In depth: Nano-formulation processes for long-acting injectables (Slides courtesy of Barrett Rabinow)

- Historical development
  - insoluble drug candidates
  - modified pharmacokinetics
  - technical decision criteria for selection of techniques
- Manufacturing processes
  - surfactant stabilized crystalline drug core
    - homogenization
    - microprecipitation
    - wet milling
  - polymeric microspheres
  - emulsion templated freeze dried solid drug nanoparticles
- Quality by design considerations
- Commercialized products
- Risk-based decision criteria for selection of technique

Historical development of long-acting nanoparticle technologies

- During the 1990's High Throughput Screening technology was developed to identify drug molecule candidates which were strongly bound to a 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, is to become bioavailable.
- As a result of the large number of insoluble drug candidates which suddenly appeared, new drug delivery technologies such as nanosuspensions were developed to handle the problem.
- Besides resolving insolubility, nanosuspensions also offered prolonged duration of action

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

B.E. Rabinow, “Nanosuspensions in Drug Delivery”. Nature Reviews Drug Discovery 3:785-796 (2004).

Technical Decision Tree

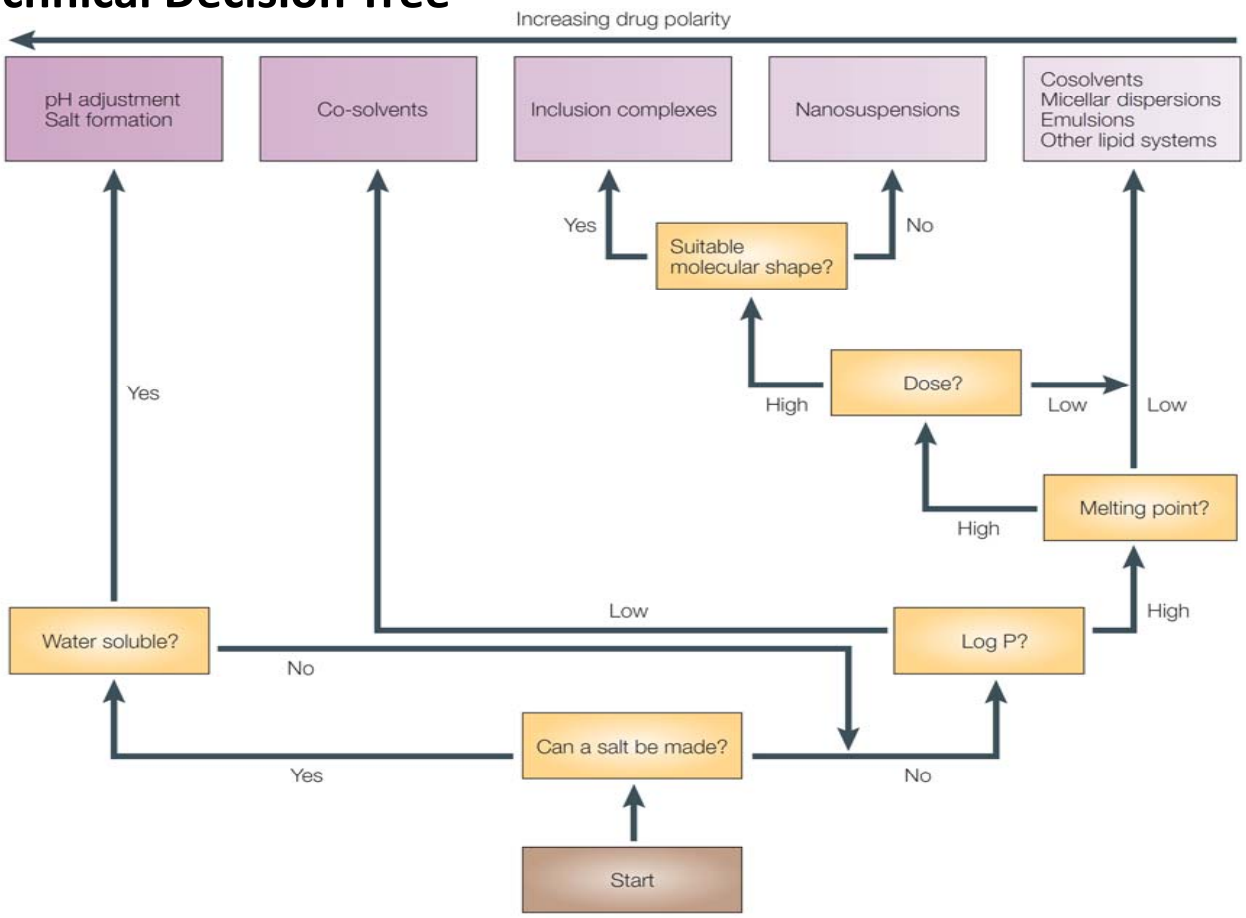


Figure 1 | **Decision tree for selection of formulation approach.** The easiest applicable approaches are utilized. If a salt can be made, or solubility increased by simple pH adjustment, these are done preferentially. If the drug is not particularly insoluble, co-solvents are tried next. If there is 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.

