Formulation and Process Development to Support GMP Manufacture of Sterile NanoCrystal Suspensions

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DRUG DEVELOPMENT SERVICES

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Presentation Outline

- Brief introduction to Particle Sciences, Inc.
- Background
  - The origin of NanoCrystal™ Technology – Sterling Winthrop Pharmaceuticals Research Division and Eastman Kodak
- Overview of NanoCrystal Suspensions
- Marketed parenteral NanoCrystal Suspension-based products
- CMC
  - Formulation
  - Manufacturing
  - Sterilization
- *In vivo c*onsiderations, pharmacokinetics, and pharmacodynamics

About Agno Pharma

- USA-based end-to-end global CDMO with ~ 550 employees & 3 sites worldwide
- Offering API, intermediate, drug product, drug implants and analytical development along with cGMP manufacturing solutions from pre-clinical through commercialization
- Vast experience with commercial cGMP RSMs, INTs, API and DP supply to US/EU Markets
- Consistent track records of successful US FDA cGMP inspections; FDA-approved cGMP manufacturing facilities in both USA and Asia. Successfully passed 6 FDA inspections in 10 years
- World leaders in sterile API, sterile powder-fill, aseptic suspensions (coarse and nano), aseptic milling/nano-milling, and drug implant technology
- Capability of handling high potency, beta-lactam, controlled substance, and hormone drug products
- Well capitalized via PE investments – Vivo Capital & Bain Capital have majority ownership interest as of Q1 2024

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Bethlehem, PA, USA Site

(52,000+ ft^2 / 3 acres)

Drug Product & Drug Implants Development & Manufacturing

(FDA-PAI, 2021)

1 Commercial Aseptic Fill Line
2 Grade A Suites for Sterile Clinical Supply
2 Grade D Suites for Clinical Supply

Origin of the Technology

- Problem: low aqueous solubility of Active Pharmaceutical Ingredient
- Options:
  - Solubilizing approach, i.e., use organic cosolvents, solubilizing agents, coarse suspensions, and/or pH extremes
- Solution:
  - Sterling Winthrop Pharmaceuticals Research Division was charged with developing drug delivery technology leveraging Kodak's fine particle expertise

