Oral nanomedicines: An examination of approved and late-stage investigational products

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Disclosures:
Hardeep Oberoi was an employee of AbbVie at the time of the study. The design, study conduct, and financial support for this research were provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the publication.

Outline

- Introduction
- Analysis of oral nanomedicines on the market & in late-stage investigation
  - By product type (NME vs Generic) & approval year
  - By therapeutic area, API solubility
  - By technology employed
- Focus on prevalent technology
- Upcoming therapeutics in late stage
- Summary
- Outlook

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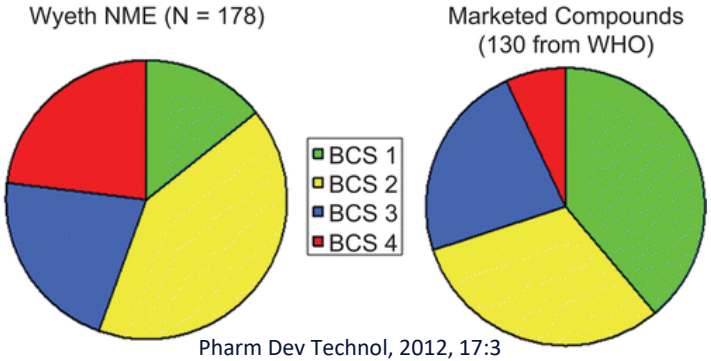
Motivation

Approximately 70% of active pharmaceutical ingredients (APIs) in development are considered to have poor aqueous solubility, resulting in reduced bioavailability of these poorly soluble compounds
(Pharm Dev Technol, 2012, 17:3)

Formulators interest in mature platforms to expand toolbox for enabling such NCEs

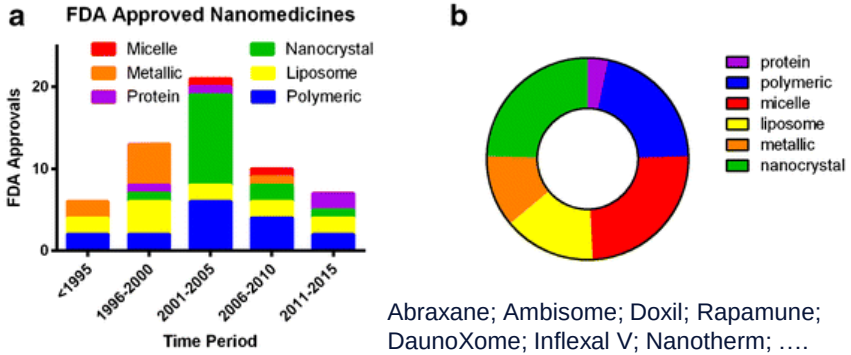
A number of nanoparticle based products have been commercialized

> 100 overall products/applications



Pharm Dev Technol, 2012, 17:3

Pharmaceutical Research, 2016, 33, 2373–238



Abraxane; Ambisome; Doxil; Rapamune; DaunoXome; Inflexal V; Nanotherm; ….

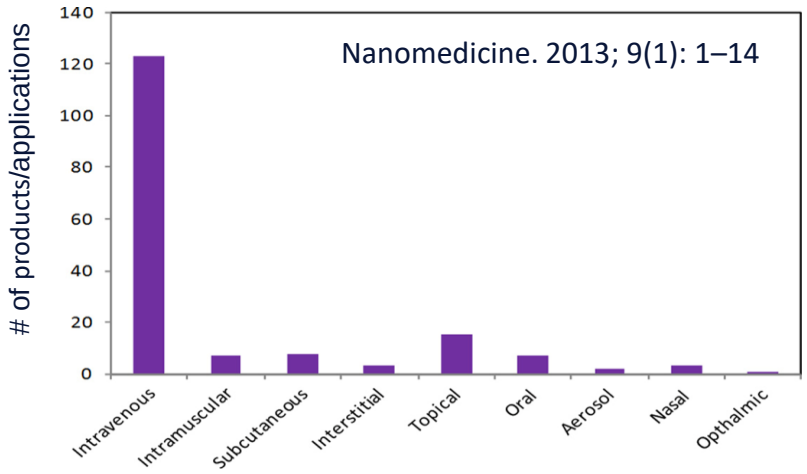
Background

Review for approved products indicates primarily parenteral route of administration

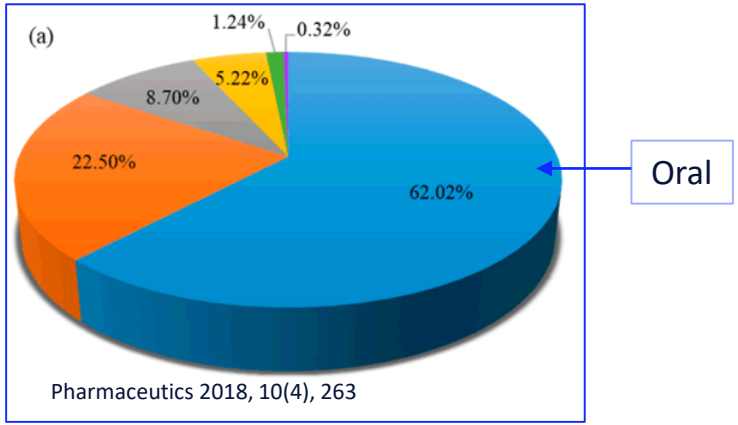
Over 120 (or 73%) of the directly administered applications and products were intended for IV use

Oral route is the most common/preferred route of drug administration

Route of administration of approved nanoparticle based products



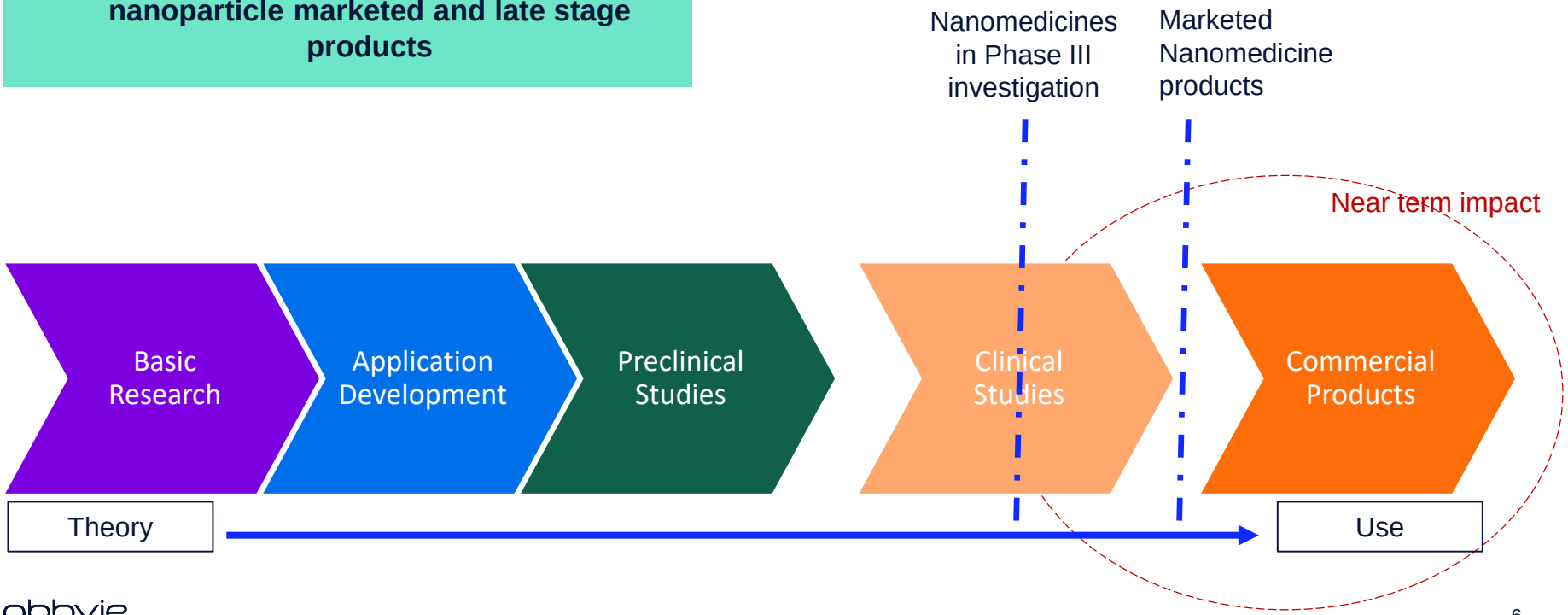
Overall distribution by administration route of FDA-approval pharmaceutical products



Analysis Methodology

Excluded in situ NP generation, SNEDDS, ASDs, etc.