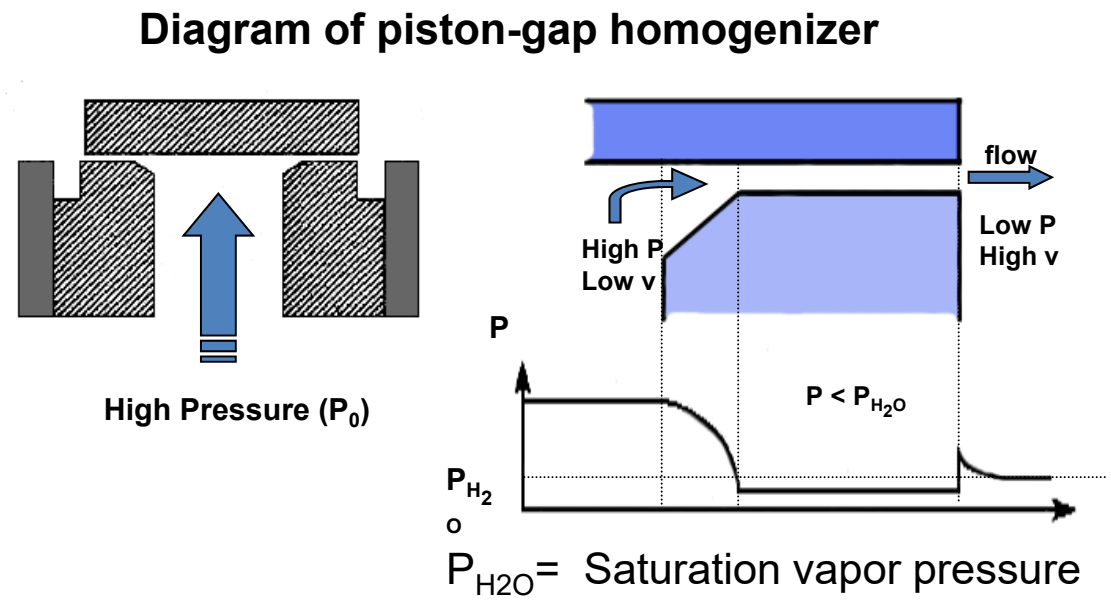
B.E. Rabinow, "Nanosuspensions in Drug Delivery". Nature Reviews Drug Discovery 3:785-796 (2004).

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

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

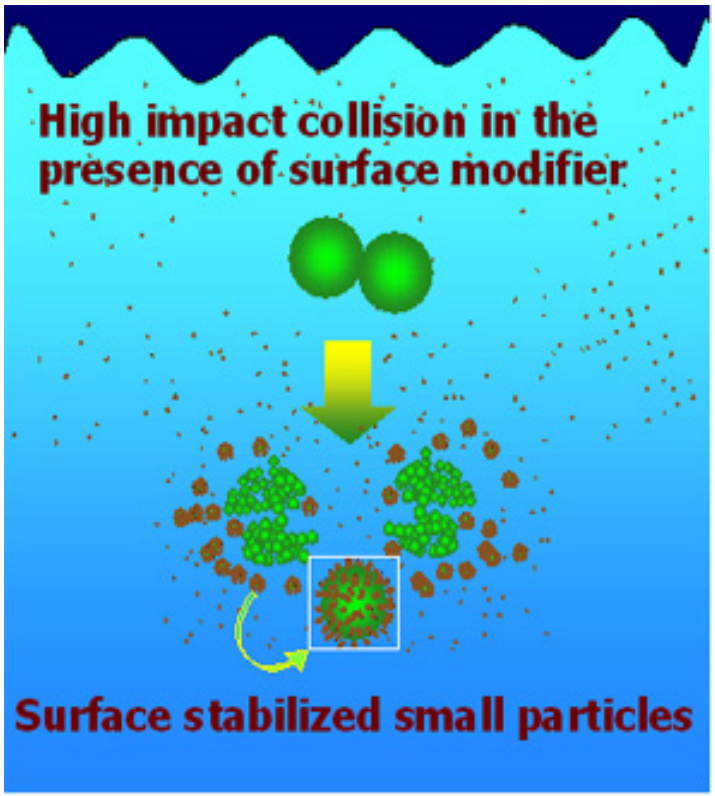
Homogenization process for forming nanosuspensions



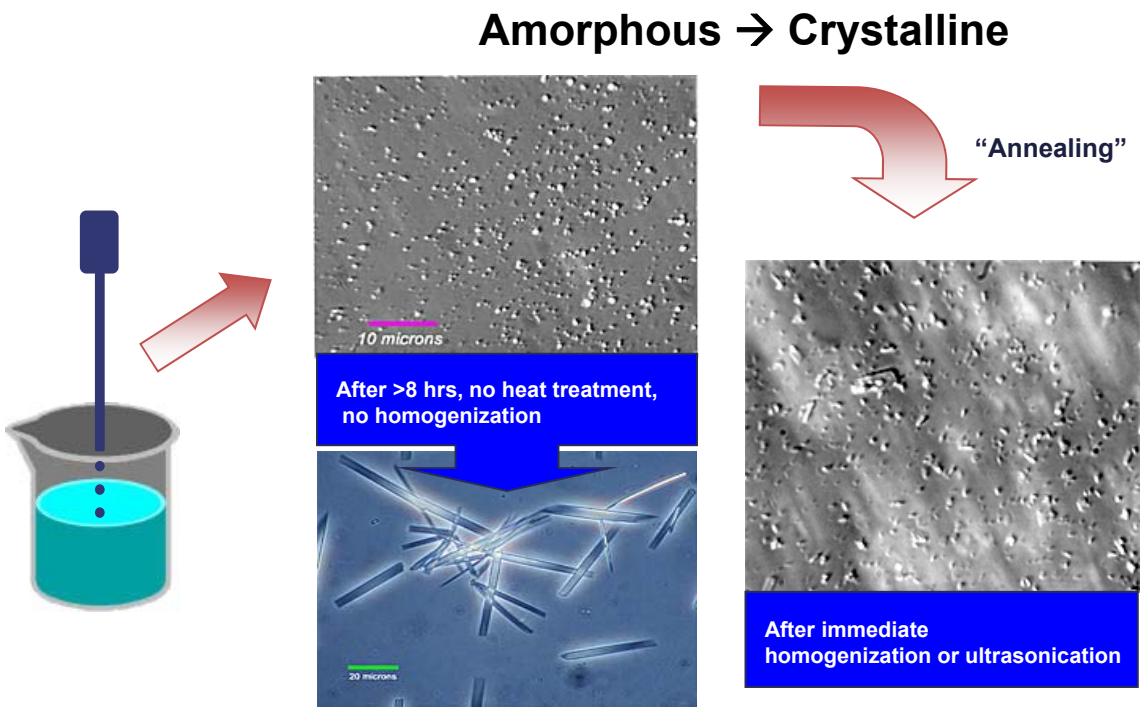
- Homogenization involves the forcing of a suspension under pressure through a valve that has a narrow aperture.
- Bernoulli's law requires that the high velocity of the suspension that results from flow past the constriction is compensated by a reduction in static pressure. (this is the principle by 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

