FONDAZIONE PER LA RICERCA FARMACOLOGICA GIANNI BENZI ONLUS

UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

XVI FORESIGHT TRAINING COURSE
Repurposing to cover unmet needs: the current scenario in Europe and the proposed changes to the Pharmaceutical Legislation

PHARMACEUTICAL TECHNOLOGY PLATFORMS REPURPOSING ACTIVE PHARMACEUTICAL INGREDIENT

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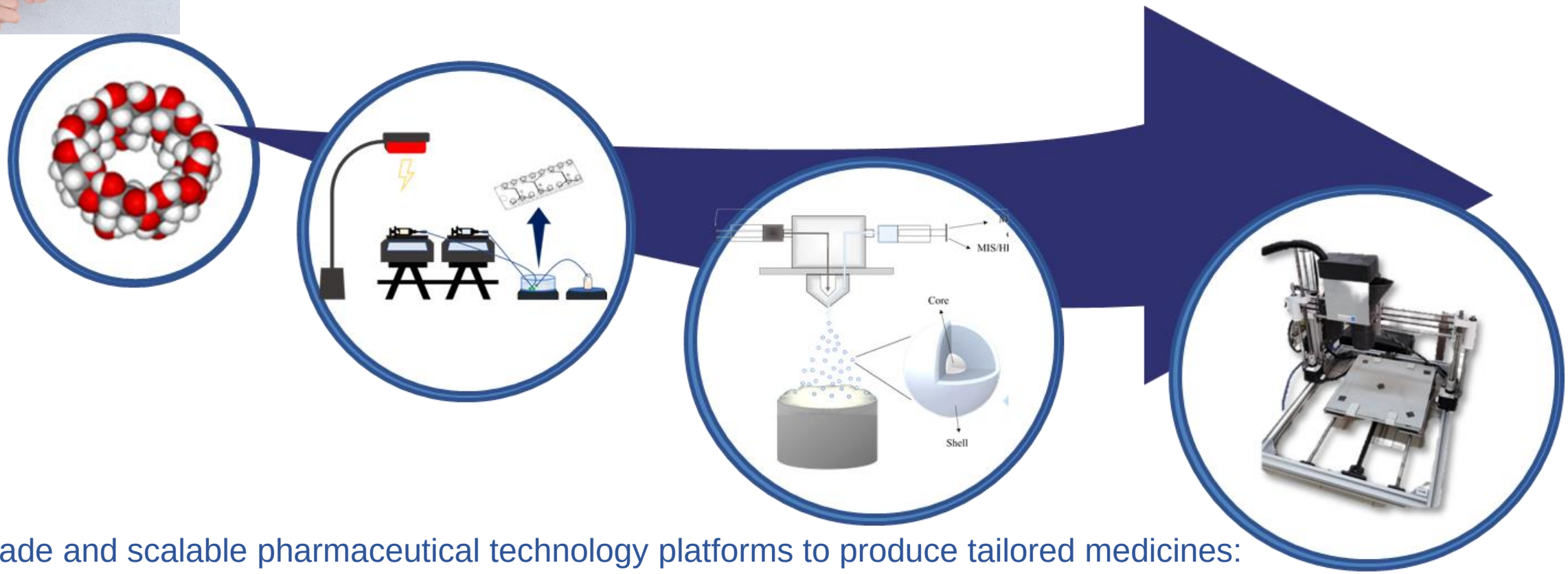
Pharmaceutical Technology Platforms



Lab-made and scalable pharmaceutical technology platforms to produce tailored medicines:

- Cyclodextrins and their derivatives (CycloDES) to produce **molecular**-therapeutics;
- Microfluidics to produce **nano**-therapeutics;
- Microfluidics, prilling and spray-drying technologies to produce **micro**-therapeutics;
- Direct powder extrusion 3D printing to produce **macro**-therapeutics.

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Outline

Pharmaceutical technology platforms repurposing drugs

Case studies:

Successful drug repurposing examples: Minoxidil and Celecoxib;

Diazoxide repurposing for treating Friedreich's ataxia;

Dasatinib/HP-β-CD inclusion complex based aqueous formulation as a promising tool for the treatment of paediatric neuromuscular disorders;

Direct cyclodextrin-based powder extrusion 3D printing for one-step production of the BCS class II model drug niclosamide.