>>> NanoCrystal™ Technology

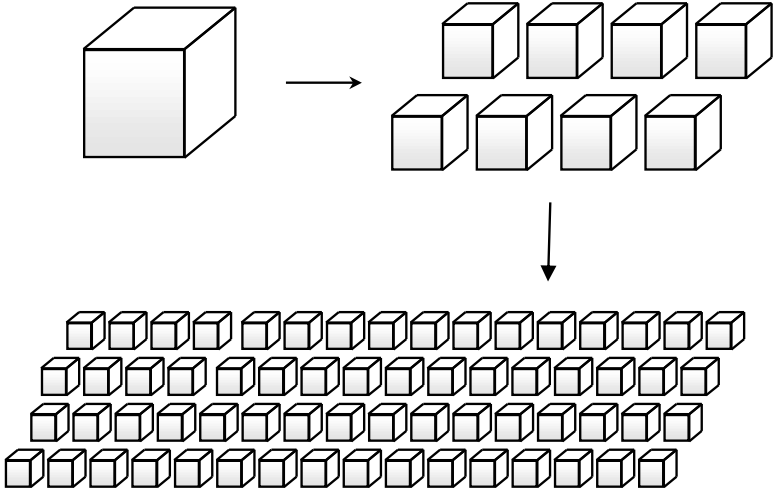
Intellectual Property

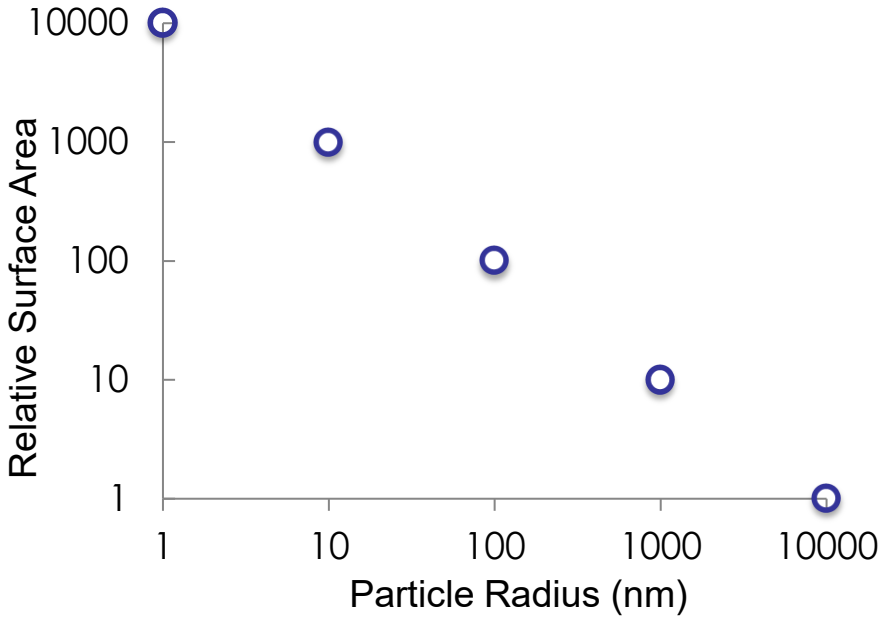
- Patent Number: 5,145,684
- Title: Surface Modified Drug Nanoparticles
- Filed: Jan 25, 1991
- Claim #1:

> **1.** Particles consisting essentially of 99.9–10% by weight of a crystalline drug substance having a solubility in water of less than 10 mg/ml, said drug substance having a non-crosslinked surface modifier adsorbed on the surface thereof in an amount of 0.1–90% by weight and sufficient to maintain an effective average particle size of less than about 400 nm.

- Covered: broad API and excipient space, ceramic milling media, ultrasonic energy, dispersion vehicles including water, safflower oil, ethanol, t-butanol, hexane, and glycol

What are NanoCrystals?





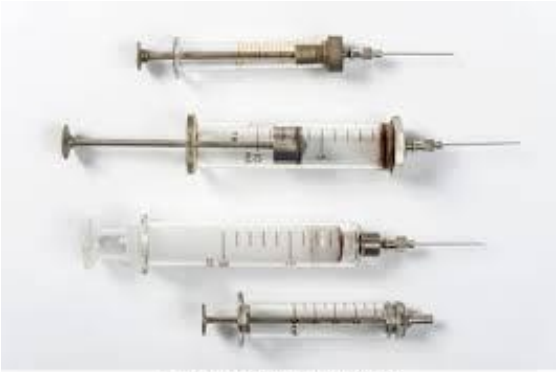
Smaller Particle → Increased Surface Area → Higher Dissolution Rate

Advantages of NanoCrystal Suspensions

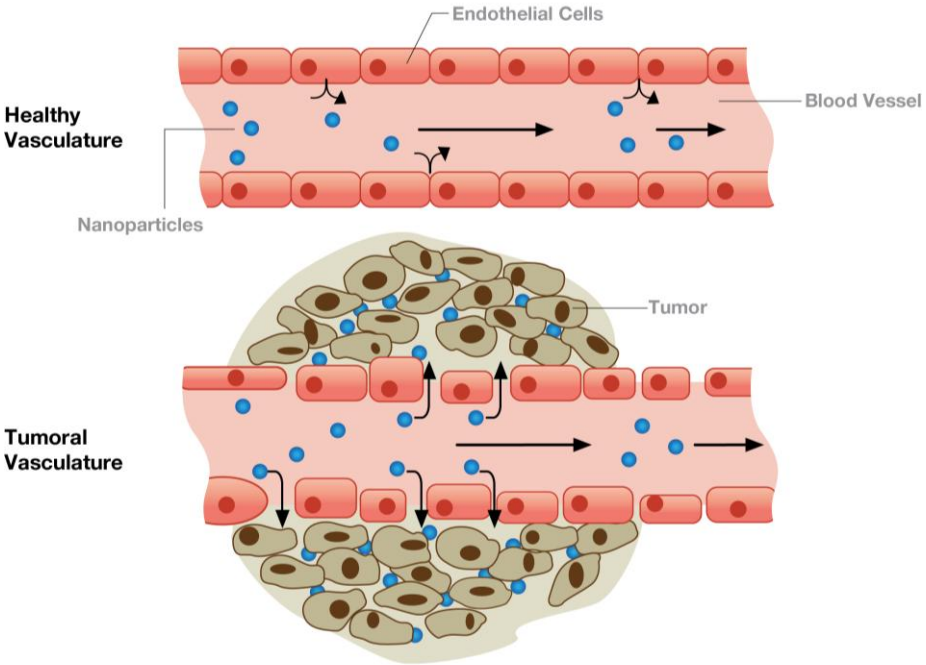
- Conceptually simple, practically straightforward
- Liquid form or lyophilized
- Increased bioavailability
  - High surface area / high dissolution rate
  - Increased solubility
- Reduced fast-fed effect
- Sterile processing feasible
- Enables IV injection of water-insoluble APIs
- Enables long-acting injections via IM and SC