Homogenization process

- Particle fracture processes
  - High shear
  - Cavitation
  - Impaction
  - Attrition
- Features
  - Sizes: 300 to 600 nm
  - High loading (10 – 200 mg/mL)
  - Long-term stability (up to 2 yrs)

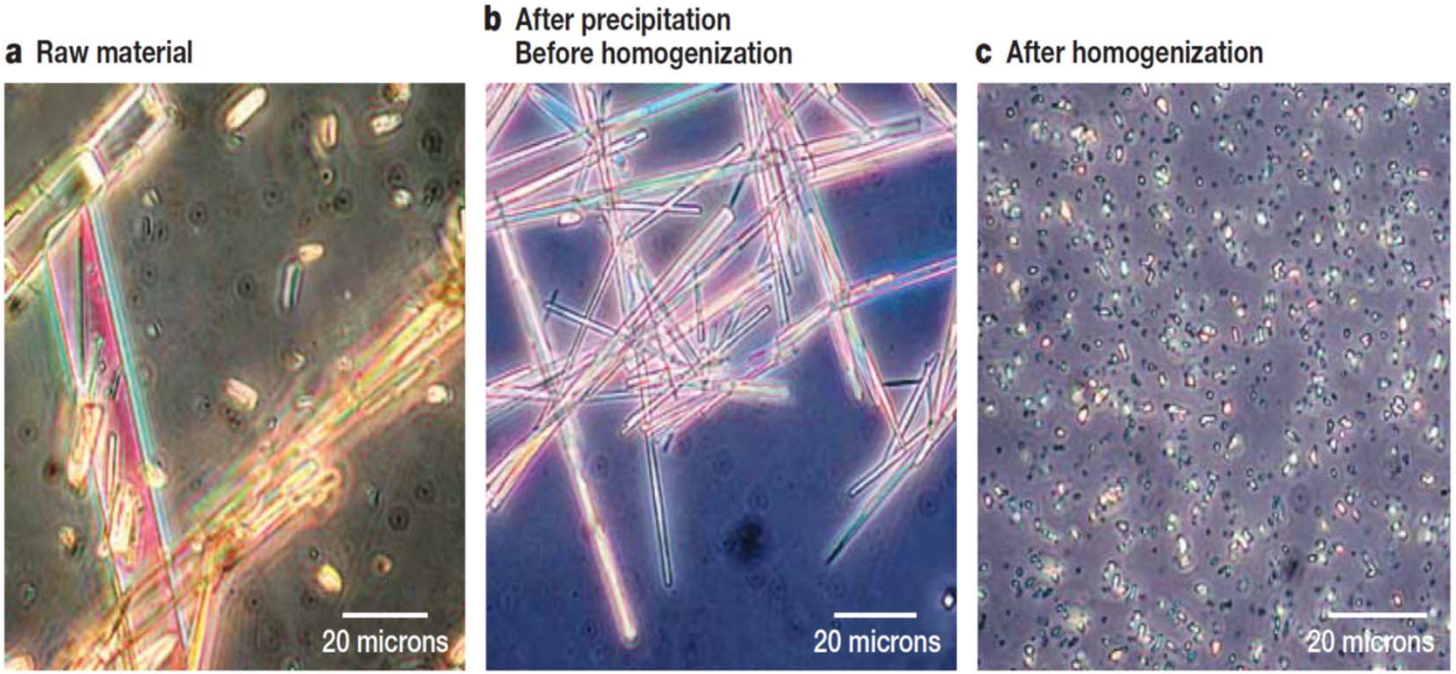


Microprecipitation process for forming nanosuspensions



- Homogenization resolves three problems of rapid precipitation.
- The crystal defects induced by rapid precipitation render the crystal more susceptible to rupture by the subsequent mechanical shock of homogenization.
- The initially formed needles are more susceptible to breakage because of the narrow dimension induced, which must bear the full applied force.
- The mechanical energy enables initially formed, unstable amorphous particles that result from rapid precipitation to undergo subsequent crystallization to a stable state.