Pharmaceutical technology platforms repurposing active pharmaceutical ingredient

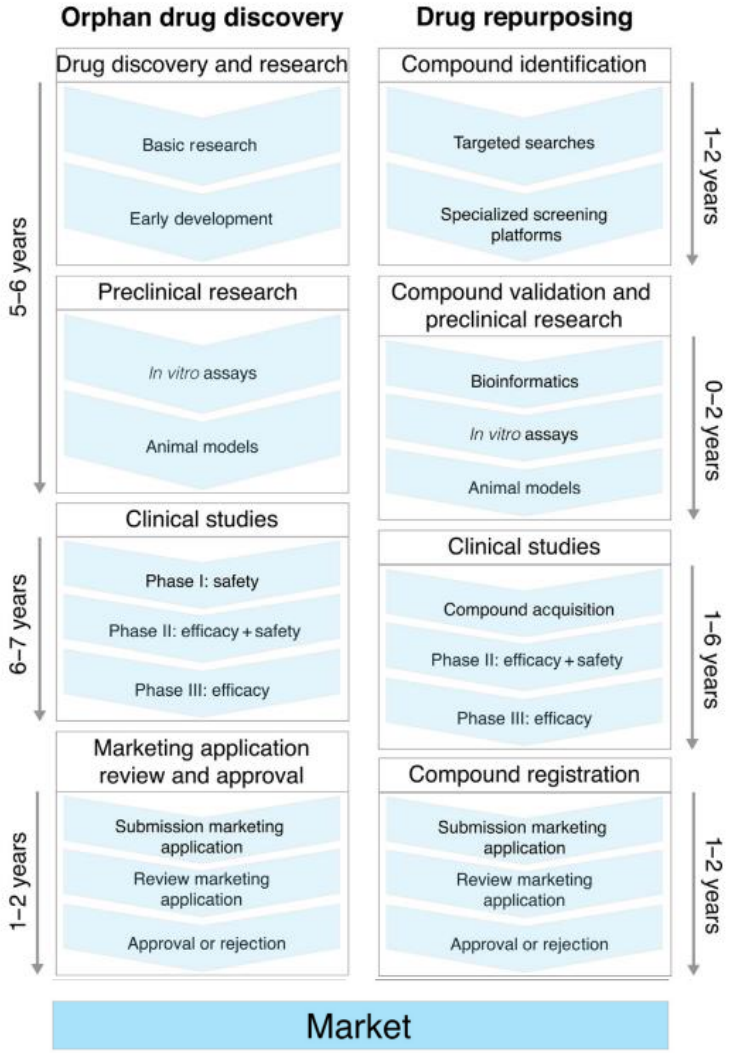
Drug repurposing (also called drug repositioning, reprofiling or re-tasking) **is a strategy for identifying new uses for approved or investigational drugs that are outside the scope of the original medical indication.**

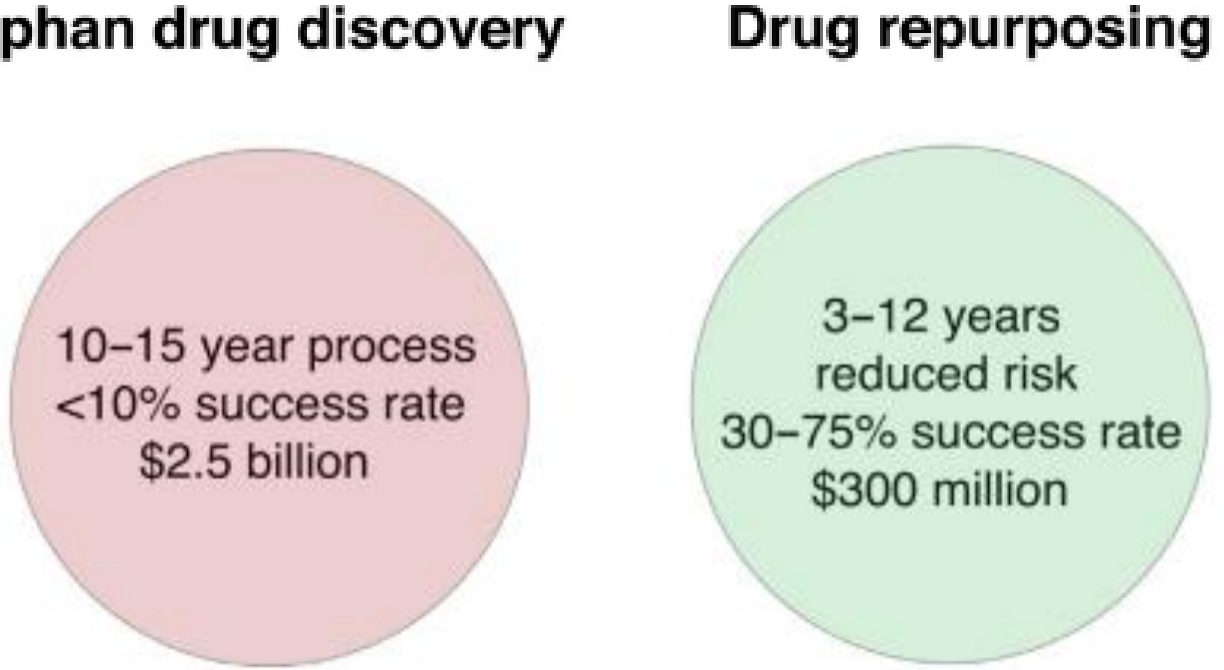
Drug repurposing: progress, challenges and recommendations. *Nat. Rev. Drug Discov.* doi:10.1038/nrd.2018.168

Advantages:

- the risk of failure is lower;
- the time frame for drug development can be reduced;
- less investment is needed.