Focused search and examination of oral nanoparticle marketed and late stage products



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Oral Marketed Nanomedicine Products & Approval Years

Pharmaceutics 2023, 15(3), 774

Trade Name	Approval Year	Drug Agent	Company
Gris-PEG®	1998	Griseofulvin	Recro Gainesville LLC (Gainesville, FL, USA)
Rapamune®	2000	Rapamycin/sirolimus	Wyeth (Philadelphia, PA, USA)
Avinza®	2002	Morphine sulfate	King Pharma (Bristol, TN, USA)
Ritalin LA®	2002	Methylphenidate hydrochloride	Novartis Novartis (Basel, Switzerland)
Emend®	2003	Aprepitant	Merck (Rahway, NJ, USA)
Tricor®	2004	Fenofibrate	Abbott (North Chicago, IL, USA)
Triglide®	2005	Fenofibrate	Skye Pharma (San Diego, CA, USA)
Megace®ES	2005	Megestrol acetate	Par Pharma (Petaluma, CA, USA)
Naprelan®	2006	Naproxen sodium	Wyeth (Philadelphia, PA, USA)
Cesamet®	2009	Nabilone	Lilly (Indianapolis, IN, USA)
Injectafer®	2013	Iron nanoparticles	Polynuclear iron (III) oxyhydroxide iron particles	For Int. (Waltham, MA, USA)
Monofer®	2010	Iron nanoparticles	Iron molecule with unbranched carbohydrate iron particles	Pharmacosmos (Rorvangsvej, Holbæk, Denmark)

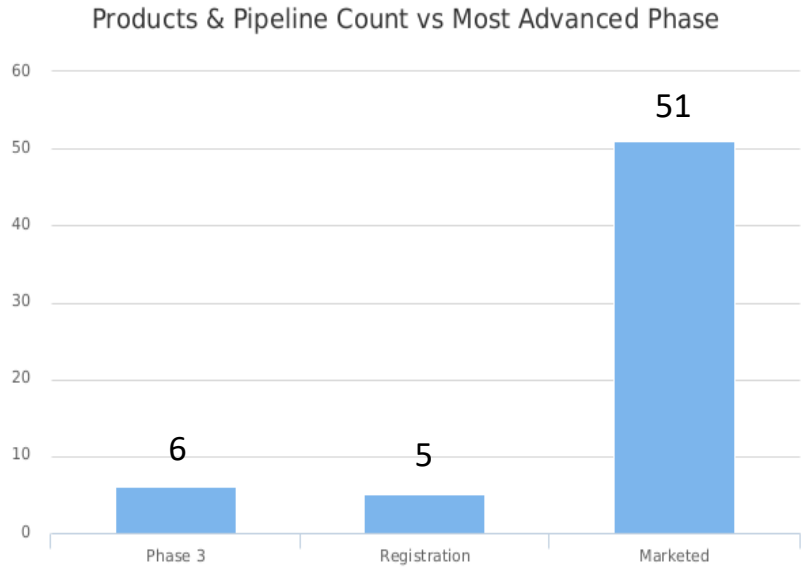
Acta Pharmaceutica Sinica B, 2015, 5:5, 442-453

Trade name	Drug	Indication	Drug delivery company	Innovator company
Rapamune®	Rapamycin, sirolimus	Immunosuppressant	ElanNanosystems	Wyeth
Emend®	Aprepitant	Anti-emetic	ElanNanosystems	Merck & Co.
Tricor®	Fenofibrate	Hypercholesterolemia	Abbott Laboratories	Abbott laboratories
Megace ES®	Megestrol	Anti-anorexic	ElanNanosystems	Par Pharmaceuticals
Triglide®	Fenofibrate	Hypercholesterolemia	IDD-P Skyepharma	ScielePharma Inc. King
Avinza®	Morphine sulfate	Phychostimulant drug	ElanNanosystems	Pharmaceuticals
Focalin	Dexmethyl-phenidate HCl	Attention deficit hyperactivity disorder (ADHD)	ElanNanosystems	Novartis
Ritalin	Methyl phenidate HCl	CNS stimulant	ElanNanosystems	Novartis
Zanaflex Capsules	Tizanidine HCl	Muscle relaxant	ElanNanosystems	Acorda

- Literature search for marketed products – limited, known products
- Some are misclassified as oral nanoparticles (Injectafer, Monofer)

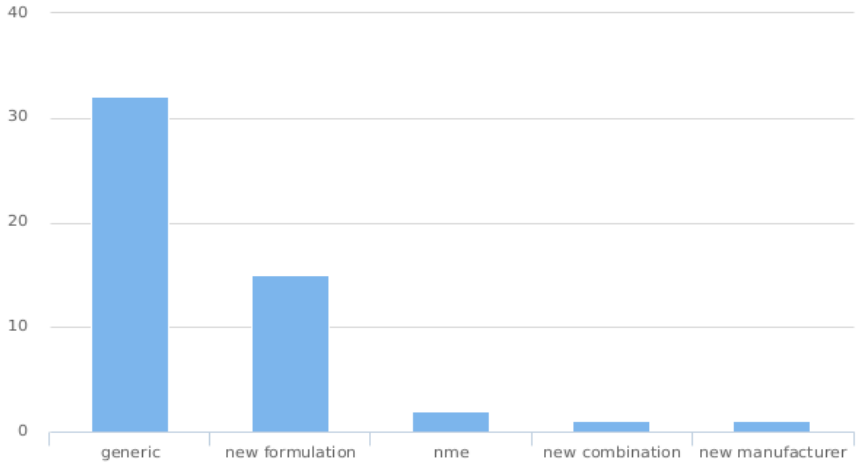
Oral Global Marketed Nanomedicine Products
(Source: PharmaCircle)

