Long-Acting Injectable Nanoparticle Technologies

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This paper outlines the development of nanoparticles as a drug delivery platform for long-acting injectable drugs. This broad category of small particles comprises subsets, defined by their formulation technique. Several will be considered here, including nanoprecipitation, homogenization, nanomilling, emulsion freeze/spray drying, as well as biodegradable polymeric microparticles. The evolution of the technology will be described which explains how this modality became available for consideration. Alternative technologies and decision rules about when to use which will be explained. The most promising candidate technologies are those that are used commercially, and those products will be summarized. The advantages and disadvantages of long-acting injectables will be noted. Additionally, the recommended approach for forming long acting injectables has also been extensively validated in commercialized oral dosage forms, conferring a variety of advantages, such as increased bioavailability, reduced fed-fasted difference, higher peak blood concentration, etc.

Exponential advances in understanding the mechanism of molecular physiology were made in the last half of the twentieth century. Analytical chemistry and X-ray crystallography were developed to analyze protein structure. This includes the geometry of the protein receptor, which binds small signaling molecules, either natural ligands or drugs. Receptor binding in turn changes the shape of the protein which then accomplishes the next step in a desired molecular process, eventually accomplishing a desired end goal.

Pharmaceutical companies made use of this understanding to expedite drug development. During the 1990's High Throughput Screening technology was developed to identify molecules which were strongly bound to the protein receptor pocket, thus achieving targeting while reducing the amount of drug required to exert the effect. Less drug means less toxicity, all else being equal. As a result of this sea change in drug development, very targeted drug candidates were developed which turned out to be highly insoluble, reflecting the chemical nature of the hydrophobic protein receptor pocket. Candidates emerging from these screens have high molecular weight and hydrophobicity, factors contributing to insolubility.

Insolubility poses a problem for a drug because it needs to dissolve in an aqueous medium if a tablet, for example, to become bioavailable. As a result of the large number of insoluble drug candidates which suddenly appeared, new drug delivery technologies were accordingly developed to handle the problem. Table 1 summarizes advantages and disadvantages of several drug delivery technologies developed to address this issue[1].

[1] Z Loh, A Samanta , P Heng. Review Overview of milling techniques for improving the solubility of poorly water-soluble drugs Asian J Pharm Sci 1 0: 255-274 (2015).
https://www.sciencedirect.com/science/article/pii/S1818087615000100

Table 1 – Key advantages and disadvantages of common strategies employed to improve drug dissolution and bioavailability.

Technique	Advantages	Disadvantages
Use of co-solvents	• Simple technique • Lower costs involved • Applicable for a wide range of drugs	• Toxicity of solvents • Risk of drug precipitation *in-vivo* • Limited to liquid formulations
Complexation using cyclodextrins	• Improves the chemical stability of the drug • May potentially enhance drug absorption by modification of lipid barrier	• Successful complexation depends on both chemical and geometrical properties of drug molecule • Large amounts of cyclodextrins may be required due to low complexation efficiencies • Higher costs involved
Solid dispersions	• Creates fine drug particles without excessive application of energy • Fine particles are readily wetted with minimal risk of agglomeration • Wide range of hydrophilic polymers are available as drug carriers	• Preparation method is difficult to scale up • Amorphous drug forms created are physically unstable and may convert to crystalline forms during storage, accelerated by moisture absorption by the hydrophilic carrier
Chemical modification (e.g. prodrugs)	• Prodrugs may enable drug targeting and improve drug stability	• Toxicity potential of prodrugs • Fate of prodrugs is difficult to predict *in-vivo* due to biological variations in the way they are handled in the body
Lipid formulations	• Exploits the innate lipid digestion mechanisms of the body to enhance drug bioavailability • Emulsifiable lipid formulations further enhance lipid digestion and drug bioavailability • Diversity of lipid excipients allow formulation flexibilities • Lower risks of drug precipitation *in-vivo*	• Amount of lipids typically present in the formulation may be insufficient to trigger an appropriate physiological response to enhance drug bioavailability • Quality control of lipid-based formulations is challenging due to the complex and diverse physicochemical properties of lipids and the lack of standardized testing methods

In view of the multitude of approaches, it is advantageous to have a decision tree to select among them and guide formulation development, Fig. 1[2].

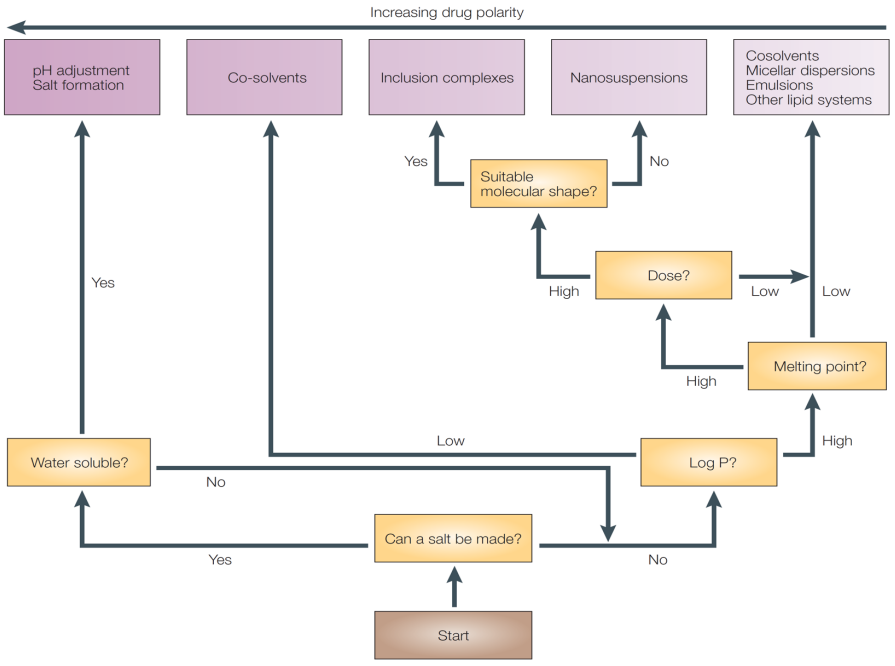


Figure 1 | **Decision tree for selection of formulation approach.** The easiest applicable approaches are utilized. If a salt can be made, or solubility increased by simple pH adjustment, these are done preferentially. If the drug is not particularly insoluble, co-solvents are tried next. If there is adequate solubility in lipidic systems, then micelles, emulsions and so on are tried. Inclusion complexes, as with cyclodextrins, can be considered. For the most intractable compounds — those with high Log P, high melting point and high dose — nanosuspensions are used.