Pharmaceutical technology platforms repurposing active pharmaceutical ingredient





Drug Repurposing for Rare Diseases. *Trends in Pharmacological Sciences*, April 2021, Vol. 42, No. 4. doi.org/10.1016/j.tips.2021.01.003

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Pharmaceutical technology platforms repurposing active pharmaceutical ingredient

Historically, drug repurposing has been largely opportunistic and serendipitous

Once a drug was found to have an off-target effect or a newly recognized on-target effect, it was taken forward for commercial exploitation.

Indeed, the most successful examples of drug repurposing so far have not involved a systematic approach

Drug repurposing: progress, challenges and recommendations. *Nat. Rev. Drug Discov.* doi:10.1038/nrd.2018.168

Table 1 | **Selected successful drug repurposing examples and the repurposing approach employed**

Drug name	Original indication	New indication	Date of approval	Repurposing approach used	Comments on outcome of repurposing
Zidovudine	Cancer	HIV/AIDS	1987	In vitro screening of compound libraries	Zidovudine was the first anti-HIV drug to be approved by the FDA
Minoxidil	Hypertension	Hair loss	1988	Retrospective clinical analysis (identification of hair growth as an adverse effect)	Global sales for minoxidil were US$860 million in 2016 (Questale minoxidil sales report 2017; see Related links)
Sildenafil	Angina	Erectile dysfunction	1998	Retrospective clinical analysis	Marketed as Viagra, sildenafil became the leading product in the erectile dysfunction drug market, with global sales in 2012 of $2.05 billion[8]
Thalidomide	Morning sickness	Erythema nodosum leprosum and multiple myeloma	1998 and 2006	Off-label usage and pharmacological analysis	Thalidomide derivatives have achieved substantial clinical and commercial success in multiple myeloma
Celecoxib	Pain and inflammation	Familial adenomatous polyps	2000	Pharmacological analysis	The total revenue from Celebrex (Pfizer) at the end of 2014 was $2.69 billion (Pfizer 2014 financial report; see Related links)
Atomoxetine	Parkinson disease	ADHD	2002	Pharmacological analysis	Strattera (Eli Lilly) recorded global sales of $855 million in 2016
Duloxetine	Depression	SUI	2004	Pharmacological analysis	Approved by the EMA for SUI. The application was withdrawn in the US. Duloxetine is approved for the treatment of depression and chronic pain in the US
Rituximab	Various cancers	Rheumatoid arthritis	2006	Retrospective clinical analysis (remission of coexisting rheumatoid arthritis in patients with non-Hodgkin lymphoma treated with rituximab[144])	Global sales of rituximab topped $7 billion in 2015 (REF.[145])
Raloxifene	Osteoporosis	Breast cancer	2007	Retrospective clinical analysis	Approved by the FDA for invasive breast cancer. Worldwide sales of $237 million in 2015 (see Related links)
Fingolimod	Transplant rejection	MS	2010	Pharmacological and structural analysis[146]	First oral disease-modifying therapy to be approved for MS. Global sales for fingolimod

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Pharmaceutical technology platforms repurposing active pharmaceutical ingredient