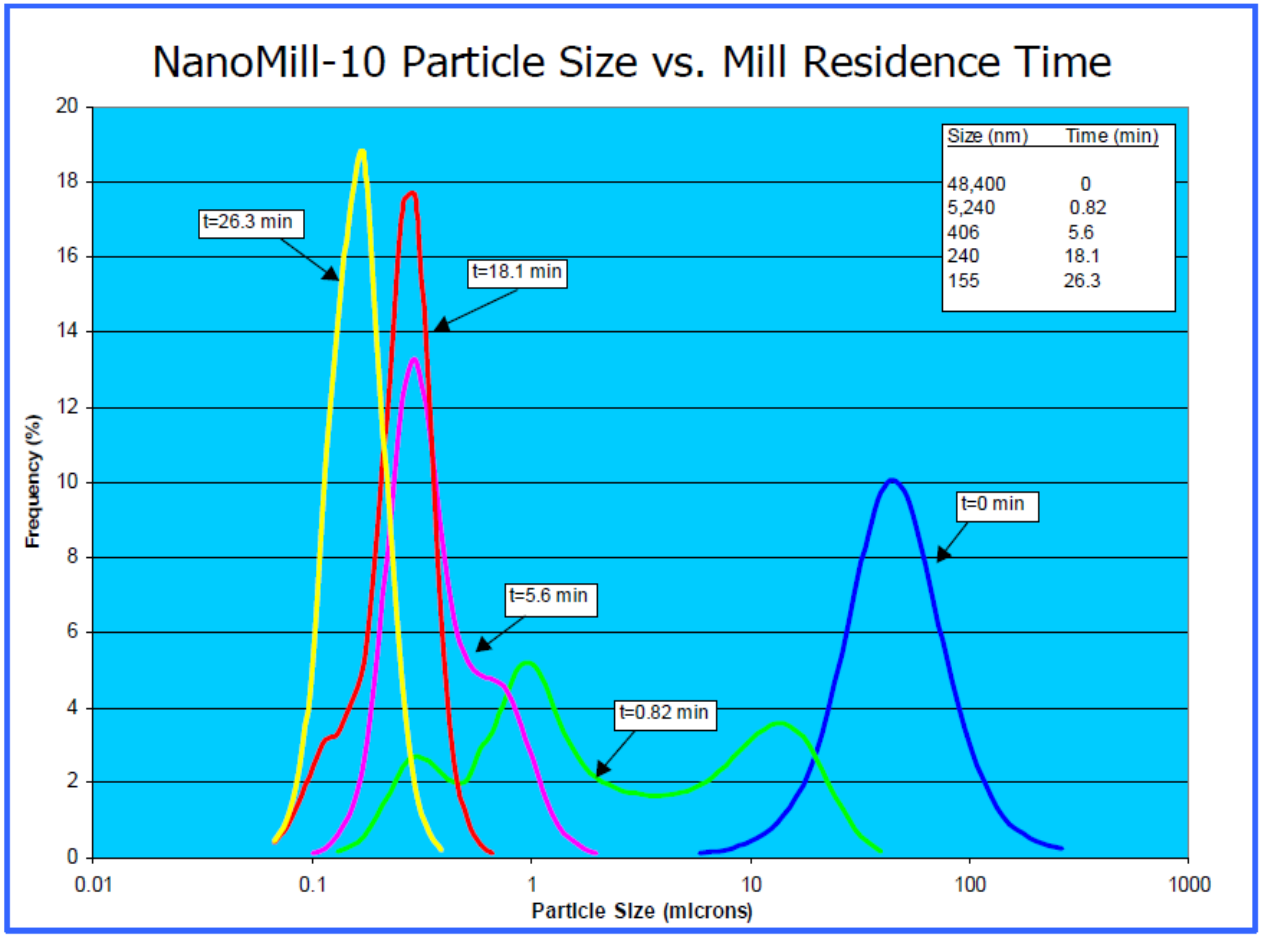
Engineering breakable crystals with a combination of microprecipitation and homogenization



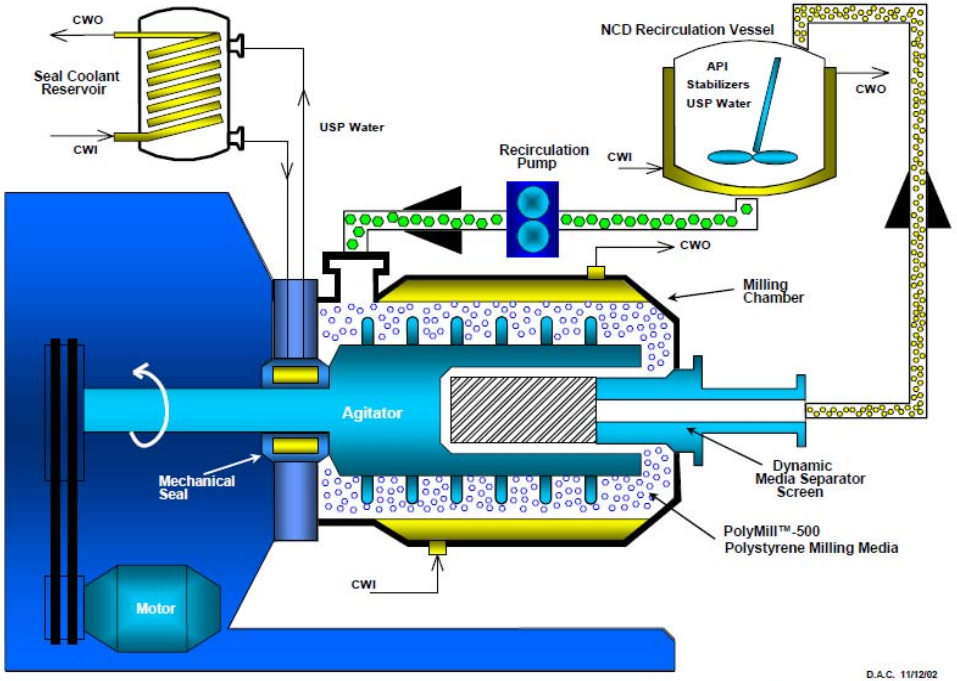
Crystal morphology of raw drug material is modified to facilitate breakage into smaller nanoparticles. a. Crystals of starting raw material are too large and hard to run efficiently through a homogenizer. b. the raw material is solubilized, filter sterilized and precipitated, so as to yield crystals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