LOG P
Log of the octanol–water partition coefficient, which is a measure of a drug's lipophilicity. Defined as the ratio of un-ionized drug distributed between the octanol and water phases at equilibrium. Higher values imply greater lipophilicity.

WATER INSOLUBLE
Less than 0.1 mg per ml solubility in water.

CYCLODEXTRINS
5–8mer of cyclic linked amylose or glucan molecules that forms a hydrophobic interior to accommodate an insoluble compound, and a hydrophilic exterior to solubilize in water.

BIOAVAILABILITY
A measure of the rate and extent of drug absorption from an administered dose, expressed as a ratio to an intravenously administered dose.

[2] B.E. Rabinow, "Nanosuspensions in Drug Delivery". Nature Reviews Drug Discovery 3:785-796 (2004).

Nanosuspensions can be used for compounds that are insoluble in water but are soluble in oil (high log P), although other lipidic system such as liposomes and emulsions can be used to formulate these compounds as well. Nanosuspensions are the preferred solution, however, when no other approach will work. In contrast to lipidic systems, nanosuspensions can be used to successfully formulate compounds that are insoluble in both water and oils. This occurs when the crystal energy is high, indicated by a high melting point, which reduces the tendency to dissolve regardless of the solvent. Nanosuspensions overcome delivery issues for these compounds by avoiding dissolving them, and by maintaining the drug in the preferred crystalline state as particles, albeit sufficiently small for pharmaceutical acceptability.

In addition, utilization of the dense, solid state confers an additional advantage of higher weight per volume loading. This is crucial when high dosing is required. Such cases often fail with approaches involving molecular complexation (e.g. cyclodextrins) because of the high molar ratio of complexing excipient that must be used. A related benefit of high loading is reduced administration volume, crucial for low volume intramuscular and subcutaneous applications.

Conventional approaches often attempt to solubilize insoluble drugs with the use of excessive amounts of co-solvents, which pose toxicity concerns. Formulation via nanosuspensions dispenses with solvents. As a result of this advantage, drug candidates once abandoned could now be rescued.

The above needs have driven development of nanosuspension technology, which has subsequently revealed secondary benefits that are now beginning to be realized, Table 2. For example, the particulate nature of the dosage form may offer alternative pharmacokinetic profiles in IV delivery that can offer less toxic, more efficacious regimens. By decreasing the particle size of the solid form of the drug, the surface area for the same weight of drug is increased. Inasmuch as dissolution rate increases linearly with surface area, a number of issues related to poor oral bioavailability are addressed. The solid state of the drug offers solutions to chemical stability issues, and the small size confers increased physical stability with respect to sedimentation.

Table 2. Benefits of Nanosuspensions

Physicochemical characteristic	Potential benefits
Increased drug amount in dosage form without harsh vehicles (extreme pH, co-solvents)	Intravenous: reduced toxicity, increased efficacy
Reduced particle size: increased drug dissolution rate	Oral: increased rate and extent of absorption, increased bioavailability of drug: area under plasma versus time curve, onset time, peak drug level, reduced variability, reduced fed/fasted effects. Pulmonary: increased delivery to deep lung
Solid state: increased drug loading	Reduced administration volumes; essential for intramuscular, subcutaneous, ophthalmic use
Solid state: increased stability	Increased resistance to hydrolysis and oxidation, increased physical stability to settling
Particulate dosage form	Intravenous: potential for intravenous sustained release via monocyte phagocytic system targeting, reduced toxicity, increased efficacy. Oral: potential for reduced first-pass hepatic metabolism

To maintain their beneficial properties, it is important for the particle size of the nanosuspension to remain stable. There is, however, an inherent tendency toward increasing growth of the particle. If the particles approach each other too closely, they will agglomerate. This must be prevented, in order to have a stable system. Energetically, this requires placement of a sufficiently high energy barrier at

relatively long separation distances, to prevent the particles from coming too close. Therefore, a nonionic polymeric surfactant is also used that coats the surface with a hydrophobic chain and permits a hydrophilic tail to project into the water. Compression of the polymeric coating, as by approach of a similarly coated particle provides the necessary repulsive barrier between two neighboring particles. The polymeric coating performs a dual role by inhibiting crystal growth, thus reducing particle size."[2]

"Early approaches to the formation of nanosuspensions involved nanoprecipitation and nanoprecipitation combined with homogenization.

Precipitation involves first preparing a solution of the drug in a liquid solvent in which it is soluble. For poorly water-soluble drugs, this means identifying an organic solvent which can solubilize the drug. The drug is present in the solvent at the molecular level and the resulting solution is optically clear. Next, a solvent in which the drug is insoluble, i.e. an anti-solvent like water, is introduced to the solution of the drug in the organic solvent. This causes the drug to come out of solution or precipitate to form fine particles.

Precipitation conditions are chosen so as to minimize particle size. The conditions involve temperature, rate of addition of the one liquid to the other, and the rate of mixing. While attempts have been made to theoretically predict ideal conditions, this is still largely an art, because there are two competing processes that must be considered: the initial creation of crystal nuclei, and their subsequent growth. Formation of a stable suspension with the smallest particle size requires a high nucleation rate (speed at which nuclei form) but low growth rate. Both process rates are dependent on temperature, as well as on supersaturation (condition where the drug concentration exceeds its solubility limit.).High-supersaturation conditions are chosen for rapid nucleation by metering small amounts of a water-miscible organic solution of the drug to the non-solvent water, under rapid mixing. This rapid dilution of solvent results in high-supersaturation conditions, which causes spontaneous nucleation and a subsequent reduction of the supersaturation condition in the immediate vicinity of the nucleating crystals; this reduces growth rates.

