore, there is an urgent need to find solutions for the formulation of these poorly soluble drugs. Preferably, such a new formulation principle should be applicable to almost any poorly soluble drug, independent of its chemical structure and spatial molecular dimensions. A simple approach to improve the bioavailability of orally administered drugs is micronization. However, especially for drugs with low saturation solubility, the achieved increase in dissolution velocity might not lead to sufficiently high blood levels. Therefore, alternative formulation techniques to existing approaches need to

be developed. To achieve a broadly applicable technology, increasing interest has been focused on drug nanoparticles in the last few years. Going beyond micronization leads to a further increase in the dissolution velocity due to an even larger surfacearea. An additional effect can be achieved by a controlled structural change in drug nanoparticles, which means reducing the crystallinity and increasing the amorphous fraction. Examples of drug nanoparticles with structural changes are the products NanoMorph™ marketed by Knoll/BASF Pharma (company brochure) and the drug nanosuspensions marketed under the name DissoCubes . DissoCubes combine the advantages of using a size reduction technique (i.e., NonoCrystals) with the advantages of a precipitation technique (i.e., Hydrosols™, NanoMorph™) opening the opportunity to induce structural changes, which means increasing the amorphous fraction

II. Historical Development

The technique for preparing hydrosols was developed by Sucker based on the traditional "via humida paratum" for ointments. For long-term stabilization, lyophilization of the drug nanoparticle suspension is recommended. A significant limitation of this method is the need for the drug to be soluble in at least one solvent and, simultaneously, that this solvent be miscible with a nonsolvent. However, many newly developed drugs are simultaneously poorly soluble in aqueous and organic media, thus excluding use of the precipitation technique. Jet milling leads to powders with lowest mean diameters of around 3–5µm. The size distribution ranges from approximately a few hundred nanometers to about 25 µm and the total fraction of nanoparticles is extremely low. Ball or pearl mills can create suspensions with the majority of particles being in the nanometer range. However, problems associated with these mills are long milling times, up to almost 1 week, and erosion from the pearls contaminating the product. The task was therefore to use a technique for size reduction, providing the required features for an industrial process [e.g., simple, cost-effective, no or low product contamination with heavy metals (below 10 ppm), and simultaneously open features to change the structure of particles as is possible in a precipitation process]. This was realized by developing the DissoCubes technology, which means production of a suspension of drug nanoparticles (nanosuspension) by high-pressure homogenization.

III. Description of the Dissocubes Technology

A. Production Technique for DissoCubes

The preparation process for DissoCubes nanosuspensions is very simple. The powered drug is dispersed in an aqueous surfactant or polymer solution to yield a traditional macrosuspension. The dispersion is performed by high-speed stirring, for example using a Silverson homogenizer or an ultraturrax stirrer. The **DissoCubes** obtained so-called "presuspension" is then high-pressure-homogenized using a piston-gap homogenizer, for example APV Gaulin machines (APV Homogenizer Deutschland GmbH, Lu beck/Germany). Typical pressures applied are between 500 and 1500 bar; in general a minimum of five homogenization cycles and a maximum of 15–20 cycles is required. High-pressure homogenization leads to a very fine product even allowing intravenous administration. Intravenous particulate products require a very low content of particles in the range of a few micrometers to avoid blocking of the capillaries. In general, nanosuspensions of DissoCubes contain fewer particles larger than 5 µm than emulsions for parenteral nutrition. For oral administration, the content of particles the size of a few micrometers is less critical. However, it should be very low to benefit from the special features of drug nanoparticles, increased dissolution velocity but—even more important—increased saturation solubility. The effect of an increase in saturation solubility is only pronounced below a particle size of approximately 1–2 µm; therefore, the content of drug microparticles should be minimized to fully benefit from the nanosuspension properties.

B. Special Features of DissoCubes

Two general features of drug nanoparticles should be highlighted:

(a) The increase in dissolution velocity and

(b) The general adhesiveness of nanoparticles.