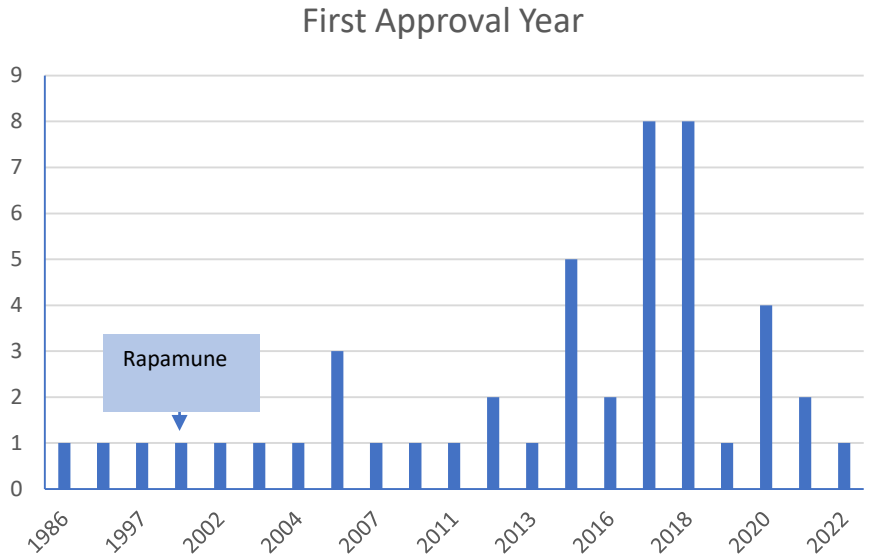
Envarsus XR Tablets	Megace ES Oral Suspension, Generic HI-TECH PHARMACAL
Fenoglide Oral Tablets	Entocort EC MR Capsules, Generic Zydus
TriCor NanoCrystal Oral Tablets	Triglide Oral Tablets, Generic Sun Pharma
Ritalin LA Capsules	Entocort EC MR Capsules, Generic Amneal
Entocort EC MR Capsules	Emend Oral Capsules, Generic Glenmark
Megace ES Oral Suspension	Entocort EC MR Capsules, Generic Appco
Emend Oral Capsules	Aprepilor Oral Capsules
Rapamune Oral Tablets	Vivlodex Oral Capsules, Generic Novitium
Triglide Oral Tablets	NanoStilbene Oral Solution
Emend Oral Capsules, Generic Sandoz	Triglide Oral Tablets, Generic Mankind
Entocort EC MR Capsules, Generic Viatris	TriCor NanoCrystal Oral Tablets, Generic Prinston
Megace ES Oral Suspension, Generic TWi	Tivorbex Oral Capsules, Generic Chartwell
Bestor FN Oral Tablets	Emend Oral Capsules, Generic Heumann
Rapamune Oral Tablets, Generic Zydus	Emend Oral Capsules, Generic Betapharm Arzneimittel GmbH
Rapamune Oral Tablets, Generic Dr. Reddy's Laboratories Ltd.	Emend Oral Capsules, Generic Aurobindo
Emend Oral Powder For Suspension, Hybrid Generic Merck And Co.	Emend Oral Capsules, Generic Zentiva
Daily Immune Support Supplement, SilverBiotics	TriCor NanoCrystal Oral Tablets, Generic Mylan
Focalin XR Capsules	Emend Oral Capsules, Generic Sawai
Zanaflex Oral Capsules	INEPITANT Oral Capsules
Cholib Oral Tablets	CimetrA Oral Spray
Tivorbex Oral Capsules	Emend Oral Capsules, Generic Torrent
Ztalmy Oral Suspension	Rapamune Oral Tablets, Generic Glenmark
TriCor NanoCrystal Oral Tablets, Generic Aurobindo	RaparoBell Oral Tablets
Entocort EC MR Capsules, Generic Mayne	Rapamune Oral Tablets, Generic Alkem
Vivlodex Oral Capsules, Generic Lupin	Montelukast Oral Tablets, Meda Biotech
Yonsa Oral Tablets	Aprepitant Mylan Oral Capsules



- PharmaCircle search pulls much larger number of products
  - Products from global market
  - Few products in Ph3 and registration

Oral Nanomedicine Products Including Ph3/Registeration (Source: PharmaCircle)

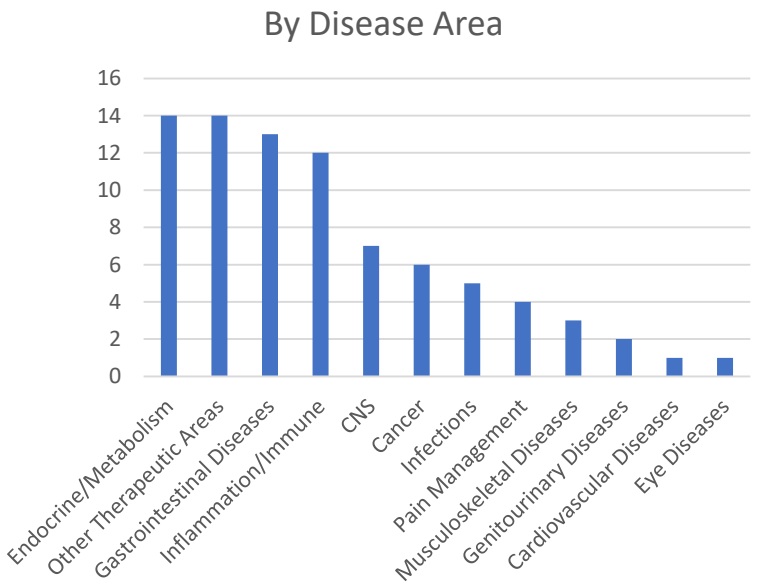


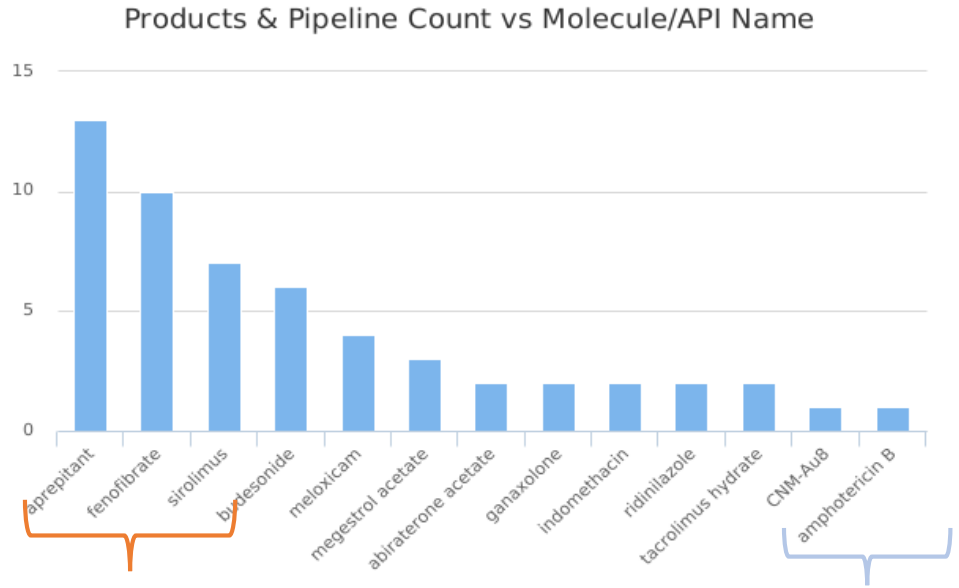


- Most are generics
- New formulations are frequent (likely indicate product life cycle management, improve product presentation)
- New molecular entities are very few

Likely indicates emergence of generic products at the end of patent protection

Oral Nanomedicine Products by Disease Area and API Name (Source: PharmaCircle)