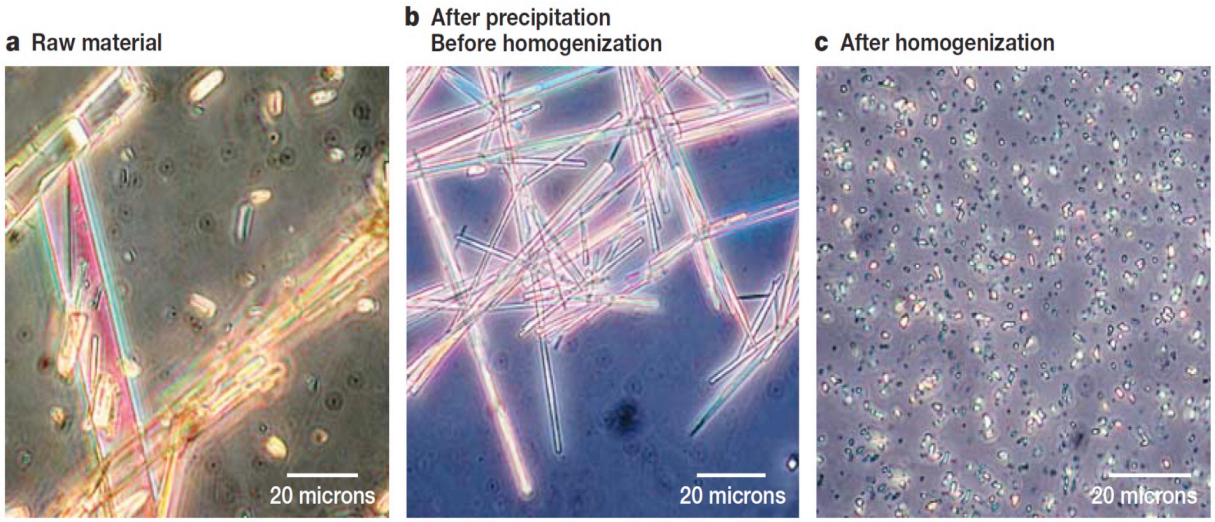
Rapid crystallization favors the formation of less stable crystal forms of the drug, which can subsequently convert to more stable forms. This instability poses an obstacle unless secondary processing is utilized to modify the crystal form (see below). The rapid-nucleating conditions have two additional consequences, which can be exploited to further reduce particle size. First, at high-supersaturation levels, the crystal habit, or external appearance (as opposed to the internal, periodic crystal lattice structure), is changed to a needle-like or dendritic morphology. These crystals are easily broken, forming additional nuclei, which catalyses the nucleation process at the expense of growth. Second, in comparison with crystals grown more slowly, rapidly grown crystals tend to be more imperfect, and often incorporate impurities and dislocations. This occurs because of the insufficient time afforded for accurate incorporation of solute in to the growing crystal lattice. This effect is more pronounced for flexible molecules that can assume many different configurations. Both the dendritic morphology, as well as the crystal defects, can be utilized in subsequent processing by homogenization to reduce particle size further.

Homogenization. Homogenization involves the forcing of a suspension under pressure through a valve that has a narrow aperture. Bernoulli's law requires that the high velocity of the suspension that results from flow past the constriction is compensated by a reduction in static pressure. (this is the principle by which planes are kept from falling out of the sky). This, in turn, causes bubbles of water vapour to form in the liquid subject to these reduced pressure conditions. The bubbles collapse as they

exit the valve. These cause cavitation-induced shock waves, which crack the particles. Crystals are susceptible to such breakage to varying degrees. Pure crystals have a theoretical tensile strength that is 100–1,000 times stronger than what is observed in practice. However, the inevitable crystal defects — dislocations and impurities — weaken mechanical behaviour by migrating and accumulating at crystal-grain boundaries, which furnishes a nidus of weakness.

Homogenization is advantageously utilized to exploit three consequences of rapid precipitation to either further reduce particle size or to resolve other potential difficulties. First, the crystal defects induced by rapid precipitation render the crystal more susceptible to rupture by the subsequent mechanical shock of homogenization. Second, fracture mechanics predict that the dendritic morphology itself is more susceptible to breakage because of the narrow dimension induced, which must bear the full applied force (FIG. 2). Third, the mechanical energy supplied by the homogenizer enables initially formed, unstable amorphous particles that result from rapid precipitation to undergo subsequent crystallization to a stable state.

Figure 2. Engineering breakable crystals with a combination of microprecipitation and homogenization.



Crystal morphology of raw drug material is modified to facilitate breakage into smaller nanoparticles. a. Crystals of starting raw material are too large and hard to run efficiently through a homogenizer. b. the raw material is solubilized, filter sterilized and precipitated, so as to yield crystals of needle-like morphology, which are easily broken during homogenization. c. Homogenization yields nanoparticles suitable for parenteral injections."[2]