The increase in dissolution velocity is due to an increase in surface area going beyond that of micronized products. Fine powders/particles possess an increased adhesiveness very well known from powder technology. These features improve bioavailability. Much in vivo data generated with drug nanoparticles by NanoSystems confirm this. However, there are two more interesting features of drug nanoparticles (i.e.,DissoCubes): (a) an increase in saturation solubility and (b) structural changes inside the particles. The latter depends very much on the means of production.

C. Release Properties of DissoCubes

A general problem with poorly soluble drugs is their low saturation solubility and related slow dissolution velocity. To achieve sufficiently high bioavailability,fast dissolution and an increase in saturation solubility are beneficial. Therefore,DissoCubes having a controlled release often is not the major point when applying a poorly soluble drug

orally. Achieving a sufficiently high blood level is enough. That means the highest priority must be to create fast-dissolving drug nanoparticles with improved drug solubility. Prolonged release will occur anyway because, despite producing drug nanoparticles, the dissolution process is still much lower than with a highly soluble drug. Fast disolution and increased saturation solubility are special features of DissoCubes as discussed above.

IV. Research and Development of Dissocubes Formulations

A. Feasibility Studies

Many different drugs have been processed by high-pressure homogenization to produce DissoCubes. Up to now each drug investigated could be converted into a nanosuspension. Examples include carbamazepin, bupravaquone, cyclosporine,paclitaxel ,azodicarbonamide, and prednisolone.Amphotericin B as a poorly soluble drug is also of high interest for oral administration. Amphotericin B was dispersed in an aqueous solution containing Tween 80 (0.25% w/w), Pluronic F68 (0.25%w/w), and cholic acid sodium salt (0.04%w/w). This presuspension was homogenized at 1500 bar for up to 15 cycles. To determine the content of micrometer particles, the nanosuspension was also analyzed by laser diffractometry using a Coulter LS 230. The laser diffractometer gives a volume distribution, which means the distribution is extremely sensitive to a few very large particles. The diameters of 95% and 99% are suitable parameters for assessing minimization of the microparticulate content.

B. Fabrication Technique for DissoCubes

The DissoCubes are produced by high-pressure homogenization, which means the product is an aqueous suspension. However, such an aqueous suspension is in some cases only the desired final formulation for the market. More convenient formulation forms for the patient are tablets, capsules, or coated tablets. A major advantage of DissoCubes technology is that it can be combined as a novel technology with traditional dosage forms. The nanosuspension itself can be used as granulation fluid for producing granules and, if desired, compressing it into tablet.

C. Scale-up Production of DissoCubes

High-pressure homogenization is a broadly used technique in different areas. Especially in the food area, large capacities of production are required, and highcapacity homogenizers are available. In the pharmaceutical industry, emulsions for parenteral nutrition are produced by high-pressure homogenization (e.g., Lipofundin, Intralipid). Typical batch sizes for these products are a few thousand kilograms. DissoCubes technology requires a minimum of approximately five homogenization cycles to be run. The basic arrangement for large-scale production is to pass the batch several times through the same homogenizer in a feedback loop, which means the batch will go from product container 1 through the homogenizer to product container 2 and back and back and so on (below diagram). To minimize production time it is recommended to place two homogenizers in series such that one passage.