Opportunities for Parenterals

- Issues with solubilizing approaches
  - Organic, water-miscible cosolvents
    - Physiological incompatibility, toxicity
  - Solubilizing agents
    - Cyclodextrins - low loading, immediate release profile
    - Surfactants - anaphylaxis, toxicity
  - pH extremes
    - Physiological incompatibility
- Rapid and complete dissolution of lyophile
- Potential for IV administration
- Terminally sterilized product possible



Enhanced Permeation and Retention Effect



First GMP Sterile NanoCrystal Suspension

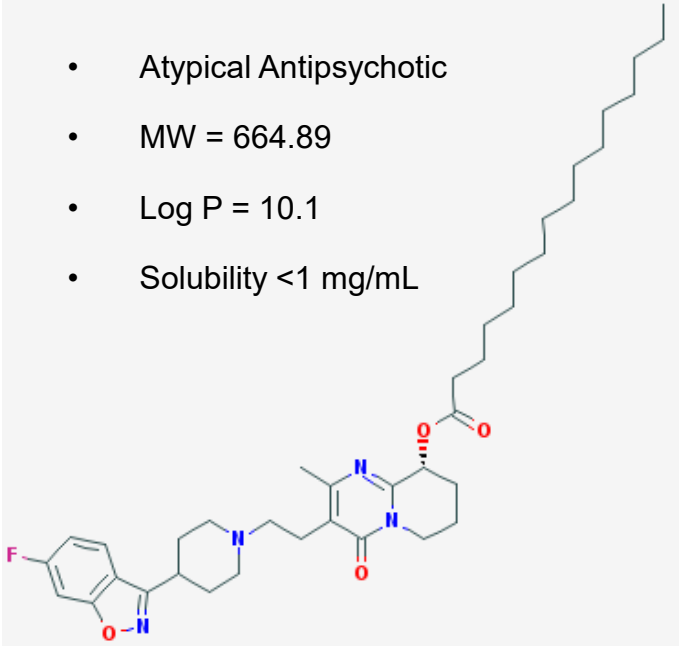
- Phase I study (1995) with Naproxen NanoCrystal Suspension
- Formulation attributes
  - Intramuscular administration
  - High naproxen concentration – 400 mg/mL
  - Microbial preservative system
  - Aseptic process using heat sterilization of unmilled bulk drug slurry
  - Manufactured on a Microfluidizer M110EH
    - Hundreds of passes…
- Successfully met two clinical end points
  - No site of injection irritation
  - No pain on injection