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

Wet milling reduces particle size with increased residence time in mill



NanoCrystal® Colloidal Dispersion NanoMill™ Process



FOLEY 28 élan NanoSystems

- **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.**
- **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 separates the suspended, milled particles from the milling media**

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: 255-27

NanoMill™ Equipment Summary

	NanoMill™-001	NanoMill™-01	NanoMill™-1 Mag-Drive	NanoMill™-2	NanoMill™-10	NanoMill™-60
Chamber Volume(s)	10ml	10ml 50ml 100ml	500ml 1,000ml	2L	10L	60L
Process	Batch	Batch	Batch	Recirculation	Recirculation	Recirculation
Minimum Batch Size	100mg	100mg	10g	1kg	10kg	100kg
Maximum Batch Size	1,000mg	10,000mg	100g	10kg	100kg	500kg
Application	Discovery	Discovery & GLP Tox	GLP Tox & GMP Clinical	GMP Clinical	1/10th Scale GMP Clinical	Commercial Manufacturing

FOLEY 38 élan NanoSystem

- **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**

NanoMill™-60 Pilot Plant

100-500kg API Batch Sizes

Commercialized nanocrystal-based drug formulations

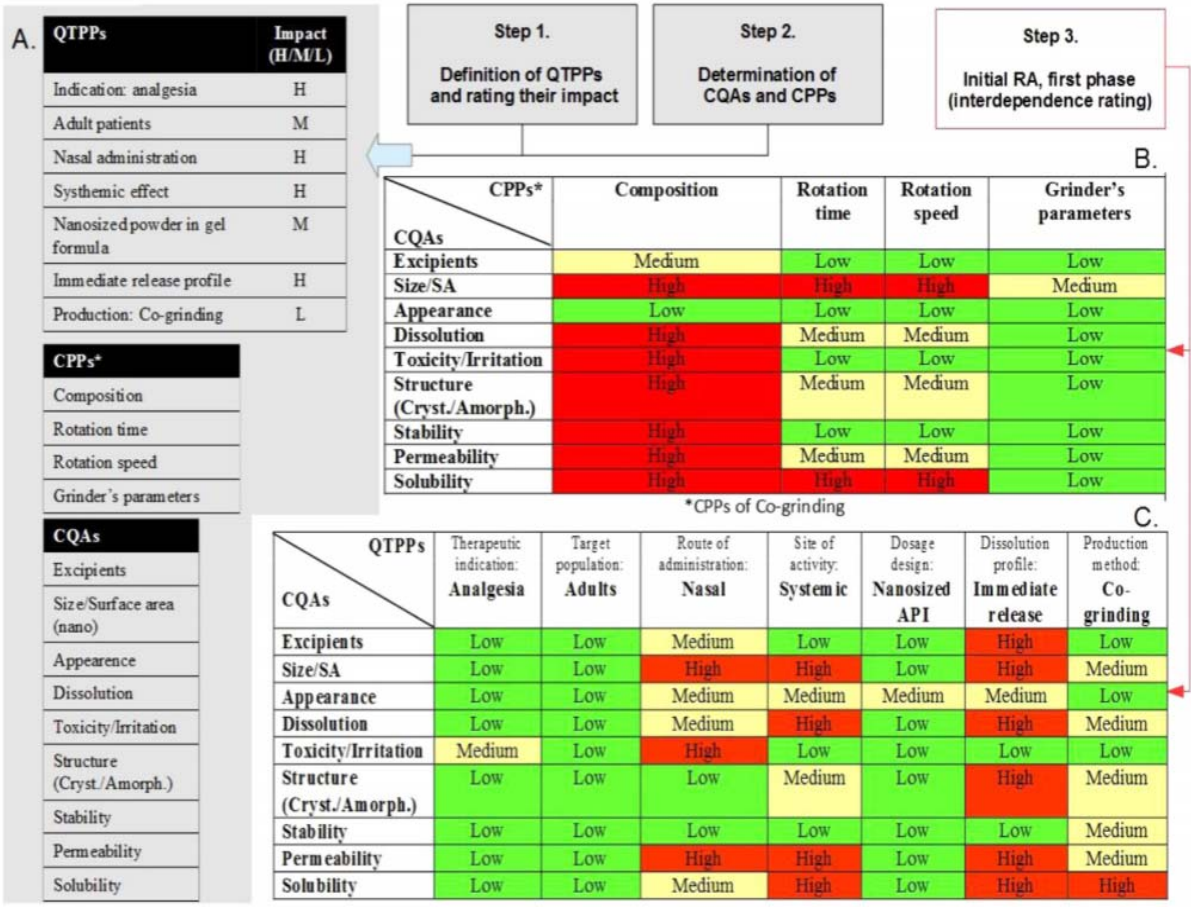
Company	Trade Name	Drug	FDA Approval date	Description	Technology	Advantage
Wyeth Pharmaceuticals	Rapamune®	Sirolimus	August 2000	Tablet	Wet milling	Improved bioavailability, dose proportionality, absorption variability
Merck	Emend®	Aprepitant	March 2003	Capsule	Wet milling	Eliminating food effect
Abbott labs	TRICOR®	Fenofibrate	December 2004	Tablet	Wet milling	Eliminating fed/fast effect
Par Pharmaceuticals	Megace ES®	Megestrol acetate	July 2005	Oral suspension	Wet milling	Rapid onset of action, lower dosing regimen
Nucryst Pharmaceuticals	NPI 32101	Silver	July 2007	Topical cream	Magnetron sputtering	Enhanced antimicrobial activity
Janssen Pharmaceuticals	Invega® Sustenna™	Paliperidone Palmitate	July 2009	Extended release injectable suspension	Wet milling	Reducing risk of relapse