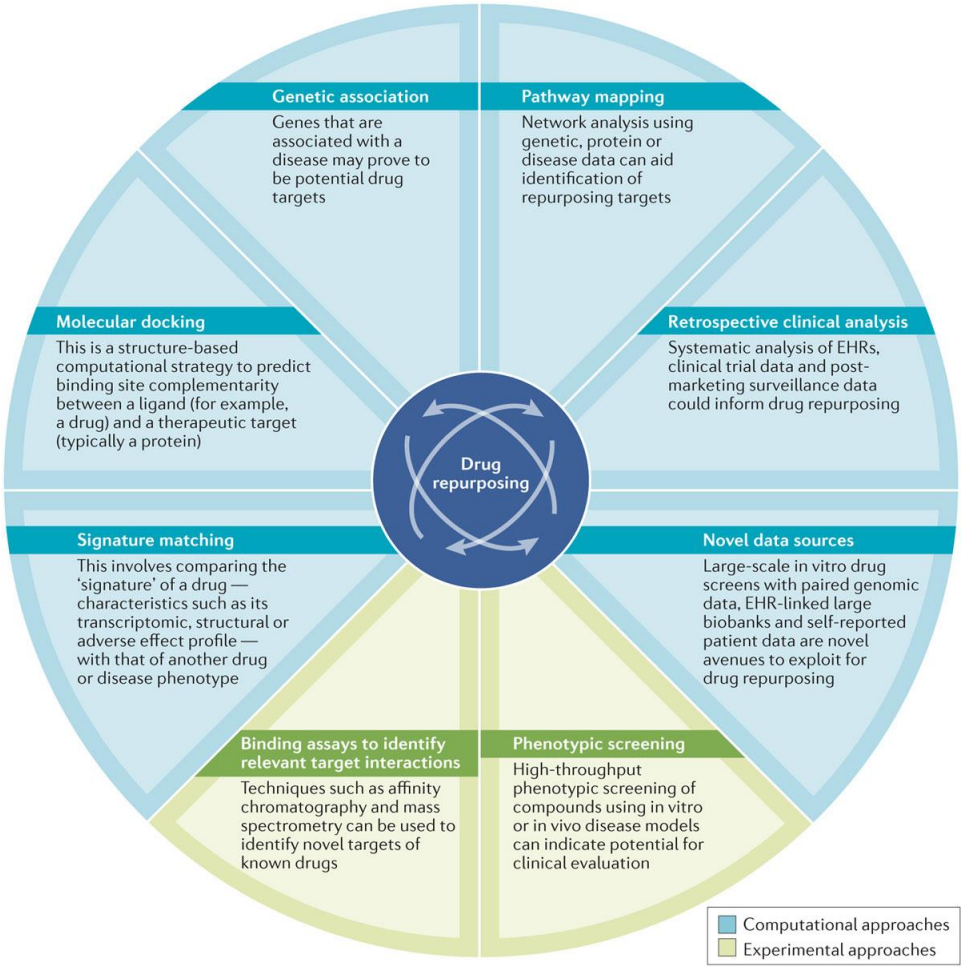
Approaches in use for drug repurposing

Various computational approaches can be used individually or in combination to systematically analyse different types of large-scale data to obtain meaningful interpretations for repurposing hypotheses.

Experimental approaches can also be used to identify repurposing opportunities.

Both approaches are increasingly being used synergistically.

Drug repurposing: progress, challenges and recommendations. *Nat. Rev. Drug Discov.* doi:10.1038/nrd.2018.168



Nature Reviews | Drug Discovery

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Pharmaceutical technology platforms repurposing active pharmaceutical ingredient

Repurposed Drugs may have special formulation requirements

- Overcome limitations associated with the physical-chemical properties of the drug:

1. Poor water solubility;
2. Low permeability trough biological barrier;
3. Inability to reach a specific site of action.

- Improve the chemical/enzymatic stability of the drug;

- Customize the formulation:

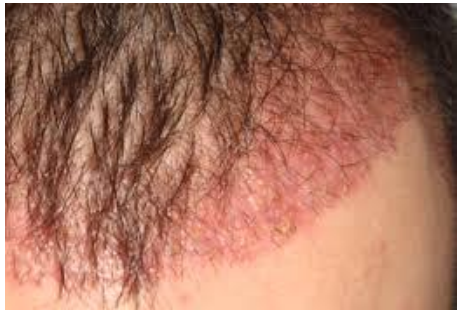
1. Dosage form and composition;
2. Release profile (kinetics, site, time);
3. Age, gender, pathology, tissue, etc.

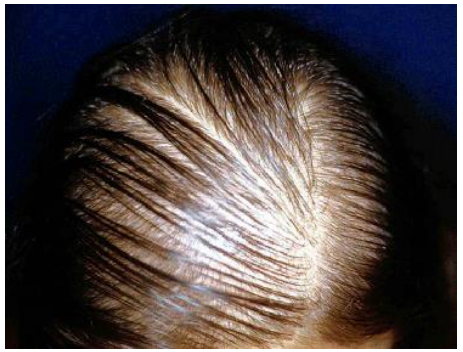
The Example of Minoxidil

Minoxidil: an active ingredient widely used for the treatment of androgenetic alopecia, generally at concentrations between 1% and 5% w/w
Poor Water Solubility: 2.8 mg/mL

Current formulations for topical Minoxidil administration
usually contain high percentages of co-solvents, such as Ethanol and Propylene Glycol, due to low water solubility of the active ingredient.

Disadvantages of currently available formulations:
- severe adverse effects: scalp dryness, irritation, burning, itching, redness, allergic contact dermatitis;
- greasy residue on the scalp, due to the presence of propylene glycol;
- ethanol solvent formulations are inclined to revert minoxidil in insoluble crystalline form with reduction of its bioavailability.