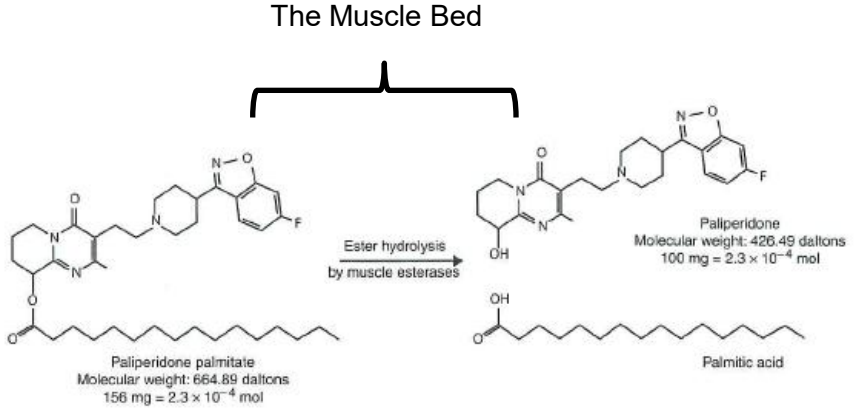
Commercial Parenteral Suspensions

BRAND	API	DOSAGE FORM	INDICATION	INNOVATOR
Abilify Maintena®	Aripiprazole	Intramuscular	Schizophrenia	Otsuka
Anjeso®	Meloxicam	Intravenous	Pain	Baudax Bio
Aristada®	Aripiprazole Lauroxil	Intramuscular	Schizophrenia	Alkermes
Aristada Initio™	Aristada initio	Intramuscular	Schizophrenia	Alkermes
Betason L.A®	Betamethasone	Intramuscular, intra-articular, intrabursal or intradermal	Inflammatory & allergic states	Caspian Tamin
Bicillin® L-A	Penicillin G benzathine	Intramuscular	Syphilis, prophylaxis	Pfizer
Depo-Medrol®	Methylprednisolone acetate	Intra-/peri-articular and intra-bursal	Epicondylitis, others	Pfizer
Depo-subQ Provera 104®	Medroxyprogesterone acetate	Intramuscular	Contraception & endometriosis	Pfizer
Invega Sustenna®	Paliperidone Palmitate	Intramuscular Injection	Schizophrenia, Schizoaffective Disorder	Janssen Pharma
Invega Trinza®	Paliperidone palmitate	Intramuscular	Schizophrenia, Schizoaffective Disorder	Janssen Pharma
Kenalog®	Triamcinolone acetonide	Intramuscular, intravitreal	Arthritis, inflammatory diseases	Bristol-Myers Squibb
Relprevv®	Olanzapine pamoate	Intramuscular	Schizophrenia	Lilly
Zyprexa®	Olanzapine pamoate	Intramuscular	Schizophrenia	Lilly

INVEGA® SUSTENNA™ (Paliperidone Palmitate)

- Atypical Antipsychotic
- MW = 664.89
- Log P = 10.1
- Solubility <1 mg/mL





Gopal et al. *Current Medical Research & Opinion*, vol 26, 377-387, 2010 & package insert

Designing a prodrug to be poorly water soluble & controlling particle size for extended release following IM dosing

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NanoCrystal Suspension – Extended Release Injectable

NEW ONCE-MONTHLY INVEGA® SUSTENNA™ paliperidone palmitate extended-release injectable suspension

Xeplion™(EU)

- Atypical antipsychotic dosed as a prodrug
- Aqueous-based formulation rather than oil
- Administered once a month
- Deltoid or gluteal muscle injection
- Prefilled syringe
- Needle size 23 or 22 gauge
- Doses: 39 (25 mg active), 78 (50 mg), 156 (100 mg), 234 (150 mg)

Formulation Development

- Must understand solid state characteristics of the API
- Formulation and manufacturing process are inseparable to a successful end-product
- Need to identify sterile process while considering
  - Physical and chemical stability
  - Homogeneity/content uniformity
  - Syringeability
  - Effect on particle size and surface morphology

NanoCrystal Suspension Excipients

- Sterile Water
- ***Stabilizers***
- Buffers/pH adjusters
- Tonicity modifiers
- Anti-oxidants
- Antimicrobial preservatives
- Cryoprotectants (if lyophilization is employed)

- GRAS (generally recognized as safe)
- Ideally used previously in desired ROA

Formulation Development

- Stabilizers
  - Key difference between solution formulations and NanoCrystal Suspensions
    - Necessary for physical stability
    - Keep particles discrete
    - Aid in redispersibility upon storage and reconstitution of lyophile
    - In conjunction with particle size, influence pharmacokinetics