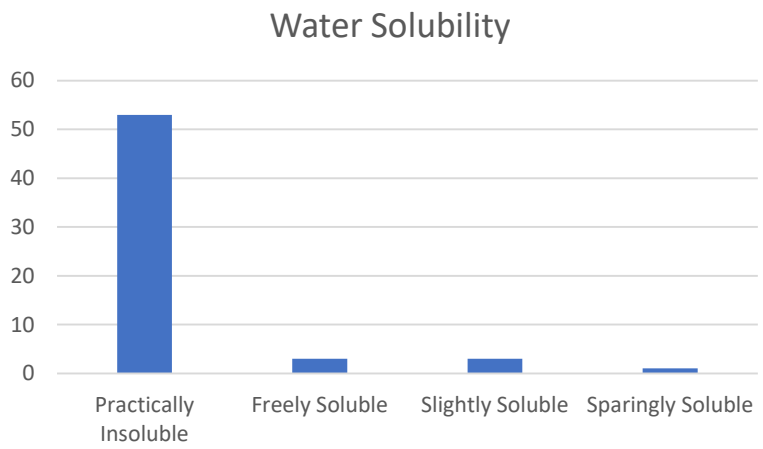


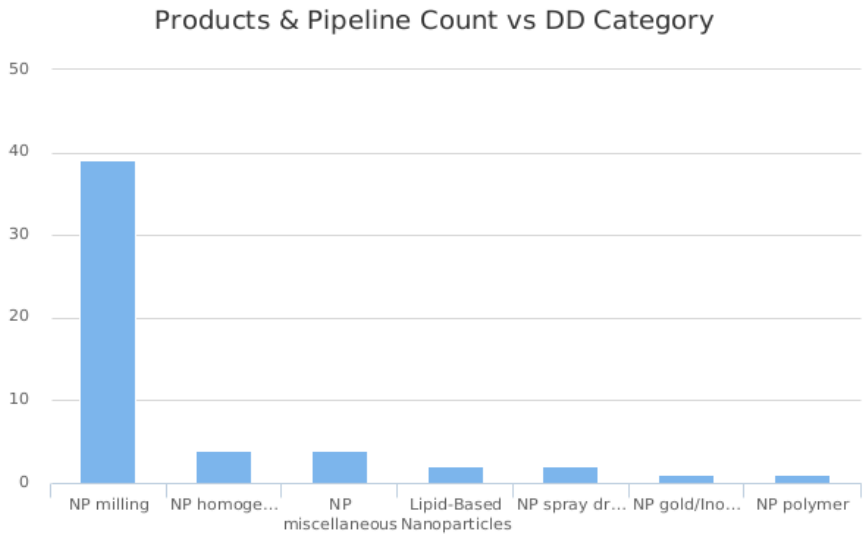
- Broad therapeutic applications
- Generics counted in disease area

Original products discussed in later section

New Ph3 discussed in later section

Oral Nanomedicine Products by Solubility and Drug Delivery Technology
(Source: Pharmacircle)





- Most compounds in oral nanomedicines are practically insoluble

- Nanoparticle milling is the most prevalent category

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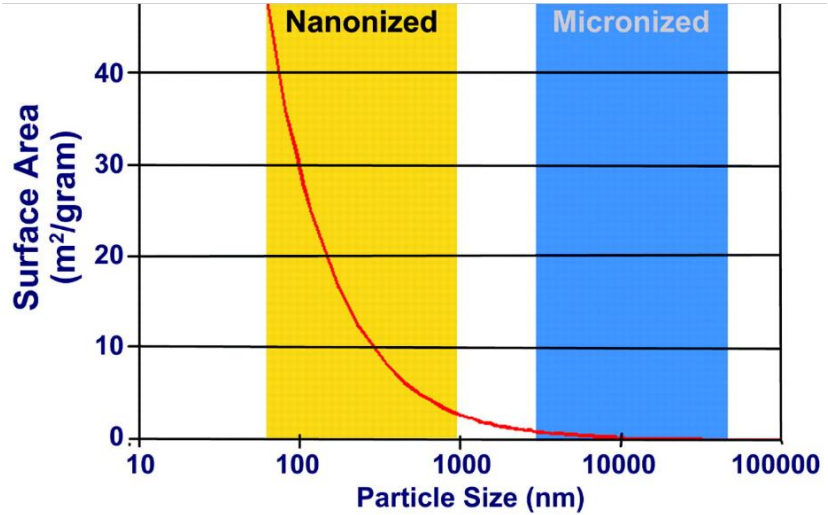
Nanosizing

- Tremendous increase in surface area which directly correlates to an increase in dissolution rate.



Toxicologic Pathology, 2008, 36:43-48

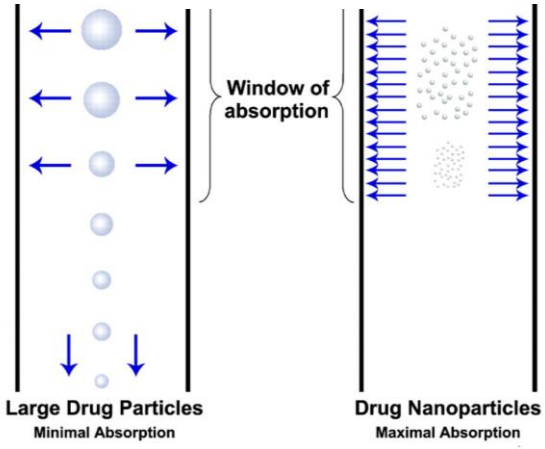
- Particularly suited to compounds with dissolution rate limiting absorption

factors that control the rate of drug dissolution are expressed by the Noyes Whitney

$$D(solid)/dt = -(D * SA/h) * (Cs-C)$$

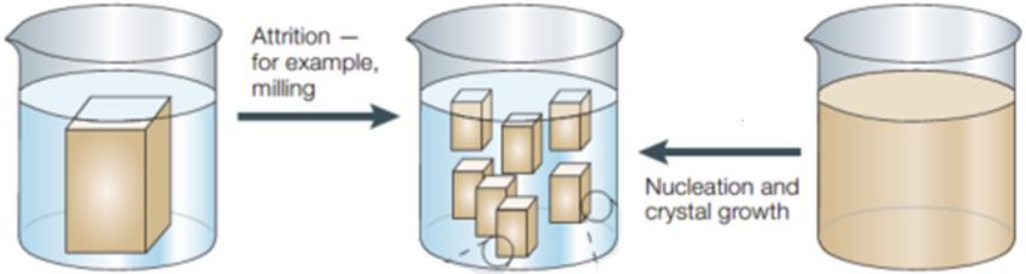
first order drug absorption rate of drugs.

$$dA/dt = Ka * Cs$$



Relevant Technologies

Nature Reviews Drug Discovery, 2004, 3, 785–796



typically sized between 150 and 500 nm

Media Milling

Homogenization

Controlled crystallization

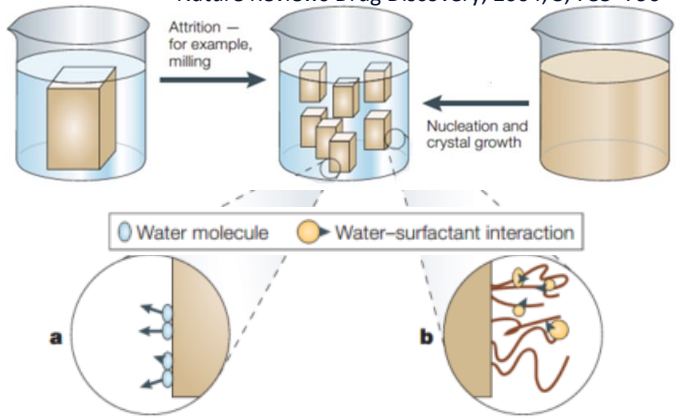
Suspension or Solid dosage form: spray drying, granulation or lyophilization
Blending with other excipients to produce either a tablet or capsule formulation

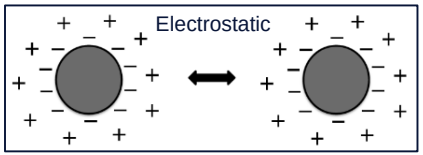
Essential that dosage form releases the nanoparticles in the intestinal media

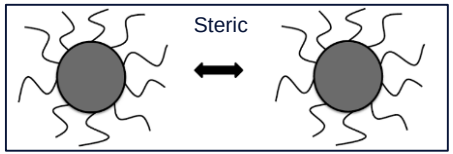
Stabilization of newly formed surfaces to prevent agglomeration