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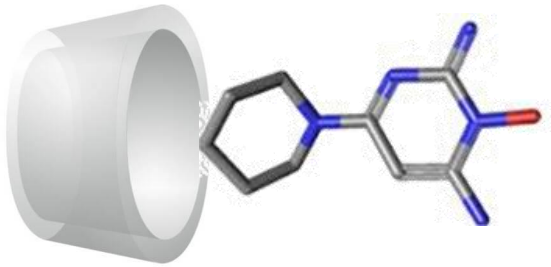

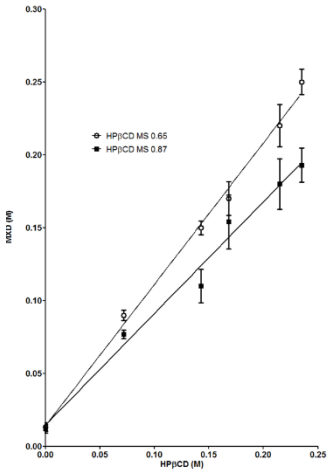

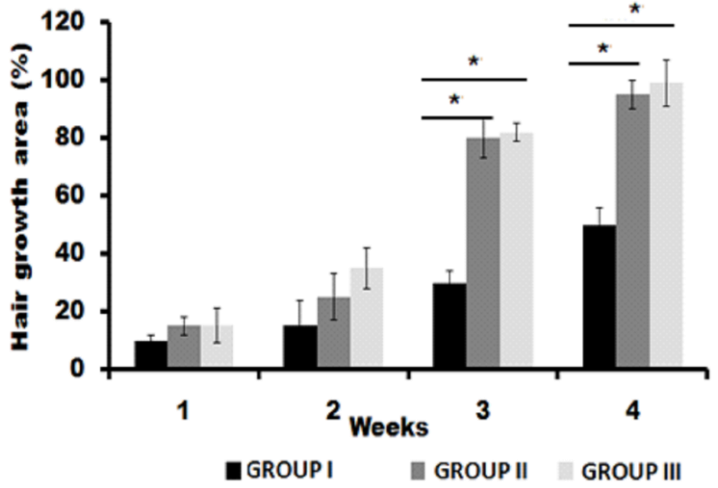

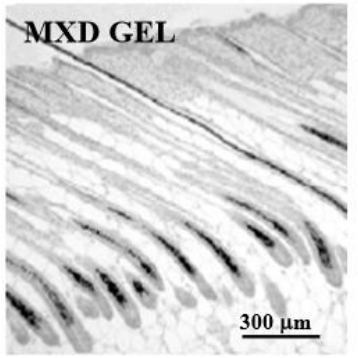

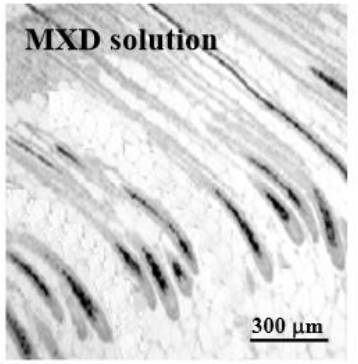

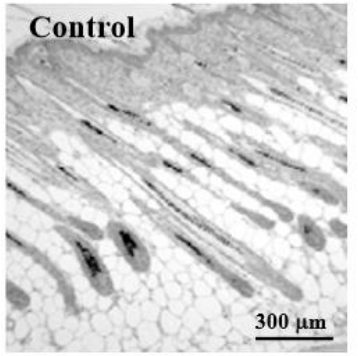

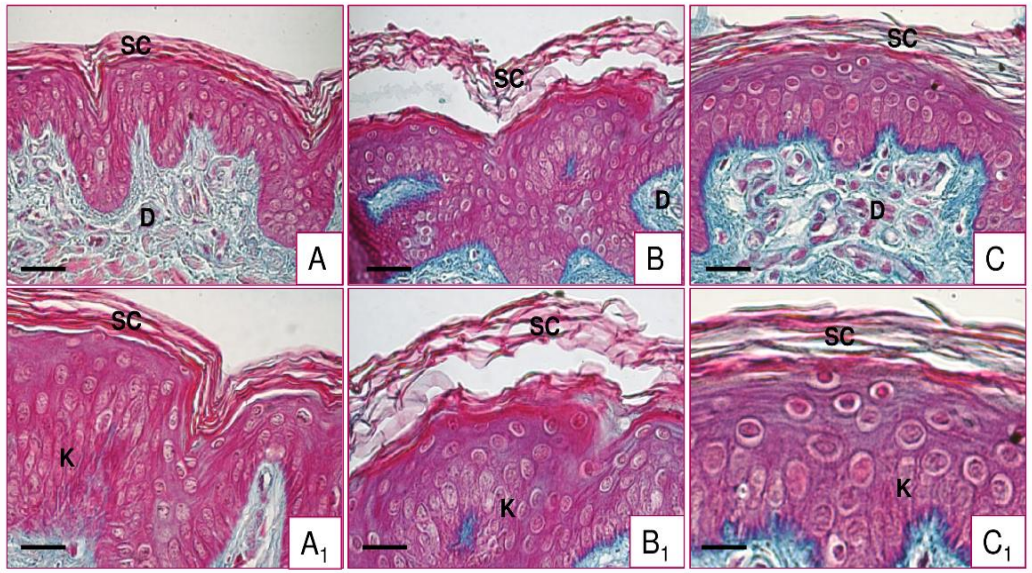

- ✓ enhanced water solubility of minoxidil, due to the cyclodextrin complexation;
- ✓ ethanol and propylene glycol free formulations.