Formulation Development

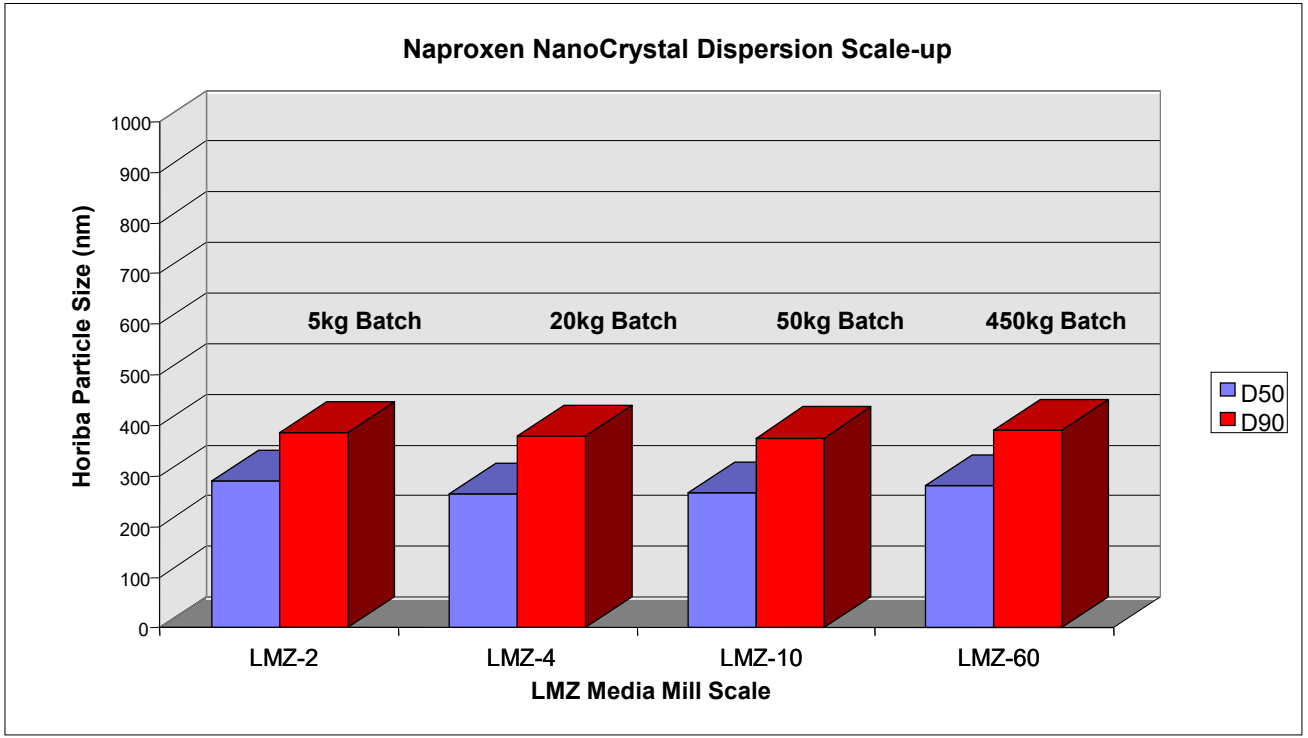
- Stabilizers
  - Ideally GRAS[1] (Generally Recognized as Safe)
  - Non-ionic or ionic
  - Polymeric or small molecule

[1] Reference: https://www.fda.gov/drugs/drug-approvals-and-databases/inactive-ingredients-database-download

High Energy Media Mills

- Scalable
- Wide selection of milling media
  - Ceramic, glass, polymeric
- Sterile or non-sterile
- Clean in place
- Commercial GMP production
- PSI SteriMill™

Manufacturing Process



NanoCrystal Suspension Sterilization

- Required for parenteral and ocular formulations
- Terminal Sterilization
  - Gamma radiation
  - Heat sterilization
- 0.2-micron filtration (requires D_{90} < ~90 nm)
- **Sterile ingredients & aseptic processing (more common)**
  - Sterilized API & excipients / sterilized equipment
  - Heat sterilized API suspension / sterilized equipment

NanoCrystal Suspension Sterilization

- Terminal Heat Sterilization of Ready-to-Use NanoCrystal Suspension
  - NanoCrystal Suspensions occasionally can be terminally heat sterilized[1] with minimal growth in mean particle size and excellent physical stability

Sample	Mean Particle Size (nm)
Pre-autoclaved	170 +/- 6 (n = 3)
Post-autoclaved	201 +/- 5 (n = 5)