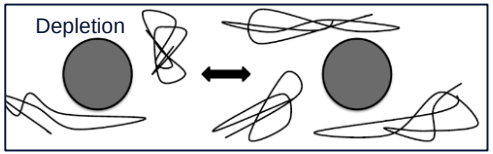
- Unstabilized hydrophobic crystal surface directly contacting water molecules - unfavorable energetics (a), lead to crystal agglomeration
- Surfactant/polymer-stabilization reduces interfacial tension and reduce tendency to agglomerate (b)
- Mechanisms of stabilization
  - Electrostatic: ionic materials (SDS, Na docusate), ≥ ± 30mV recommended
  - Steric: non-ionic materials (PEG, PVA, polysorbates), ≥ ± 10mV recommended
  - Depletion: free non-adsorbing polymer in solution, excluded volume effect above a certain polymer concentration

Nature Reviews Drug Discovery, 2004, 3, 785–796









Eur J Pharm Biopharm, 2021, 165, 345-360

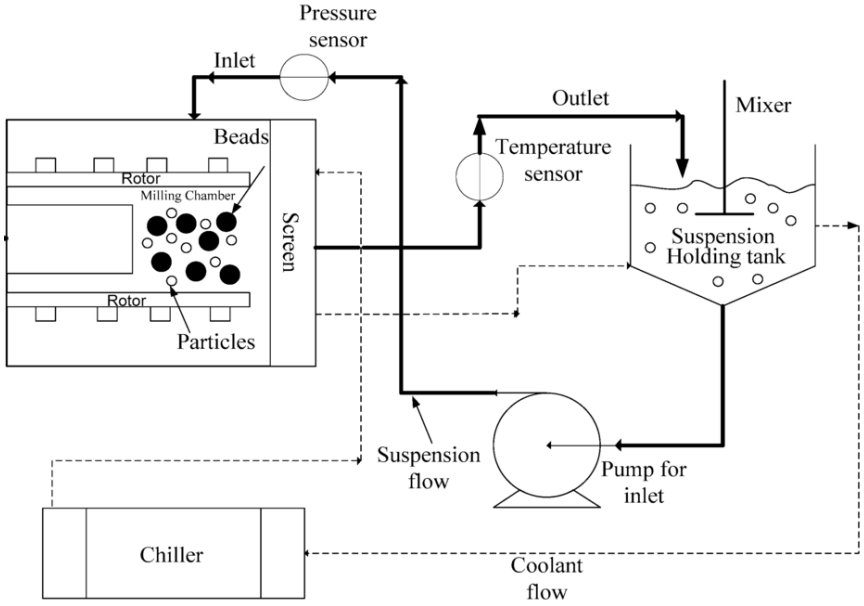
- Combinations preferred for long term stabilization
- Different drugs, different processes require different stabilizers

Wet stirred media milling (WSMM)

- Drug suspended in water or a suitable buffer, and the stabilizer(s)
- Milling media: ceramic or polystyrene beads/pearls 0.2 – 1.0 mm in size
- Mechanical energy to physically break down crystalline drug by shear

Concerns:

- Solid-State changes
- Stability
- Contamination due to media (bead) wear



Eur. J. Pharm. Sci. 2014, 51, 75–86

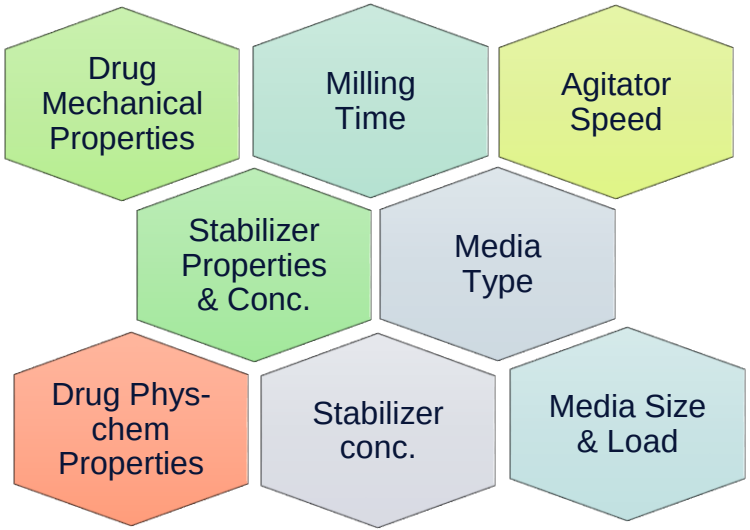
Formulation/Process considerations

Critical parameters for WSMM include:

Drugs crystal shape and brittleness

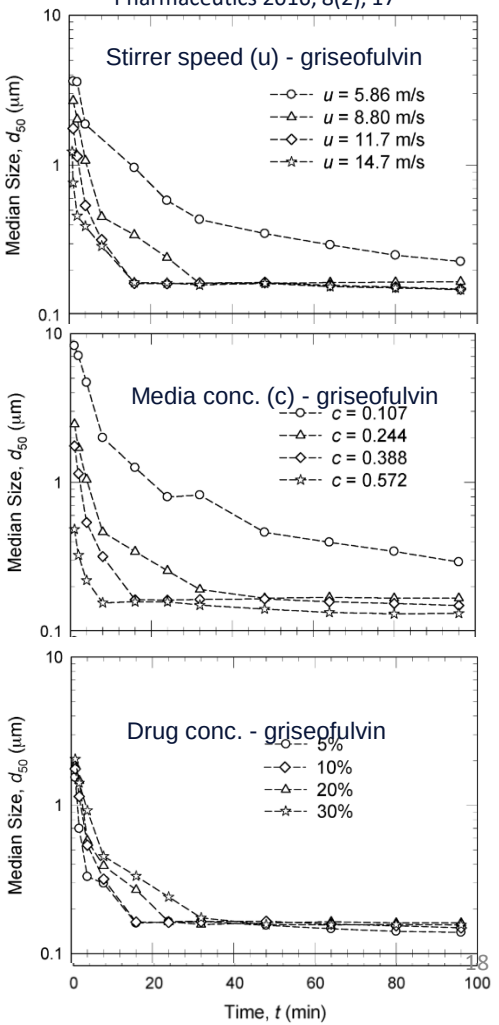
Combinations of stabilizers

Drugs with high crystal energy (high melting point), low solubility are the best candidates

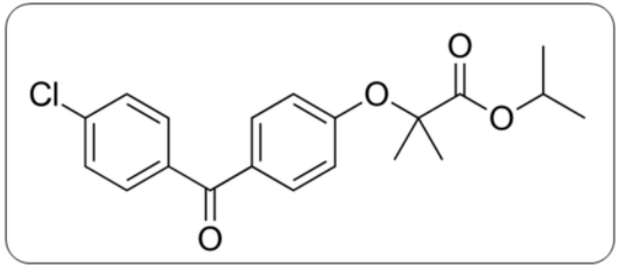


Smaller beads - smaller PS

Pharmaceutics 2016, 8(2), 17



Fenofibrate formulations



- Antilipidemic medication – hypercholesterolemia and hypertriglyceridemia
- Prodrug, hydrolyses to fenofibric acid
- BCS class II (solubility: ~6 ug/mL; logP: 5.6, melting point: 79° to 82°C
- Poor oral BA impaired by aqueous solubility and dissolution rate, original F required dosing with food (35% increase BA), compliance concerns

- Each formulation aims to increase BA by particle size reduction
- Triglide and tricor are current
- Tricor – three versions, Tricor 1 capsule & 2 tablet micronized, Tricor NP

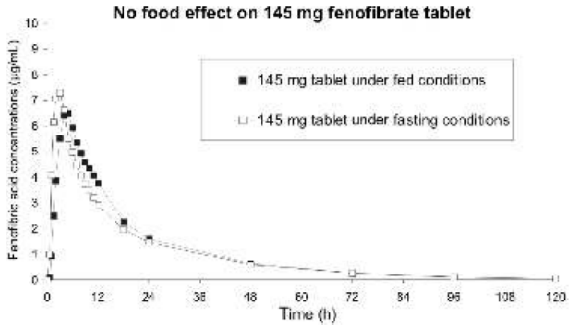
Cardiol Res. 2013 Apr; 4(2): 47–55.