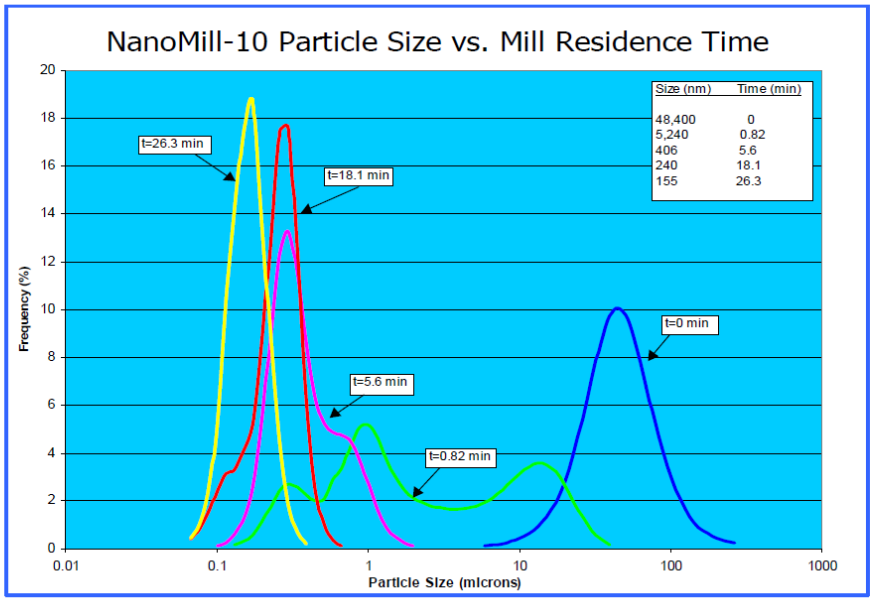
Wet milling

"The major manufacturing technique for commercially preparing nanosuspensions is wet milling, in which the active agent, in the presence of surface stabilizer(s), is broken down in size by milling media. Media milling can be considered a modernized version of the earlier ball mill, which used larger spheres in a dry state. The liquid medium prevents adhesion and subsequent compaction of the milled drug particles on the wall of the vessel and/or the surfaces of the milling balls, which is a common occurrence when the drug is milled in its dry state. This improves the yield of nanoparticles. The liquid may also serve additional purposes such as lubrication and coating of the newly-formed particle surfaces through various physicochemical interactions like electrostatic and hydrophobic interactions. Particle size here is

determined by stress intensity and the number of contact points. The stress intensity is a function of the kinetic energy of the grinding beads, while the number of contact points may be increased by utilizing smaller grinding media. Mechanical attrition and impaction of the suspended drug particles are brought about by milling media, constructed out of a variety of materials such as ceramics or highly cross-linked polystyrene resins.

A drive shaft, attached to rotating disks, provides the energy to a charge of milling beads to break the drug crystals by a compression-shear action."[1] Fig. 3 depicts how the particle size distribution profile of the drug suspension changes with increased residence in the machine.

Fig. 3. Particle Size Distribution Shifts to Smaller Size with Increased Milling Time



"Unlike ball milling where the whole vessel rotates or oscillate/vibrates whilst in operation, the vessel remains stationary in media milling. Movement of the balls is initiated by a stirring or agitating device, often represented by several discs mounted on a central shaft rotating at high velocities, 20 000 rpm and above, within the vessel. For this reason, media milling is sometimes known as "stirred-ball milling". Media milling is a continuous process wherein the drug suspension is pumped through the milling chamber to effect size reduction of the suspended material. Prior to their exit from the milling chamber, the milled particles pass through a screen that serves to separate the suspended, milled particles from the milling media"[1], Fig. 4. Various sizes of mill, from 10ml for lab scale to 60L for production scale are available. This provides process scale up as needs for material increases, from requirements for GLP animal studies, GMP Clinical supplies, 1/10th scale GMP batches for regulatory submission, to full scale production, Fig.5.

Through experience, the materials of construction of the milling media has evolved to "provide resistance to erosion, utilizing polymers and ceramics, used in the construct of the milling media as well as other key equipment components (e.g. inner walls of milling chamber and stirring device) in contact with the milled product. Optimization of key process parameters like stirring speed and in particular,

milling time, also contributes to reducing the likelihood of erosion. This is because milling durations of up to several days are not uncommon in media milling and such long milling durations are likely to promote erosion of the milling media"[1]. Commercially, media milling is exemplified by the Nano-Crystal® technology from Elan Pharmaceutical Technologies, since acquired by Alkermes. To date, NanoCrystal®-based products have been approved by worldwide regulatory agencies including the US, Canada, EU and Japan.

Fig. 4. NanoCrystal® NanoMill Process

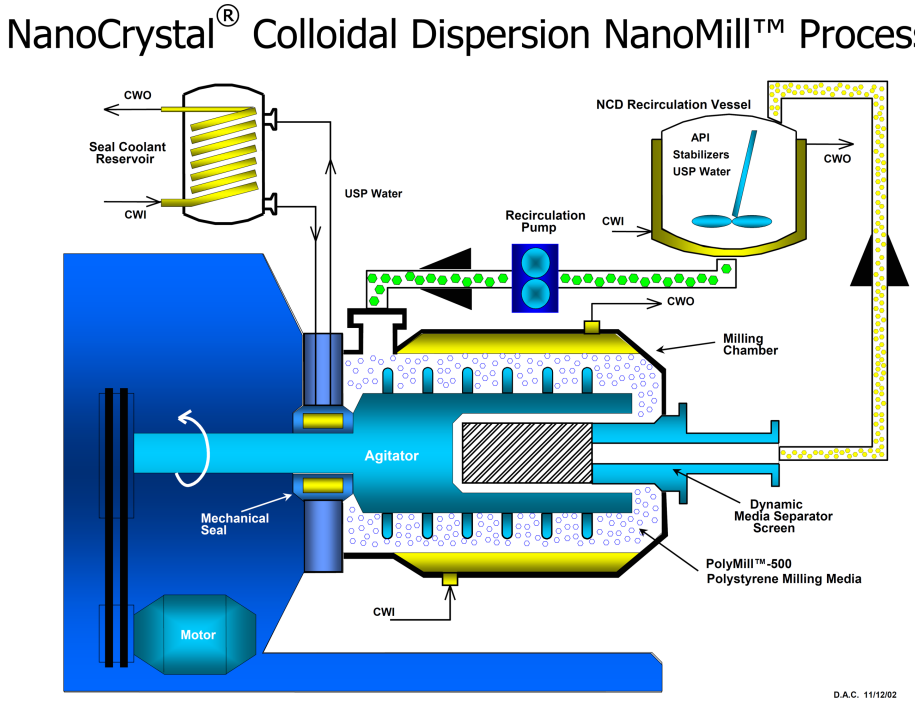
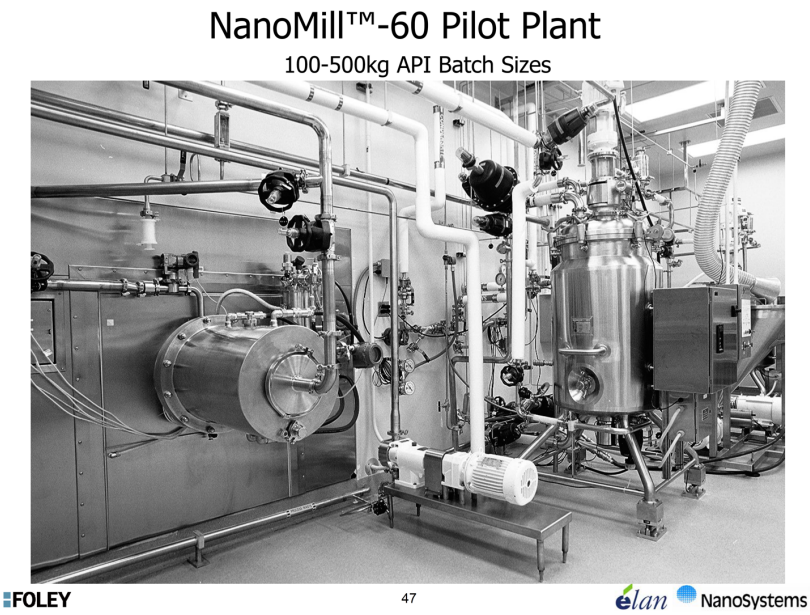