(Note: Wet milling technique is the proprietary of Elan's Nanocrystal® Technology)

R Nagarwal et al. Nanocrystal Technology in the Delivery of Poorly Soluble Drugs: An Overview. Current Drug Delivery, 2

Quality by design increases reliability, but with much additional effort

- 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 within which manufacturing variance will 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.



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

Fig. 2. Selected QTPPs, CQAs and CPPs and their interdependence rating in the initial RA process.

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).

Quality by design parameters for nanosuspensions

Pharmaceutical Operation	Sample Process Parameter	Potential Quality Attribute
Mixing	Type and shape of the mixer	Mixture uniformity
	Loading order	Particle size distribution
	Mixer loading capacity	Bulk/Tapped density
	Rotation speed and duration	Moisture content
	Mixing sticks	Flow properties
		Assay
		Impurity
Milling (granulation)	Impact/cutting/screening milling	Particle size
	Mill type and speed	Particle size distribution
	Mill type and configuration	Particle shape
	Sieve size and type	Bulk/Tapped density
	Feeding speed	Flow properties
	Fluid energy mill	Polymorphic form
	Milling nozzles	Impurity
	Nozzle pressure	
Wet granulation	In high shear granulation	Energy consumption
	Impeller, its configuration,	Mixture uniformity
	location and speed	Flow
	Tank temperature	Moisture content
	Chopper speed and	Particle size and distribution
	configuration, location and speed	Granule size and
	Spray nozzle type and location	distribution
	Binder liquid temperature	Granule strength and
	Binder addition duration	uniformity

B Mesut et al. Review article The Place of Drug Product Critical Quality Parameters in Quality by Design (QBD) Turk J Pharm Sci 12(1), 75-92, 2015

Biodegradable polymeric microspheres

- 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), 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.

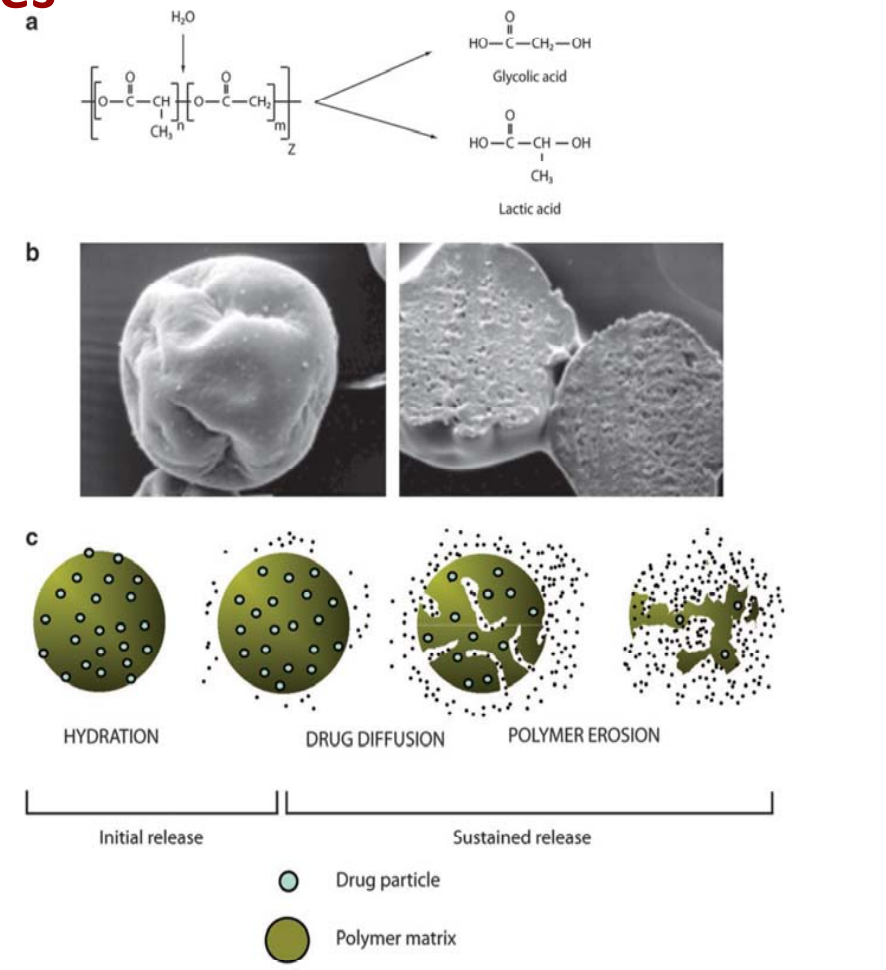


FIG. 1. Basics of poly-(D,L-lactide-co-glycolide) microspheres. (**a**) Spontaneous hydrolysis of poly-(D,L-lactide-co-glycolide) polymers. (**b**) Exenatide once-weekly microspheres exhibiting (**left**) a typical pinched raisin shape and (**right**) dense surface layer. (**c**) Mechanism of drug release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

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 Diabetes. Diabetes Tech & Therapeutics. 13:1145 (2011).