Formulation	Products
Non-micronized	Fenoglide MeltDose tablets
	Lipofen® Lidose capsule
	Antara® Micronized capsule
Micronized	Lofibra® Film-coated tablet (formerly Tricor®2) Micronized capsule (formerly Tricor®1)
	Triglide® IDD-P
Nanonization	Tricor® Nanocrystal
Salt	Trilipix

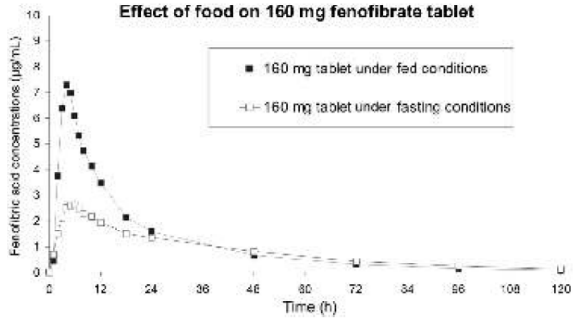
Tricor® Nanocrystal – Abbott/Abbvie

- Wet milling: stabilizers Na Docusate, SLS, HPMC → tablets: lactose, MCC, cPVP, Mag stearate and film-coating

- Tricor NP (145 mg) compared to Tricor 2 (160 mg) – no food effect



Int J Clin Pharmacol Ther 2006; 44:64–70



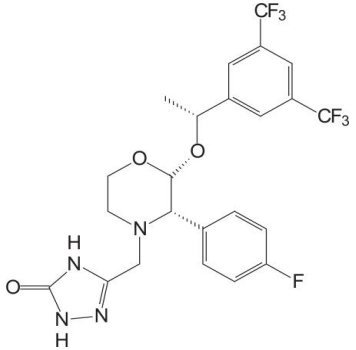
- Patients received fenofibrate 160 mg/day for ~ 8.5 months (range 6–28 mo) before switching to fenofibrate 145 mg/day
- Net gain after the switch was 11%, attributed to improved patient compliance

	No. (%) of Patients		
Patient Group	↓ LDL	↑ HDL	↓ TG
≥ 10% improvement			
Statin (n=68)	6 (9)	3 (4)	13 (19)
No statin (n=62)	8 (13)	1 (2)	19 (31)
All patients (n=130)	14 (11)	4 (3)	32 (25)
	↑ LDL	↓ HDL	↑ TG
≥ 10% worsening			
Statin (n=68)	1 (1.5)	1 (1.5)	1 (1.5)
No statin (n=62)	2 (3)	0 (0)	8 (13)
All patients (n=130)	3 (2)	1 (0.8)	9 (7)

↓ = decrease; ↑ = increase; LDL = low-density lipoprotein cholesterol; HDL = high-density lipoprotein cholesterol; TG = triglycerides.

Pharmacotherapy Volume 28, Number 5, 2008

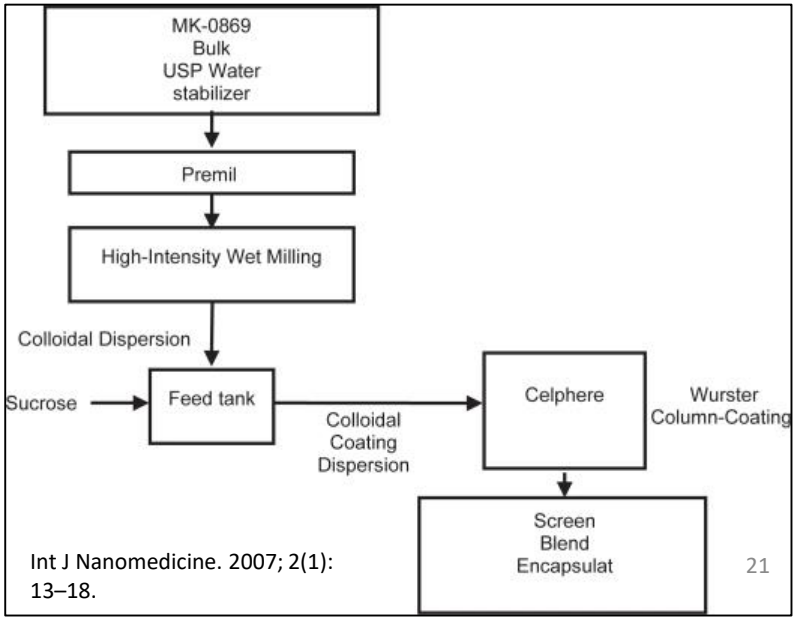
Aprepitant Formulation - Emend®/ Merck



- Antiemetic agent for prevention of chemotherapy-induced nausea and vomiting
- BCS class IV (free base solubility: 3 – 7 µg/mL, melting point: 254°C, logP: 4.8)
- Sub-proportional increases exposure and a positive food effect with micronized formulation

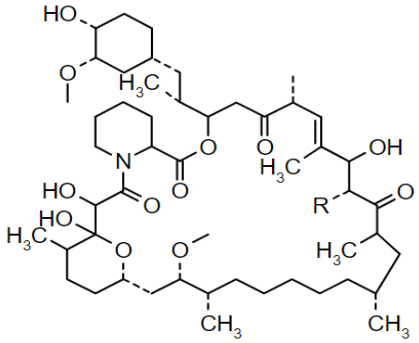
- Nanomilled formulation (licensed from Elan) key to success
- Process: nanomilling with SLS, HPC-SL → ~150 nm → bead coating (600 µm) → encapsulation (40, 80, 125 mg)

- 3–4x increase in bioavailability with the nanoparticle formulation compared with the alpine milled (mean 5 micron) drug formulation
- Food effect at 100-mg dose was minimal with the nanoparticle formulation (approximately 40%) compared with the 3–4x food effect observed with the 5 micron drug formulation



Int J Nanomedicine. 2007; 2(1): 13–18.

Sirolimus formulations

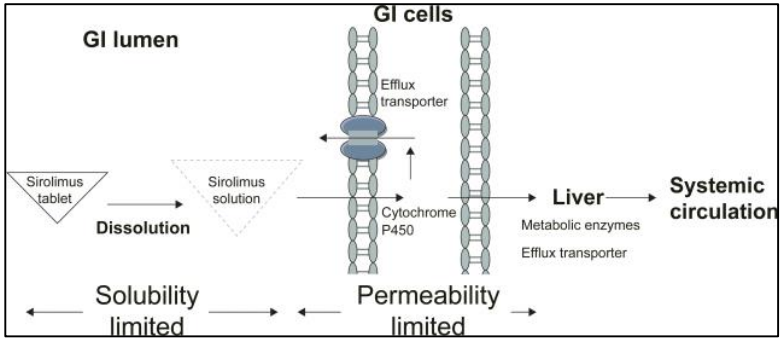


- Immunosuppressive agent, in organ transplant to prevent rejection
- BCS Class II (solubility ~ 2.6 µg/mL, logP: 4.6, melting point: 183-185 °C)

- **Rapamune (Wyeth-Pfizer)**
  - Oral solution (1mg/mL) in polysorbate 80 and Phosal 50 PG
  - Coated tablet (1 mg and 2 mg)
- Process: Nanomilling with poloxamer 188 → sucrose addition → bead coating → direct compression (lactose, PEG8K, PEG20K, MCC, Mag Stearate, and PVP listed as ingredients (from NDA 21-083/S-034, NDA 21-110/S-045))
- Particle size 200 – 350 nm

- Oral bioavailability was found to be 21% higher than conventional formulations of sirolimus

Int J Nanomedicine. 2007 Mar; 2(1): 25–32.