Fig. 5 Production Scale NanoMill Pilot Plant

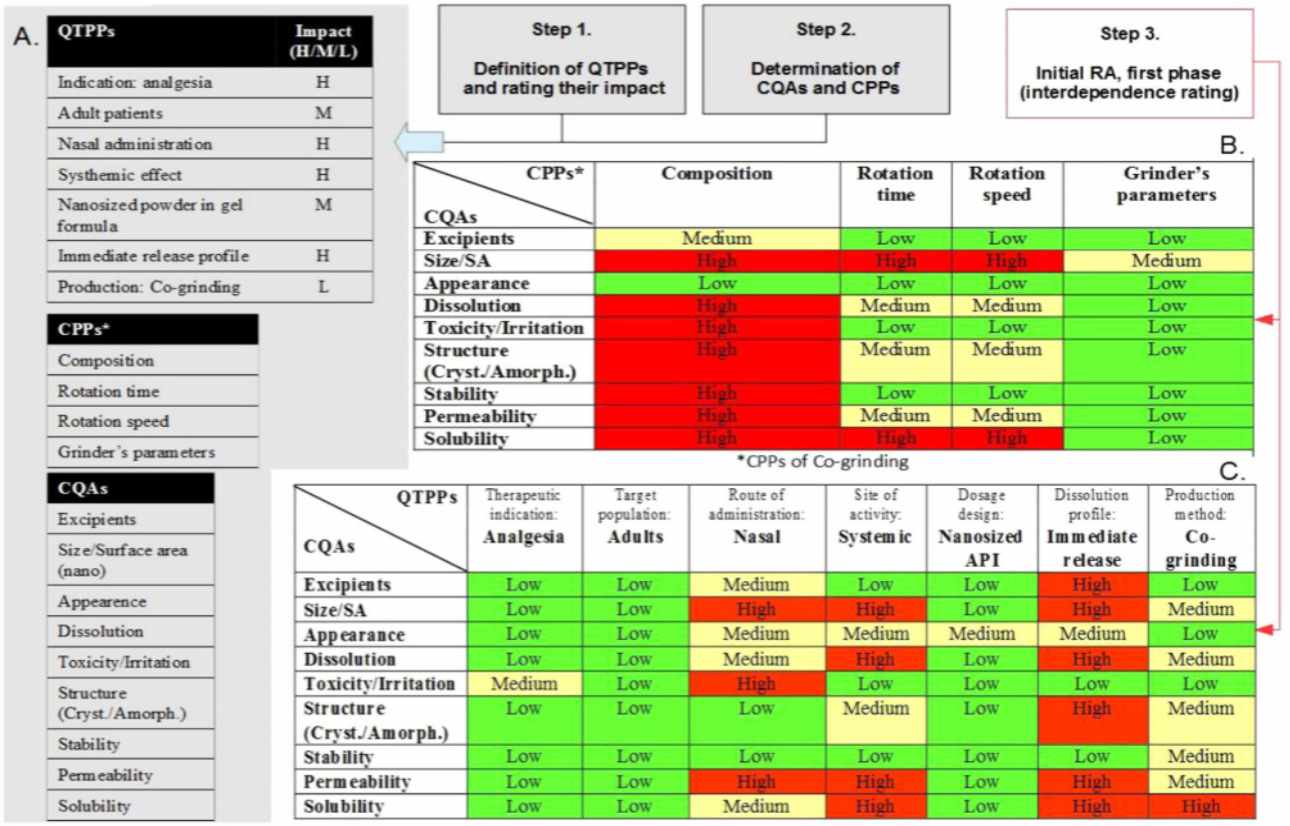


Sterility is assured by reducing particle size to 200nm, below the sterilizing filter pore size of 0.22µm (220nm). This enables the nanosuspension to be sterile filtered, while rejecting microbes which are larger than the pore size.

The current regulatory environment of US, EU, Japan requires development by Quality by Design (QbD) principles. This is a stepped, systematic way of analyzing the entire production process, identifying the quality attributes that are critical (CQA) to performance of the drug to meet its quality target product profile (QTPP), and process parameters that are critical (CPP) to assure these attributes. A design space can then be defined wherein manufacturing variance can be tolerated to still meet the CQA. This work becomes more complex to the extent there are many process parameters that must be optimized, investigating as well the interactions among parameters[3], Fig 6.

[3] E. Pallagi, et al. Adaptation of the quality by design concept in early pharmaceutical development of an intranasal nanosized formulation. Int. J. Pharm. 491:384-392 (2015).
https://www.sciencedirect.com/science/article/pii/S0378517315005384?via%3Dihub

Fig. 6. Selected QTPPs, CQAs and CPPs and their interdependence rating in the QbD process



A.

QTPPs	Impact (H/M/L)
Indication: analgesia	H
Adult patients	M
Nasal administration	H
Systhemic effect	H
Nanosized powder in gel formula	M
Immediate release profile	H
Production: Co-grinding	L

CPPs*
Composition
Rotation time
Rotation speed
Grinder's parameters

CQAs
Excipients
Size/Surface area (nano)
Appearence
Dissolution
Toxicity/Irritation
Structure (Cryst./Amorph.)
Stability
Permeability
Solubility

Step 1. Definition of QTPPs and rating their impact

Step 2. Determination of CQAs and CPPs

Step 3. Initial RA, first phase (interdependence rating)

B.