[1]Autoclave temperature of 118°C for 15F_o's

Injection Site Toxicity

- NanoCrystal Suspensions can be formulated to minimize injection site toxicity and pain on injection
  - No irritating cosolvents
  - No surfactants with toxicity
  - No pH extremes
  - Isotonic formulations are possible

IV Administration of NanoCrystal Suspensions

- When administering NanoCrystal Suspensions intravenously
  - Can use an in-line filter (1 μ)
  - In dog, there are acute Hemodynamic effects
    - Recommend slow infusion rate
    - Effect not as pronounced in man

Concentration of Solids	Infusion Rate (mL/min)	Dose Rate (mg/min)[1]	Hypotension (Y/N)
5% (50mg/mL)	1	50	Y
5% (50mg/mL)	0.1	5	N
1% (10mg/mL)	5	50	Y
1% (10mg/mL)	1	10	Y
1% (10mg/mL)	0.5	5	N

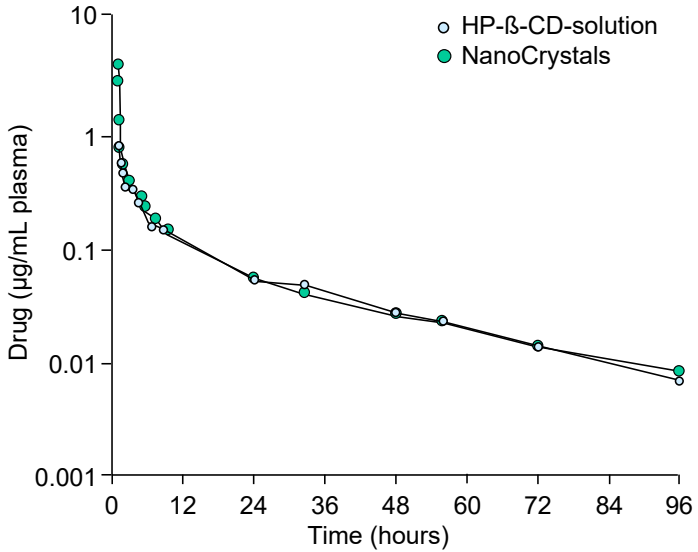
[1] Based on an average dog weight of 10kg

Reference: L. Garavilla, N. Peltier, E. Merisko-Liversidge, "Controlling the Acute Hemodynamic Effects Associated With IV Administration of Particulate Drug Dispersions in Dogs", Drug Development Research, 37: 86-96, 1996.

Pharmacokinetics and Pharmacodynamics

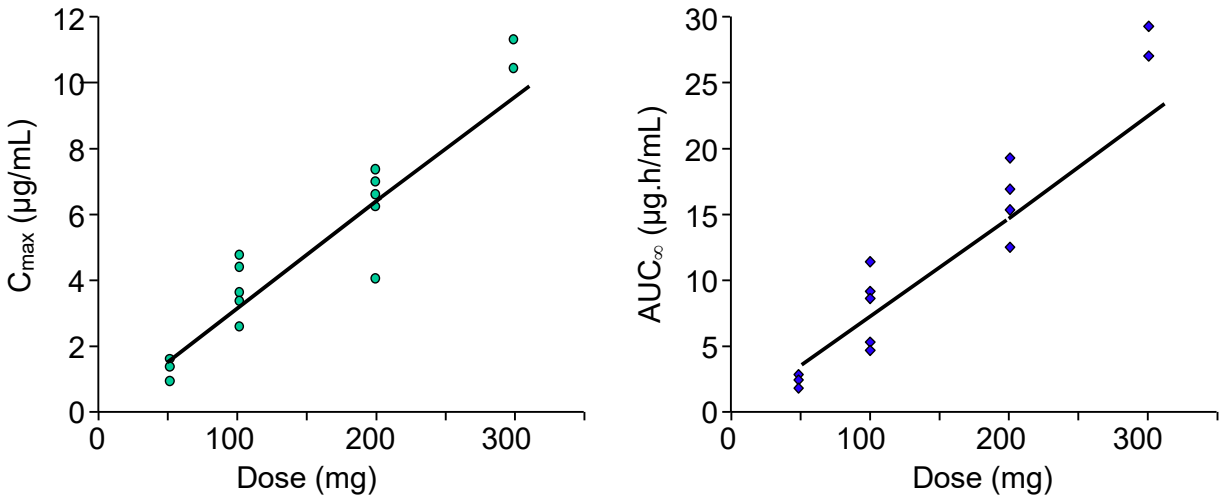
IV NanoCrystal™ Formulation vs. Soluble Formulation