Nano-amorphous Oral Sirolimus Formulation

- NanGenex Inc., Hungary; Druggability Tech, Malta
- Nano-amorphous with particle size <100 nm
- Solvent / anti-solvent precipitation method
- Stabilizers: PVP 90F in Aq phase, SDS in Organic

- Phase 1 completed with reported 28% higher AUC with 40 mg than rapamune 90 mg
- Inter-individual variability reduced

European Journal of Drug Metabolism and Pharmacokinetics (2019) 44:777–785
https://doi.org/10.1007/s13318-019-00562-y

ORIGINAL RESEARCH ARTICLE

Dose Escalation Study to Assess the Pharmacokinetic Parameters of a Nano-amorphous Oral Sirolimus Formulation in Healthy Volunteers

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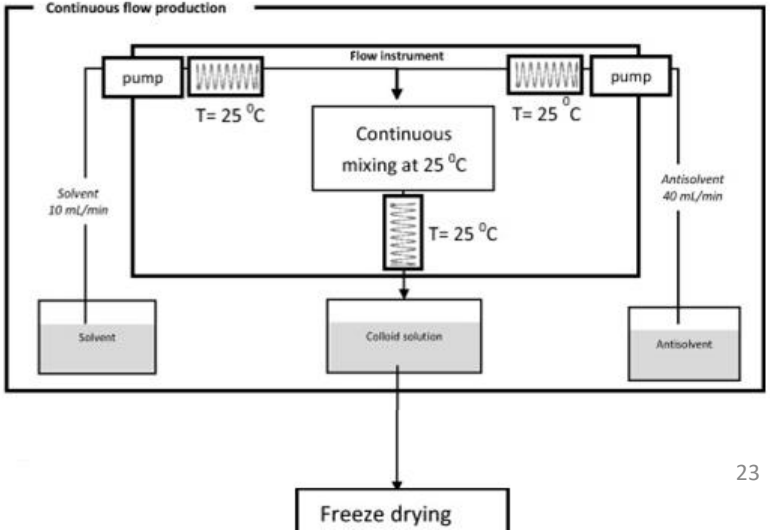

Outline

- **Introduction**
- **Analysis of oral nanomedicines on the market & in late-stage investigation**
  - By product type (NME vs Generic) & approval year
  - By therapeutic area, API solubility
  - By technology employed
- **Focus on prevalent technology**
- **Upcoming therapeutics in late-stage**
- Summary
- Outlook

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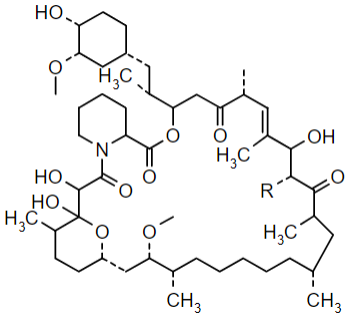
Amphotericin B formulations



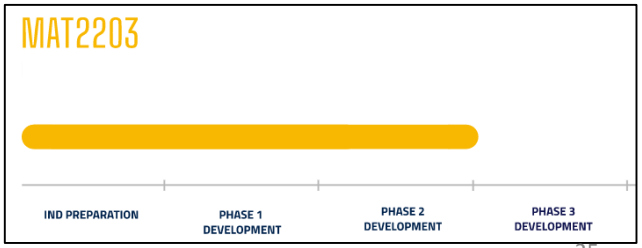
- Polyene antifungal drug discovered in 1955
- BCS Class IV (aqueous solubility: 0.75 µg/mL, melting pt.: > 170 °C, logP: 0.8)
- Broad antifungal activity, but available formulations (4) are parenteral and associated with renal toxicity

- Oral CAMB purported to improve global access / compliance and reduce toxicity

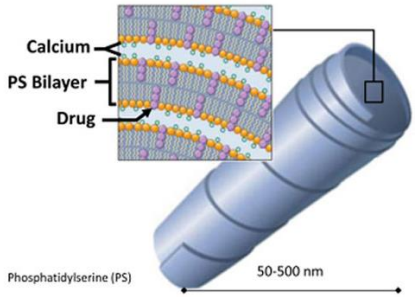
- Oral Encochleated Amp B (CAMB) being developed by Matinas® Biopharma (Bedminster, NJ, USA)
- Phase 3 registration trial for treatment of cryptococcal meningitis Q1 2023
- Phase 2 study against Refractory Mucocutaneous Candidiasis met primary endpoint

Formulation (IV only)	Products
Micellar	(Fungizone, etc.)
Lipid complex	(Abelcet)
Colloidal dispersion	(Amphotec)
Liposomal	(AmBisome)

Adv. Drug Deliv. Rev., 60:6, 2008, 692-701



Oral Encochleated Amphotericin B (CAMB) - Martinas



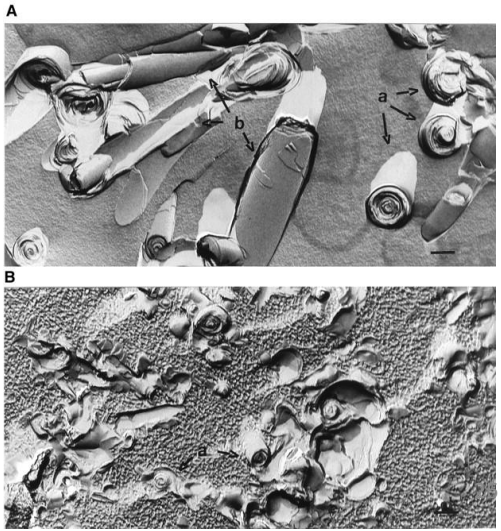
- Stable lipid nanoparticles with multiple spiral-shaped lipid bilayers
- Composed of a negatively charged lipid (i.e., phosphatidylserine) and a divalent cation (i.e., calcium)
- AmpB encapsulated in lipid bilayers
- Suggested to be stable in GI environment (J. Fungi 2020, 6(2), 66)

		Clinical trials			
• Phase IIA, CMC	CAmB	• Improvement of symptoms in 50%–85% at CAmB 400–800 mg.			
		• AE: nausea, dizziness.			
		• No organ disorders.			
• Phase II, VVC	CAmB vs. fluconazole		CAmB 200 mg	CAmB 400 mg	Fluconazole 150 mg
		Clinical cure	52 %	55 %	75 %
		Mycological response	36 %	32 %	84 %
		Overall response	16 %	14 %	69 %
		non-serious AE	22 %	27 %	9 %

CMC, chronic mucocutaneous candidiasis; VVC, vulvovaginal candidiasis;

J. Fungi 2020, 6(2), 66

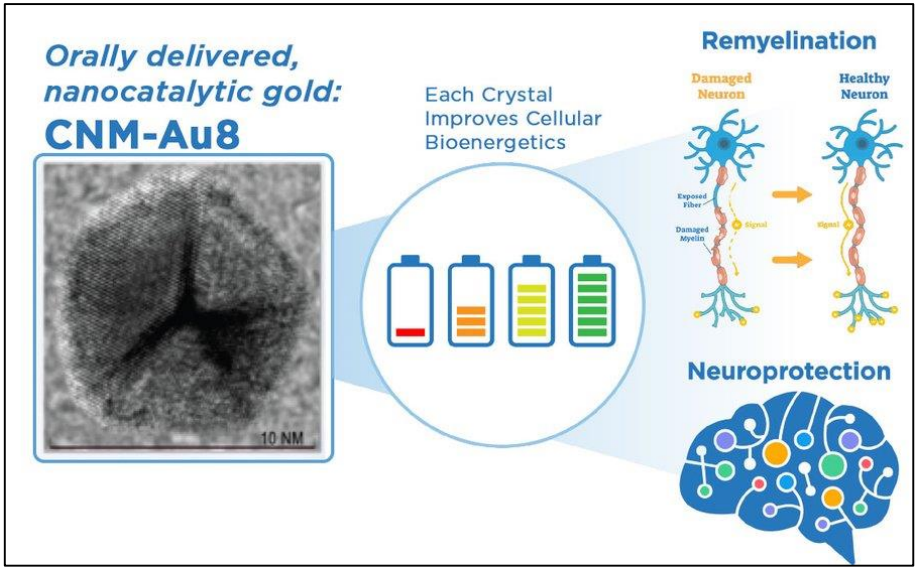
- Results are inferior to fluconazole
- Authors suggest higher doses and longer duration of treatment would get the desired performance