CQAs \ CPPs*	Composition	Rotation time	Rotation speed	Grinder's parameters
Excipients	Medium	Low	Low	Low
Size/SA	High	High	High	Medium
Appearance	Low	Low	Low	Low
Dissolution	High	Medium	Medium	Low
Toxicity/Irritation	High	Low	Low	Low
Structure (Cryst./Amorph.)	High	Medium	Medium	Low
Stability	High	Low	Low	Low
Permeability	High	Medium	Medium	Low
Solubility	High	High	High	Low

*CPPs of Co-grinding

C.

CQAs \ QTPPs	Therapeutic indication: Analgesia	Target population: Adults	Route of administration: Nasal	Site of activity: Systemic	Dosage design: Nanosized API	Dissolution profile: Immediate release	Production method: Co-grinding
Excipients	Low	Low	Medium	Low	Low	High	Low
Size/SA	Low	Low	High	High	Low	High	Medium
Appearance	Low	Low	Medium	Medium	Medium	Medium	Low
Dissolution	Low	Low	Medium	High	Low	High	Medium
Toxicity/Irritation	Medium	Low	High	Low	Low	Low	Low
Structure (Cryst./Amorph.)	Low	Low	Low	Medium	Low	High	Medium
Stability	Low	Low	Low	Low	Low	Low	Medium
Permeability	Low	Low	High	High	Low	High	Medium
Solubility	Low	Low	Medium	High	Low	High	High

The true measure of success of a technology is its commercial deployment. There are many engineering scale-up challenges, and quality issues that don't appear until a history of production units in the millions is evaluated. From this perspective, wet milling has enjoyed unqualified success as a once monthly IM injection for the drug Invega Sustenna (Paliperidone palmitate) in the anti-psychotic maintenance space. This replaced conventional patient-administered oral therapy. A key issue for oral antipsychotics up to that time is that as many as 75% of schizophrenia patients don't adhere to a routine medication regimen, as shown in a Johnson & Johnson study[4]. This led to massive over-use of hospital emergency rooms, by non-compliant patients. To address this problem, the concept of clinician-administered long-acting medication was introduced to ensure reliable administration.

Risperdal Consta® was the first long-acting, atypical antipsychotic approved by the FDA (2003) for the treatment of schizophrenia. This was a reformulation of the earlier oral extended release Risperdal (risperidone) using the Oros platform invented by Alza, subsequently acquired by J&J. Risperdal Consta utilized the same API (active pharmaceutical ingredient) formulated in the Alkermes Medisorb technology platform, providing once per 2 weeks IM delivery. Because this technology is commercially successful in the long-acting injectable space, it will be reviewed here.

[4] http://files.pharmtech.com/alfresco_images/pharma/2014/08/22/5f4fac3e-541b-4240-8795-aba6bd45610c/article-78137.pdf

The proprietary Medisorb technology encapsulates a medication of interest in injectable microspheres that slowly degrade in situ and release drug into circulation in a sustained fashion. The structural matrix of the microsphere is composed of a medical-grade biodegradable polymer called poly-(d,l-lactide-co-glycolide) (PLG) (Fig. 7), which has been used in surgical sutures, bone plates, and orthopedic implants for decades and in microsphere form as a long-acting drug delivery system since 1984. Degradation of the PLG polymer occurs by natural (i.e., noncatalyzed) hydrolysis of the ester linkages into lactic acid and glycolic acid, which are naturally occurring substances that are easily eliminated as carbon dioxide and water.

The microsphere beads are approximately 0.06mm in size (upper end of distribution, 0.1 mm), which is roughly equivalent to the diameter of a human hair. Release of drug occurs by diffusion and erosion (Fig. 7). During initial release, loosely bound and easily accessible drug molecules on or close to the surface are liberated as the microspheres hydrate immediately post-administration. Blood drug concentrations may rise transiently during this stage, which is an important consideration for medications that use this technology. The drug release profile then enters a ‘‘lag phase’’ as the polymer hydrolyzes into smaller fragments. Once the polymer molecular size declines to approximately 20 kDa (i.e. 20,000), diffusion release initiates, during which time drug molecules enter the circulation at a relatively constant rate from interstices of the microsphere fragments. It might be expected that the kinetics of diffusion release would change as the diameter of the microspheres decreases, owing to the increased ratio of surface area to volume. However, because the microspheres are soft and sticky when wet at body temperature and because hydrated microspheres tend to ‘‘fuse’’ together into amalgams, their initial diameter has only a minor effect on diffusion release, but may affect injectability and needle-gauge selection”[5].

Microspheres are produced by first dissolving risperidone and PLG in an organic solvent mixture and then mixing it with a water solution to form an emulsion. The solvent is drawn out, and the polymer microspheres containing the drug are then dried into a free-flowing powder. Before dispensing, the appropriate quantity of powder is mixed with a water-based solution to create the suspension.

Other pharmaceuticals utilizing the Medisorb technology include VIVITROL (Alkermes), an extended-release formulation of naltrexone that is used to treat alcohol and opioid dependence, and Sandostatin LAR (Novartis Pharmaceuticals, West Hanover, NJ), a long-acting release formulation of octreotide that is used to treat acromegaly, severe diarrhea associated with metastatic carcinoid tumors, and profuse watery diarrhea associated with vasoactive intestinal peptide secreting tumors. VIVITROL and Sandostatin LAR are administered by intramuscular gluteal injection every 4 weeks. Bydureon (Exenatide GLP-1 agonist) is a once weekly injectable for treatment of diabetes, marketed by Amylin.

[5]M. DeYoung, et al. Encapsulation of Exenatide in Poly-(D,L-Lactide-Co-Glycolide) Microspheres Produced an Investigational Long-Acting Once-Weekly Formulation for Type 2 Diabletes. Diabetes Technol. & Therapeu. 13:1145 (2011).