Single Dose, 1 hr infusion

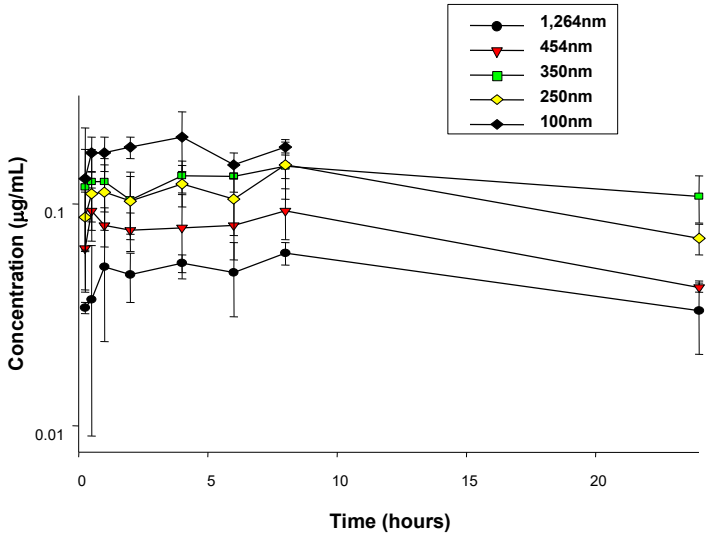


Pharmacokinetics and Pharmacodynamics

Pharmacokinetics of IV NanoCrystal™ Formulation



IM Administration of NanoCrystal Suspension

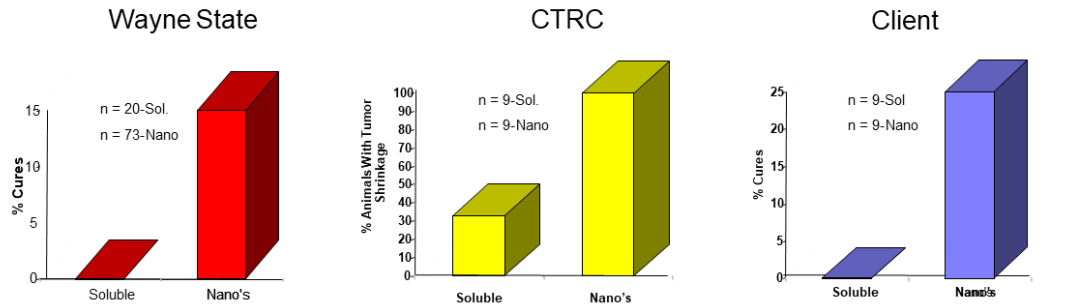


Pharmacokinetics as a Function of Particle Size for Intramuscular Administration in Rats *

* Robert W. Lee, “Case Study: Development and Scale-Up of NanoCrystal® Particles" in "Injectable Dispersed Systems: Formulation, Processing and Performance", Diane J. Burgess (editor), Taylor & Francis, 2005, 149, 355.

Pharmacokinetics and Pharmacodynamics

NanoCrystal™ Compound X vs. Soluble Formulation



Model for Breast Cancer | **Model for Lung Cancer** | **Model for Ovarian Cancer**

NanoCrystal™ Compound X is more efficacious in all three tumor models

NanoCrystal Suspension Summary

- Possible option for LAI for water insoluble, crystalline APIs
- Pharmaceutically elegant formulation technique (API dependent)
  - Aqueous based
  - Isotonic
  - Neutral pH
  - Minimal excipients
- High API concentration possible (up to 500 mg/mL)
- If ROA is IM or SQ a larger particle size may be possible for longer duration of action
- Generally applicable – sterile API needed (worse case is sterile filtration and aseptic crystallization) with aseptic process

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