Adjusting drug release rates in polymeric microspheres

Drug release rates can be modified by

- Altering the ratio of the two constituent polymers, lactide and glycolide, and
- Altering the molecular size or weight (kD= kilodalton, i.e. 1000 molecular wt. So 65 kD = Molec Wt of 65,000)

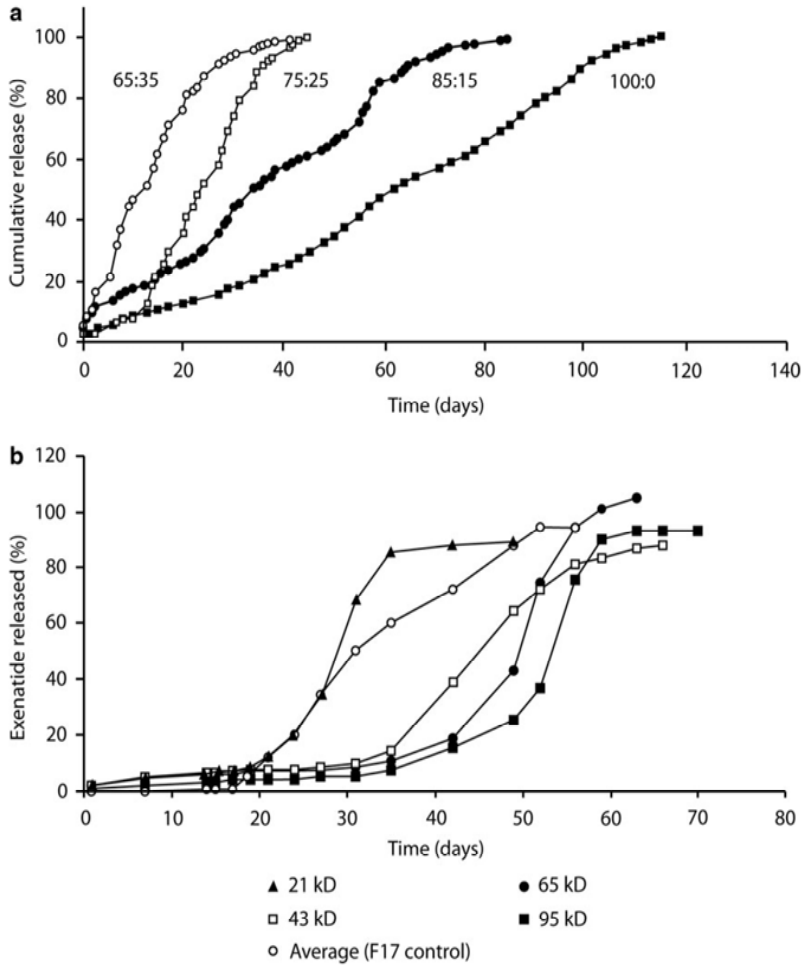


FIG. 3. Control of diffusion/erosion: (a) effect of lactide:glycolide ratio and (b) polymer molecular size on in vitro release.

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 Diabetes. Diabetes Tech & Therapeutics. 13:1145 (2011).

Alkermes technical and business drug delivery platform acquisition stra

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	Elan/ 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-rilpivirine employs NanoCrystal formulation technology