Experimental therapeutics 2000; 44:6

CNM-Au8 / Gold Nanocrystals – Clene Energy

- Nanocrystals of gold (13 nm average diameter) in the shape of hexagonal bi-pyramids, pentagonal bi-pyramids, octahedrons, and tetrahedrons
- Suspended in USP purified deionized water buffered with 6.5 mM sodium bicarbonate ($NaHCO_3$)
- Unlike bulk gold (considered inert), nanocrystals of gold can catalyze oxidation – reduction reactions
- MoA proposed to be oxidation of nicotinamide adenine dinucleotide hydride (NADH) to the critical energetic co-factor, NAD^+ involved in process of myelination



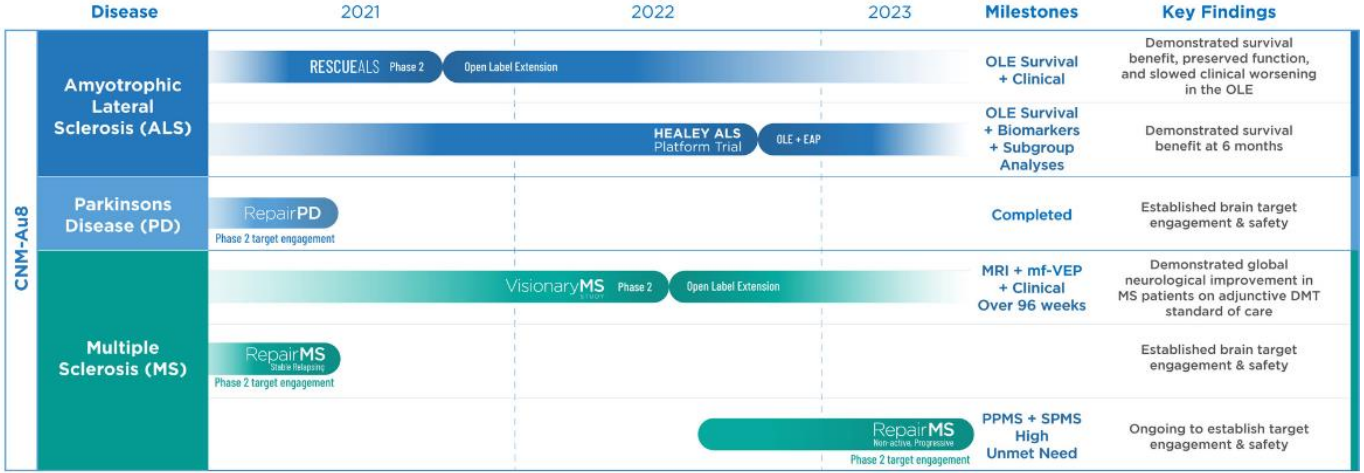
GENEDGE Genetic Engineering & Biotechnology News: Edge
Vol. 4, No. 1, September 27, 2022

pp. 712–718
DOI: 10.1089/genedge.4.1.116

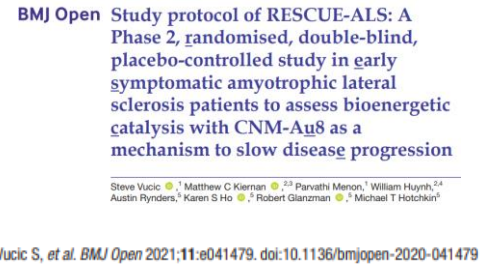
Nanotechnology

Clene Energy: Nanocrystal Developer Pursues Remyelination vs. MS, ALS

CNM-Au8 / Gold Nanocrystals

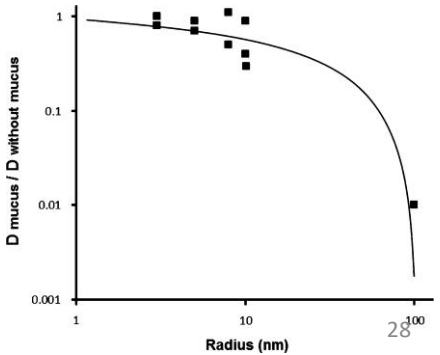


- Patients receive 30 mg of CNM-Au8, once daily by oral administration
- Slowed disease progression and there was evidence of long-term survival benefit
- **Orally bioavailable and suggest crosses the blood–brain barrier**


BMJ Open Study protocol of RESCUE-ALS: A Phase 2, randomised, double-blind, placebo-controlled study in early symptomatic amyotrophic lateral sclerosis patients to assess bioenergetic catalysis with CNM-Au8 as a mechanism to slow disease progression

Steve Vucic, Matthew C Kiernan, Parvathi Menon, William Huynh, Austin Rynders, Karen S Ho, Robert Glanzman, Michael T Hotchkin

Vucic S, *et al. BMJ Open* 2021;**11**:e041479. doi:10.1136/bmjopen-2020-041479



Eur. J. Pharm. Sci. 2013, 49, 272–277

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Summary

- Marketed oral nanoparticle medicines are predominantly nano-crystals that are:
  - produced by wet milling
  - solid dosage forms
  - BCS class II, low dose therapies

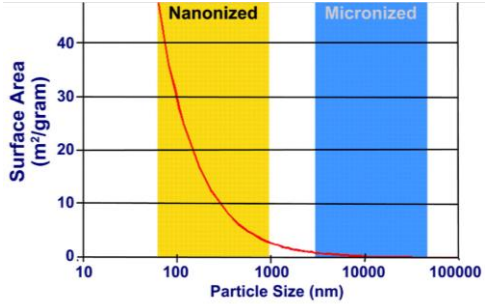
- Clinical data suggests:
  - reduction/elimination of food effect
  - improved compliance
  - improved exposure

- Limited candidates in Phase 3
  - CAMB – first oral Amp B formulation
  - CNM-Au8 – oral inorganic NP formulation indicating oral uptake of intact NPs

Outlook

- Preparation of sub-100 nm drug particles and continuous processing
- Amorphous nanomedicines
- Higher drug loading formulations
- Platforms beyond nano-crystals may allow application to BCS/DCS IV compounds by targeted delivery and permeation enhancement

Toxicologic Pathology, 2008, 36:43-48



$$\text{Amount Absorbed} = \int_0^T P_{eff} \times A \times Cdt$$

$$MAD = P_{eff} \times C_{eq} \times A \times T$$

Brouwers , Brewster and Augustigns 2008

Design of a Re-Dispersible High Drug Load Amorphous Formulation

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[b] Current Affiliation: Bristol Myers Squibb, NJ, USA
[c] Current Affiliation: BeiGene, USA

Journal of Pharmaceutical Sciences 112 (2023) 250–263

↑ 90% drug loading intermediate

Formulation and Scale-Up of Fast-Dissolving Lumefantrine Nanoparticles for Oral Malaria Therapy

Madeleine Armstrong[a], Leon Wang[a], Kurt Ristroph[a], Chang Tian[a], Jiankai Yang[b], Lirong Ma[b], Santipharp Panmai[b], Donglu Zhang[c], Karthik Nagapudi[c], Robert K. Prud'homme[a,*]

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Journal of Pharmaceutical Sciences 000 (2023) 1–9


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