A. Lopedota et al. J Pharm Sci. 2018 Apr;107(4):1046-1054. doi: 10.1016/j.xphs.2017.11.016

D. Tricarico et al. Eur J Pharm Biopharm. 2018 Jan;122:146-157. doi: 10.1016/j.ejpb.2017.10.015

Patent
IT n°1426473, 23/12/2016, titled «Formulazione Farmaceutica per l'uso topico a base di minoxidil e relativo kit».

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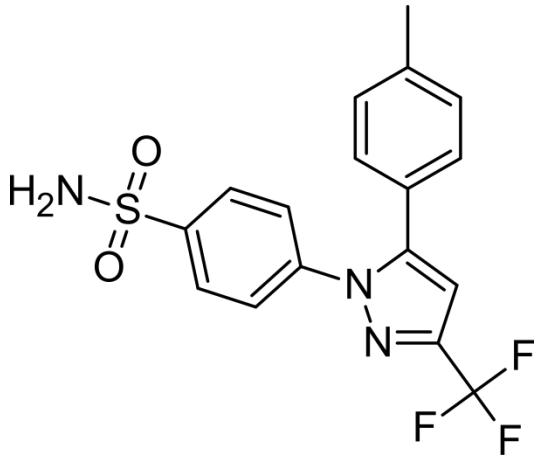
The Example of Celecoxib



Celecoxib (CB), an NSAID, is the first member of the Coxib family selectively inhibiting cyclooxygenase-2 (COX-2).
CB has been repurposed with the new indication for the treatment of familial adenomatous polyposis and is under investigation as antitumor drug for the treatment of bladder cancer.
There are many studies about the potential clinical indications of CB as cancer chemoprevention treatment.

Current formulations for Celecoxib administration
CB is administered orally, as capsule and no liquid formulations are available, due to its poor water solubility.

Disadvantages of currently available formulations:
CB oral delivery is less effective because only a small fraction of the drug reaches the bladder.

A. Lopedota et al. Pharm Res. 2016 Sep;33(9):2195-208. doi: 10.1007/s11095-016-1956-7.

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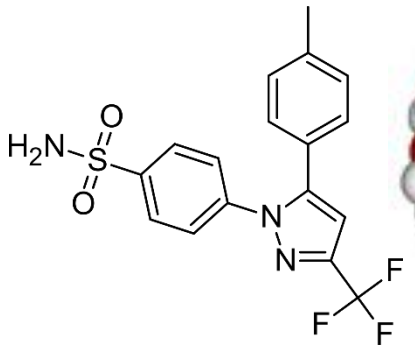