Fig. 7. The Basis of Medisorb Technology

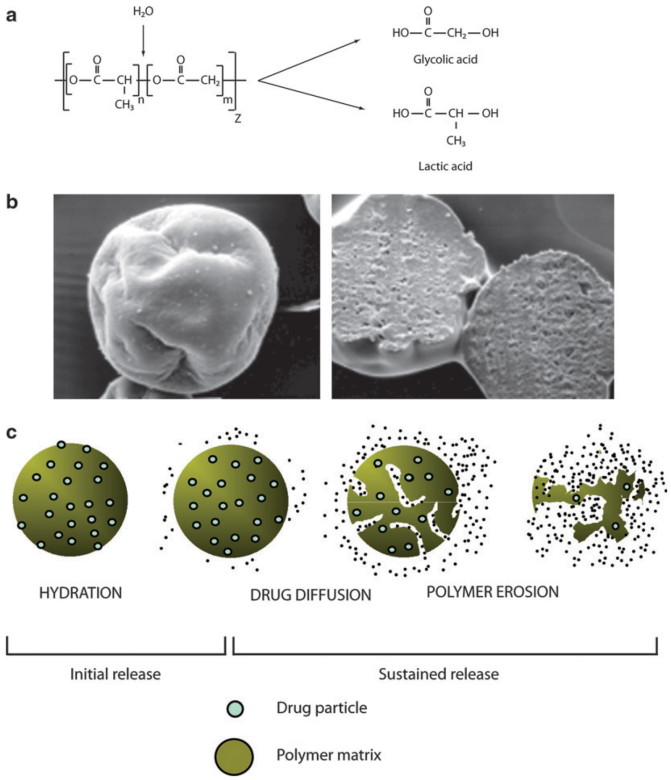


FIG. 1. Basics of poly-(D,L-lactide-co-glycolide) microspheres. (**a**) Spontaneous hydrolysis of poly-(D,L-lactide-co-glycolide) polymers. (**b**) Exenatide once-weekly microspheres exhibiting (**left**) a typical pinched raisin shape and (**right**) dense surface layer. (**c**) Mechanism of drug release from poly-(D,L-lactide-co-glycolide) microspheres.

The history of intertwining commercialization of NanoCrystals and Medisorb, the two technologies for delivery of long-acting anti-psychotics, is illustrative for both technical and business considerations, Table 3. Elan (NanoCrystal) and Alza (Oros, etc.) were the leading innovative drug delivery technology companies in the early 1990's. Alkermes tried to develop a long-acting protein and peptide delivery platform, called ProLease, also using PLGA microspheres. But their need for liquid nitrogen and cryogenics rendered their platform difficult to scale up. Accordingly, Alkermes started to build by acquisition. It acquired Medisorb to protect its protein delivery business, given the limitations of ProLease[6]. As described above, it also partnered with Janssen, J&J on Risperdal Contra, for long acting delivery of the poorly water soluble, small molecule risperidone. This business grew to become a large part of the income of Alkermes.

They feared that the next generation of the product, involving the risperidone metabolite, paliperidone palmitate, that would double the delivery time to 4 weeks, would endanger their franchise. They realized that Medisorb had limited drug loading capability because of the PLGA polymer which had to be accommodated in the limited IM injection volume. Elan's NanoCrystal technology had intrinsically high loading of insoluble molecules because the dosage forms consisted primarily of the pure API, packed as a solid crystal, which was the most efficient form possible, from a weight to volume perspective. As a result, they acquired Elan, to obtain NanoCrystal technology, and then partnered with Janssen to develop the next generation Invega Sustenna (Paliperidone palmitate) IM.

[6] https://www.thepharmaletter.com/article/alkermes-completes-medisorb-buy

Table 3. Alkermes Long-Acting Injectable Platforms

Drug	Drug Delivery Technology	Drug mfg	Drug Del Mfr	Year
Nutropin Depot	ProLease PLGA microspheres, cryogenic	Genentech	Alkermes	1999
Alkermes acquires Medisorb PLGA				1996
Risperdal (Risperidone)	Alza Oros (extended release oral) acqd by J&J	Janssen	Janssen/ Alza	2003
Risperdal Consta IM	Medisorb once per 2 wk	Janssen	Alkermes	2003
Invega Sustenna (Paliperidone palmitate) IM	NanoCrystal* once monthly	Janssen	Alkermes	2009
Vivitrol (naltrexone) injectable	Medisorb once per 4 weeks	Alkermes	Alkermes	2006
Alkermes buys Elan				2013
Bydureon (Exenatide GLP-1 agonist)	Medisorb once weekly injectable	Amylin	Alkermes	2012

**Janssen's LA-cabotegravir/rilpivirine employs NanoCrystal formulation technology*

There are additional considerations for use of long-acting injectables, including[7]:

- Long Acting injectable agents offer pharmacokinetic advantages, but do not entirely solve adherence challenges
- Use of a long acting agent that cannot be removed after administration obligates a short-acting lead-in to establish safety and tolerability
- Prolonged pharmacologic tail makes discontinuation challenging, particularly if exposures/risk are ongoing – with concern for seroconversion with resistant viral quasispecies
- Injections may be differentially acceptable in diverse populations.

Ultimately, the choice of a drug delivery technology must fit well with the intended purpose of the drug to be formulated. Because of the inevitable development issues that arise that increase time and money, it is best to work with a platform that has been reduced to practice, i.e. commercialized with a good deal of success. (Demonstration of feasibility of a drug delivery technology in animal studies, or even in an early phase human study is inadequate to anticipate the many manufacturing issues that inevitably arise subsequently.)This will demonstrate the regulatory acceptability, manufacturability, sterility, and safety of the dosage form. Partner reliability in terms of financial strength for a sustained presence is essential. Breadth of applicability of the underlying technology is a nice to have for follow-on molecules. And of course strength of the underlying patent position to avoid legal issues is critical.