Improved Efficacy of Naltrexone Implant

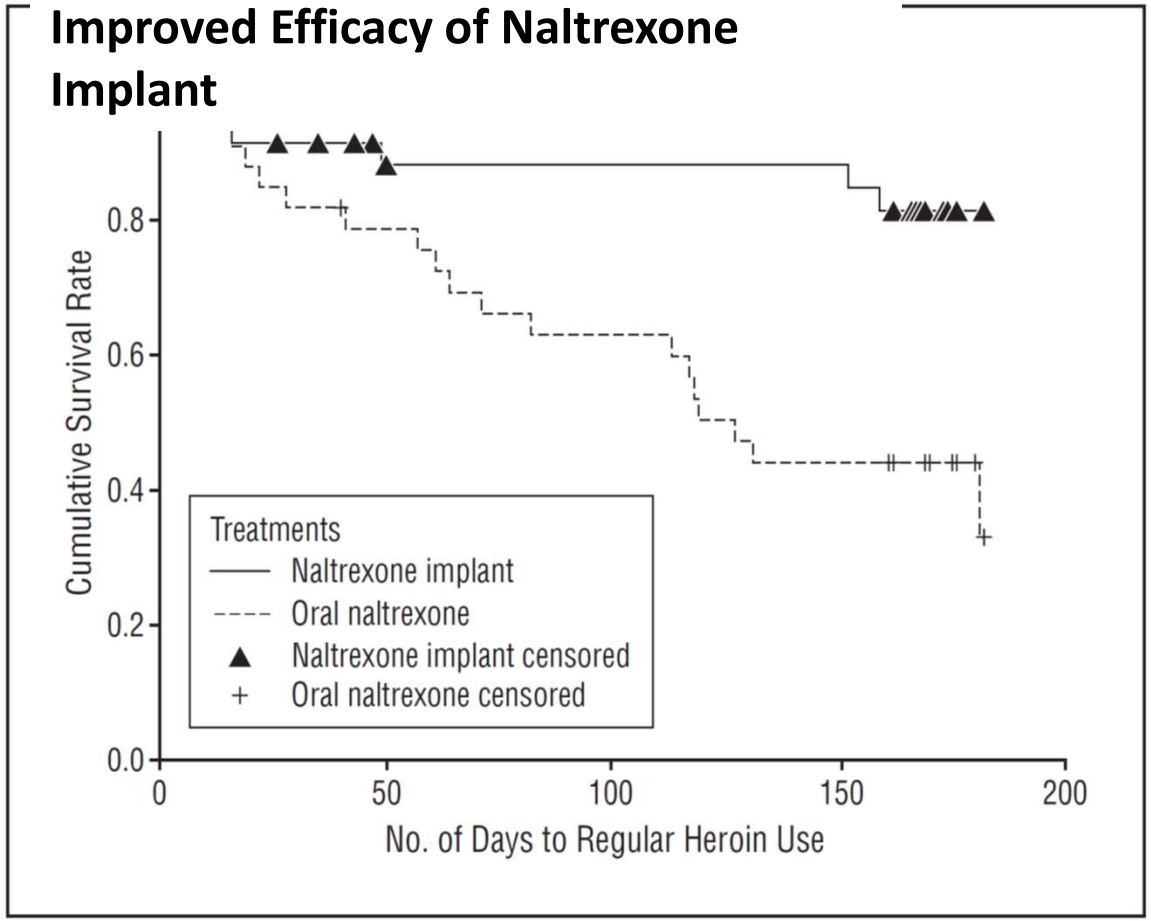


Figure 2. Cumulative survival and number of days until regular heroin use (≥4 d/wk; those unavailable for follow-up treated as return to regular heroin use). Cases were censored at study withdrawal/loss to follow-up or at last contact within 14 days before the end of study (maximum, 182 days).

Table 3. Drug-Related Study End Points and Self-reported Heroin Use[a]

End Point	6-mo Intention-to-Treat Analysis, No. (%) of Participants: Implant Naltrexone Group (n=35)	Oral Naltrexone Group (n=34)	HR (95% CI)
Self-reported heroin use			
Regular heroin use[b]	6 (17)	21 (62)	5.57 (2.18-14.24)[c]
1-3 d/wk	2 (6)	4 (12)	. . .
1-3 d/mo	5 (14)	0 (0)	. . .
Abstinence	22 (63)	9 (26)	. . .
Self-reported opioid abstinence and urinalysis results validation	17 (49)	7 (21)	1.77 (0.90-3.28)
Self-reported any use of illicit/misuse of licit substances	33 (94)	26 (76)	0.58 (0.32-1.05)

Abbreviations: CI, confidence interval; ellipses, not calculated; HR, hazard ratio.

[a] Covariates in the Cox model were sex, baseline age, years of regular heroi use, body mass index, and treatment group.

[b] Regular heroin use was defined as 4 or more days per week or unavailable for follow-up.

[c] $P < .001$.

Hulse. Improving Clinical Outcomes in Treating Heroin Dependence *Randomized, Controlled Trial of Oral or Implant Naltrexone.* Arch Gen Psychiatry. 2009;6

Emulsion templated freeze-dried solid drug nanoparticles

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 particles 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

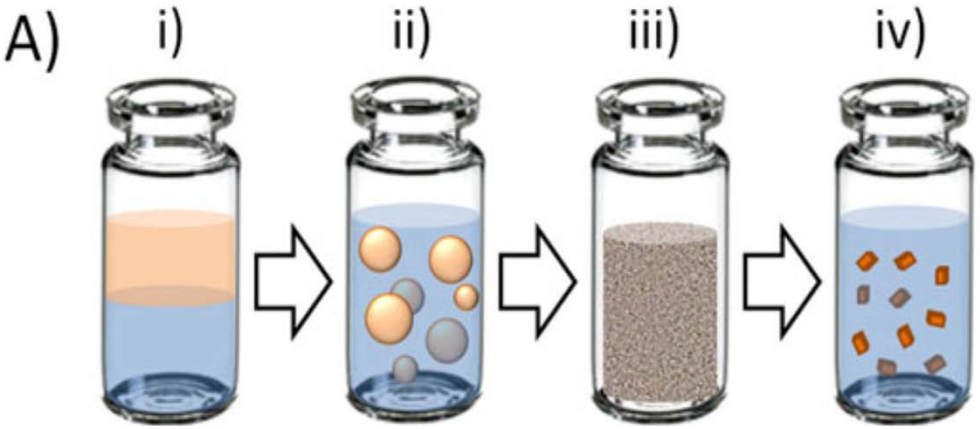


Figure 1. Schematic illustration of solid drug nanoparticle formation techniques. (A) Emulsion-templated freeze drying involves the following: (i) the dissolution of poorly soluble drug compound into a water-immiscible solvent and the dissolution of water-soluble excipients into water; (ii) emulsification; (iii) freezing and freeze-drying to yield a dry, porous monolith; and (iv) redispersion into water.

P. Curley, et al. In vitro characterisation of solid drug nanoparticle compositions of efavirenz in a brain endothelium cell line. J Interdisciplinary Nanomedicine,2017; 2(3). M. Giardiello et al. Accelerated oral nanomedicine discovery from miniaturized screening to clinical production exemplified by paediatric HIV nanotherapies. Nature Commun. 21Oct2016.