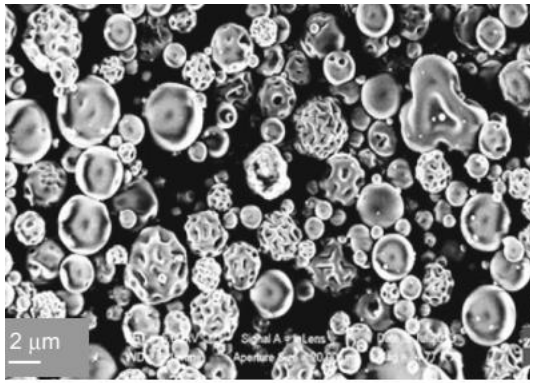

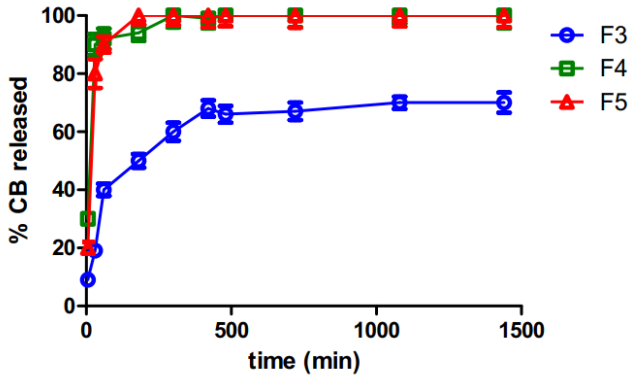

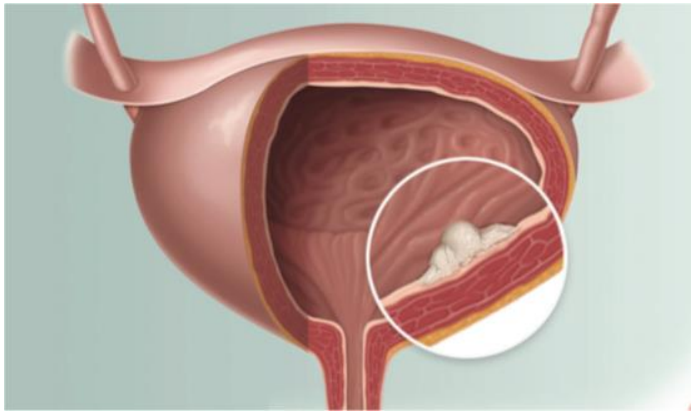

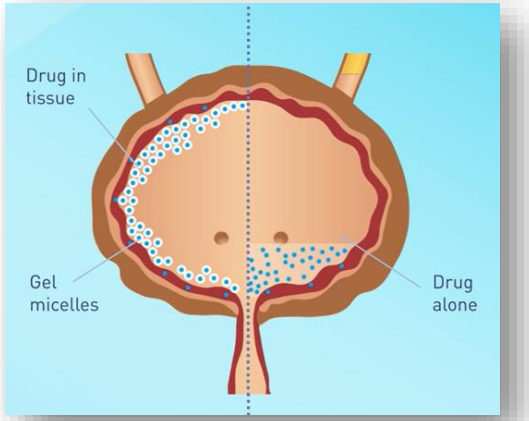

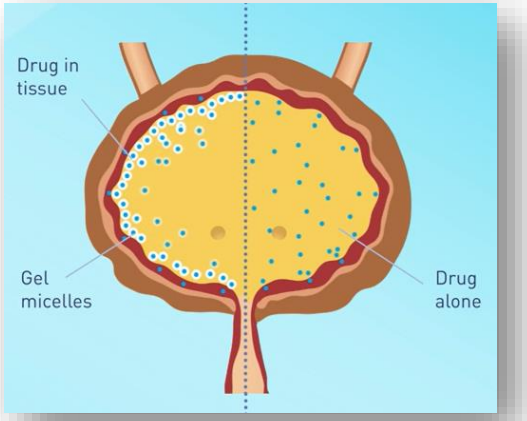

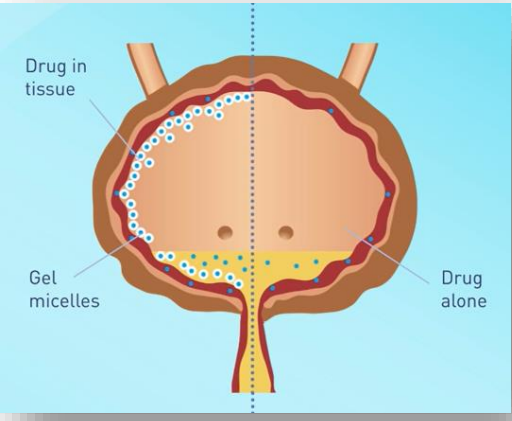

A. Lopedota et al. Pharm Res. 2016 Sep;33(9):2195-208. doi: 10.1007/s11095-016-1956-7.

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Drug repurposing may be particularly attractive for the development of treatments for rare diseases.

Almost 8000 rare diseases exist worldwide, affecting approximately 350 millions people.

Nevertheless, only 5% receive a specific authorized or licensed treatment.

Drug repurposing in rare diseases: Myths and reality. *Therapies (2020). doi.org/10.1016/j.therap.2020.02.006*

Advantages:

- the risk of failure is lower;
- the time frame for drug development can be reduced;
- less investment is needed.

Friedreich's ataxia (FRDA)

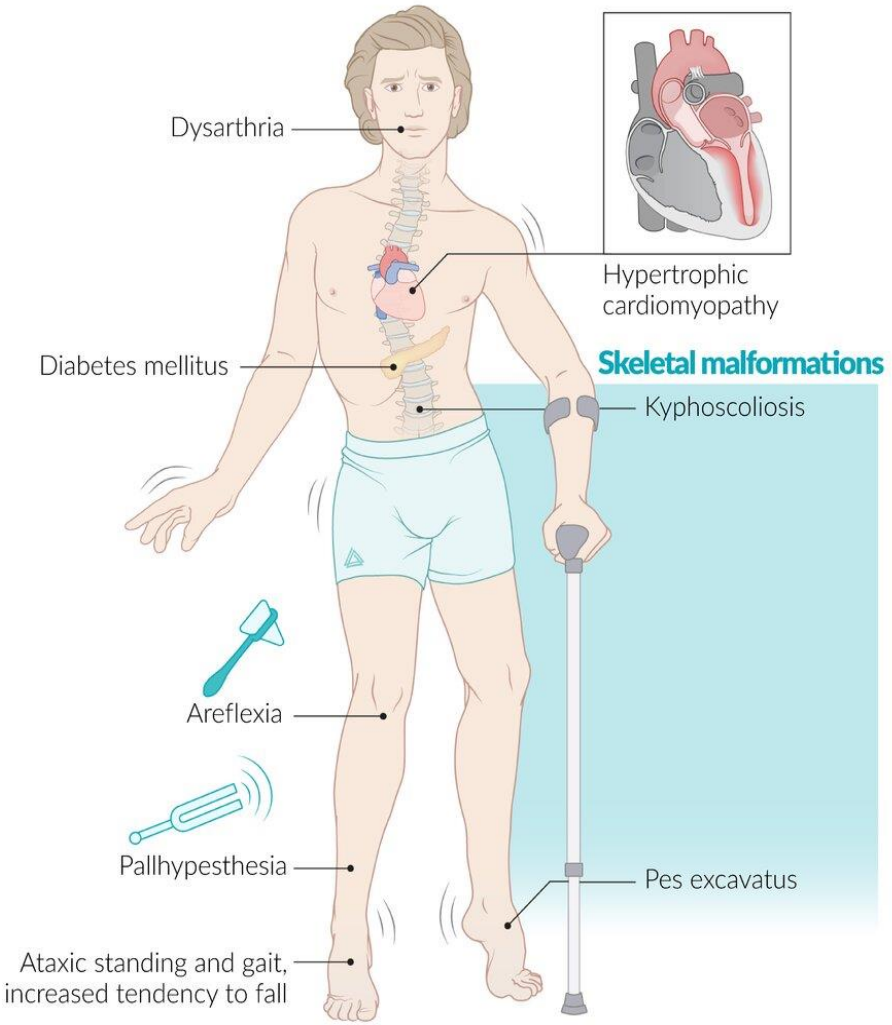
Epidemiology
Incidence: 3-4:100000
Onset of symptoms: childhood and adolescence