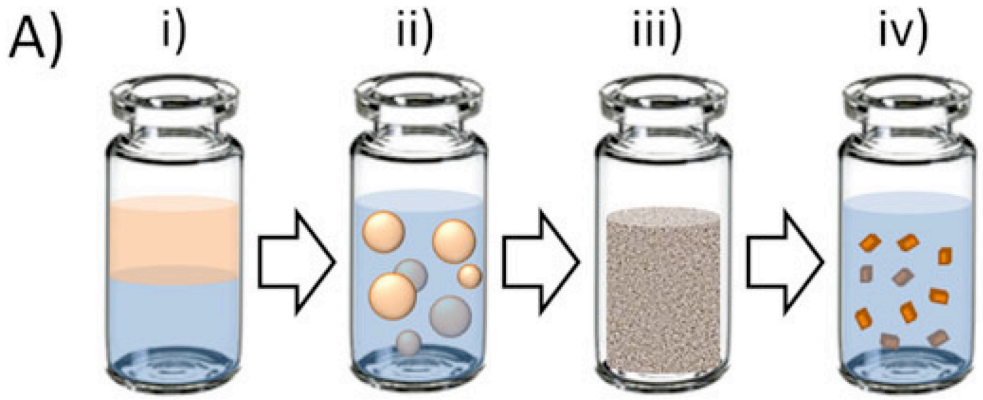
By comparison with the very few drug delivery technologies that have achieved commercial success, there are hundreds of approaches that are far less developed. An example is emulsion templated freeze-drying (ETFD), as elaborated by Andrew Owen[8], a manufacturing technique that has been applied to oral HIV drugs.

[7] R. Landovitz et al.The Promise and Pitfalls of Long Acting Injectable Agents for HIV Prevention *Curr Opin HIV AIDS*. 2016 January; 11(1): 122–128

[8] M. Giardiello et al. Accelerated oral nanomedicine discovery from miniaturized screening to clinical production exemplified by paediatric HIV nanotherapies. Nature Commun. 21Oct2016.

Initially, an oil-in-water (O/W) emulsion (like Italian dressing) is generated using a volatile organic solvent oil phase containing a dissolved drug, and a continuous aqueous phase containing a stabilizer or mixture of stabilizers (for example, water-soluble polymers or surfactants). The emulsion is frozen, resulting in the formation of frozen beads (2–3 mm diameter), micrometresized powders or large monolithic structures. Finally, both the water and the organic solvent are removed by freeze-drying, generating dry composite materials comprising the water-insoluble drug and water-soluble polymers/surfactants. The highly porous composites dissolve readily in water, releasing the drug as nanoparticulate dispersions, which resemble transparent molecular solutions (Fig. 8).

Figure 8. Emulsion Templated Freeze-Drying Process



Schematic illustration of solid drug nanoparticle formation techniques. (A) Emulsion-templated freeze drying involves the following: (i) the dissolution of poorly soluble drug compound into a water-immiscible solvent and the dissolution of water-soluble excipients into water; (ii) emulsification; (iii) freezing and freeze-drying to yield a dry, porous monolith; and (iv) redispersion into water.

The methods use mobile/liquid emulsions containing water-insoluble compounds dissolved within the oil phase. As the oil is slowly, controllably and selectively removed, the oil droplets shrink, and the solute concentrates and ultimately solidifies. The technique solidifies the entire emulsion by freezing to form static oil droplets. Whole-droplet motion is prevented during the simultaneous sublimation of both frozen water and solvent. In contrast to other techniques, the oil droplets are depleted of oil in the presence of a static surface structure or support. The mechanism of nanoparticle formation is complex; however, the processes operating during conventional freeze-drying of aqueous solutions are well understood. Initial freezing generates ice crystals of pure water, leading to dramatic concentration and viscosity increases within the remaining liquid. The resulting desiccation is highly efficient (99% water removal from the solute) and causes phase separation. Crystallization of the concentrated liquid regions is viscosity-inhibited (the medium is viscous like molasses which inhibits movement of the drug molecules to approach each other), and final solidification produces crystalline, amorphous or mixed solids. The technique involves the freezing/freeze-drying of emulsions with a corresponding concentration of the solute in the organic phase. The individual, isolated oil droplets have very small volumes and undergo significant local supercooling and concentration during freezing. Areas of saturated solute will develop that are subject to precipitation/crystallization during water/oil removal. Particles thus formed will be dispersed upon addition of water and dissolution of the solid porous polymer/surfactant support.

The formation of dry, redispersible solids containing nanoparticles offers significant advantages over liquid-dispersion storage and transport. As a result of using rapid freezing, emulsion stability is not critical and the choice of surfactants, hydrophilic polymers, solvents and organic active ingredients is therefore very broad, including biodegradable polymers and temperature-sensitive drugs."[9,10]

It must be emphasized that there are many functional differences between the ETFD platform and the milled crystalline nanoparticle platform. ETFD has been demonstrated for very few drugs capable of being formulated using the hydrophobic excipients available. Realize that excipients acceptable for oral dosage forms must pass a much higher bar of safety for use in injectables. Reasonably high loadings of 70% drug are reported for ETFD. This is fine for oral dosage forms, but for long-acting injectables where size of the administered volume must be minimized, higher loading is mandatory. Loadings > 90% are achievable using solid drug crystalline nanoparticles, formed by milling. These differences are summarized in Table 4.

Table 4. Comparison of Emulsion Templated Freeze-Dried Solid Drug Nanoparticles to Long-Acting Injectable Nanoparticles Formed by Milling

Evaluation Parameter	**LA milled Injectable NP**	**ETFD SDN**
Route of Administration	Injectable SC or IM (and oral)	Oral
Dosing Frequency	Once per 30-60d	qd
Proof of Formulation Concept	Many drugs	Few drugs
Commercial Validation	Yes	no
Address Long Term Drug Compliance?	Yes	?
Ratio of drug: total solids	90%	70%

[9] P. Curley, et al. In vitro characterization of solid drug nanoparticle compositions of efavirenz in a brain endothelium cell line. J. Interdisciplinary Nanomedicine. 2(3) (2017), doi: 10.1002/jin2.32, p. 157

[10] H. Zhang, et al. Formation and enhanced biocidal activity of water-dispersable organic nanoparticles. Nature Nanotechnology, September 2008 , p.506.