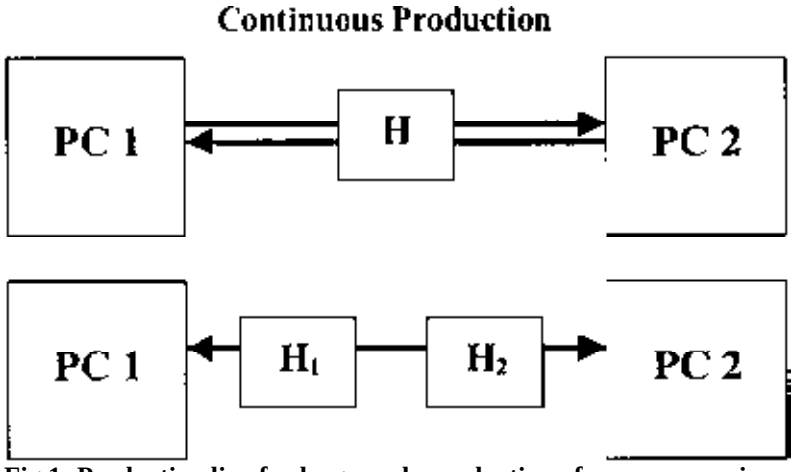

Fig 1: Production line for large-scale production of nano suspensions

In fig 1 Production line for large-scale production of nano suspensions being composed of product container PC (PC 1 and PC 2), and one (upper) or two homogenizers H (lower) for continuous production. In the lower setup one passage is equivalent to two homogenization cycles. This is possible because the equipment is off-the-shelf and therefore low-cost. Figure 1 (lower diagram) shows the diagram for such a production unit being composed of two product containers and two homogenizers. Even when assuming 10 homogenization cycles, a batch size of 1 ton (1000 kg) can be processed within approximately 4 h.

D. In Vitro Cell Culture Studies with DissoCubes

DissoCubes have been widely introduced in different in vitro cell assays including RAW macrophage cell line and peritoneal macrophages for cytotoxicity testing and macrophages in infection models like leishmaniasis and tuberculosis.Among the drugs processed to DissoCubes and introduced in test assays,there were clinically used drugs, as mentioned earlier, as well as others of preclinical interest, such as a series of natural products (aurones, aphidicolin).Using DissoCubes will be an interesting drug delivery system for infectious diseases such as leishmaniasis or tuberculosis, where macrophages as host cells are involved.

E. In Vivo Studies with DissoCubes

Extensive in vivo studies have been performed with NanoCrystals produced by pearl milling. These in vivo data are generally valid for all drug nanoparticles independent of the manner of production and are in general very impressive. Drug nanoparticles (both human and animal data) (a) improve bioavailability, (b) improve dose proportionality, (c) reduce fed/fasted variability, (d) reduce intersubject variability, and (e) enhance the absorption rate.

V. Regulatory Issues

From the regulatory point of view, the introduction of a new product has two aspects: the regulatory issues concerning the production line itself and finally the product. The production lines used for producing DissoCubes Nanosuspensions are already in use for the production of emulsions for parenteral nutrition. They are accepted by the regulatory authorities and therefore a priori no major difficulties should occur. The production lines available are made of materials suitable for pharmaceutical production. The unit itself is able to be qualified and validated.In addition, the product itself needs to fulfill the regulatory criteria, for example contamination from the production unit. Nanosuspensions were produced applying the hardest production conditions, 1500 bar and 20 homogenization cycles. The dominant material in the steel is iron; therefore, the suspensions were analyzed regarding their iron content using atomic absorption spectroscopy (AAS). The iron content was below 1 ppm, in the acceptable range. In addition, the homogenizers are handy for industrial purposes. They can be cleaned in place and sterilized in place by streaming steam.

VI. Technology Position and Competitive Advantages

The hydrosol technology developed by Sucker and the NanoMorph system marketed by Knoll/BASF Pharma are both precipitation techniques. They require that the drug is soluble in at least one solvent and simultaneously that this solvent is miscible with a nonsolvent. This restricts a priori the general applicability of these techniques. In addition, many of the newly developed drugs are simultaneously insoluble in aqueous and organic media.A much easier approach is producing nanoparticles by a deaggregation technique, which means a milling process. Competing technologies for Disso-Cubes are NanoCrystals by NanoSystems.

VII. Future Directions and Perspectives

To sum up, the production of drug nanoparticles is a universal technology to overcome the problems encountered with poorly soluble drugs, especially drugs that are simultaneously poorly soluble in aqueous and organic media. In contrast to other specialized approaches such as solubilization, complexation, and inclusion, the technique of forming drug nanoparticles can be applied universally to any drug. Industrial, regulatory, and commercial market issues need to be considered. Comparing DissoCubes technology to precipitation techniques it has clearly distinct advantages. Comparing DissoCubes technology to other milling processes, it has benefits regarding potential product contamination and especially regarding the feasibility to be introduced as an industrial largescale production process. An essential prerequisite for the market is the exclusiveness of the product.

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