Etiology
Autosomal recessive inheritance:
GAA trinucleosite repeat expansion on Chromosome 9 -> reduced expression of frataxin protein -> disorder of mitochondrial iron metabolism -> increased susceptibility to oxidative stress

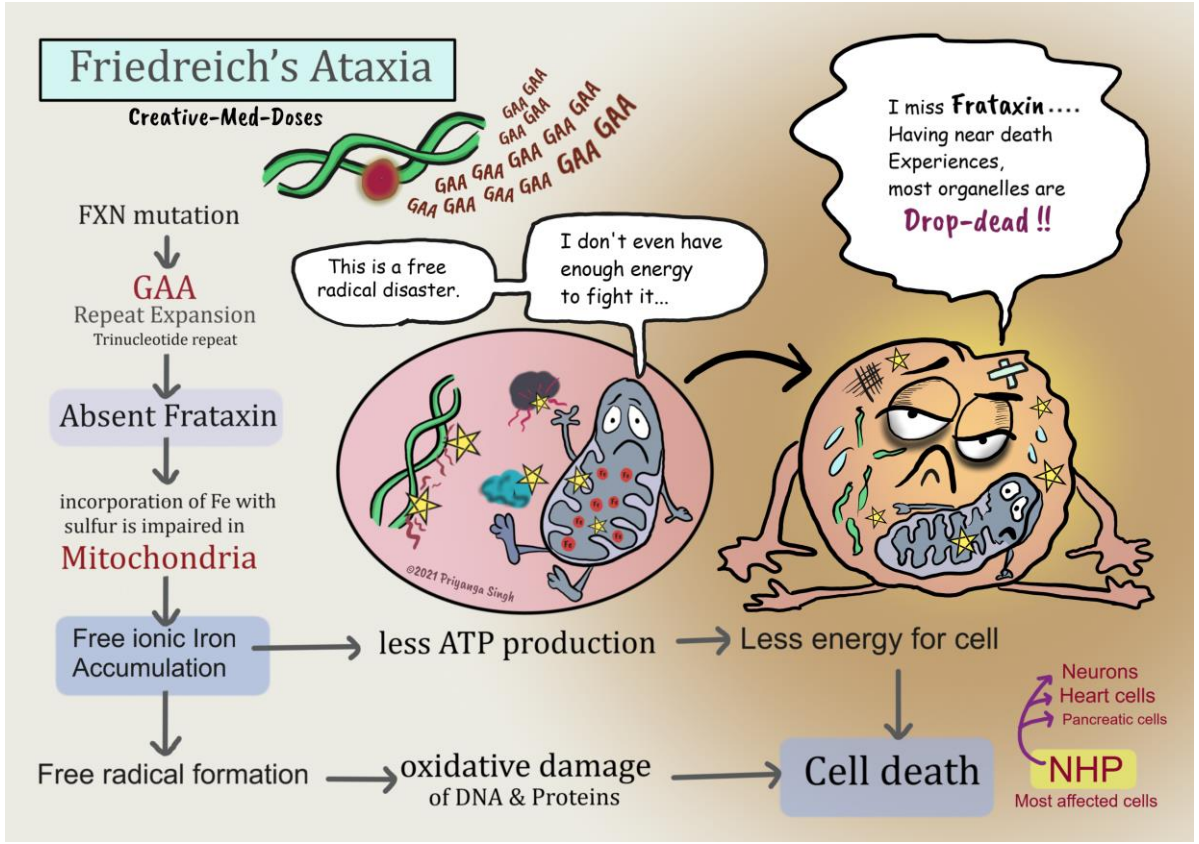
Complications
Prevalent cause of death: cardiomyopathy

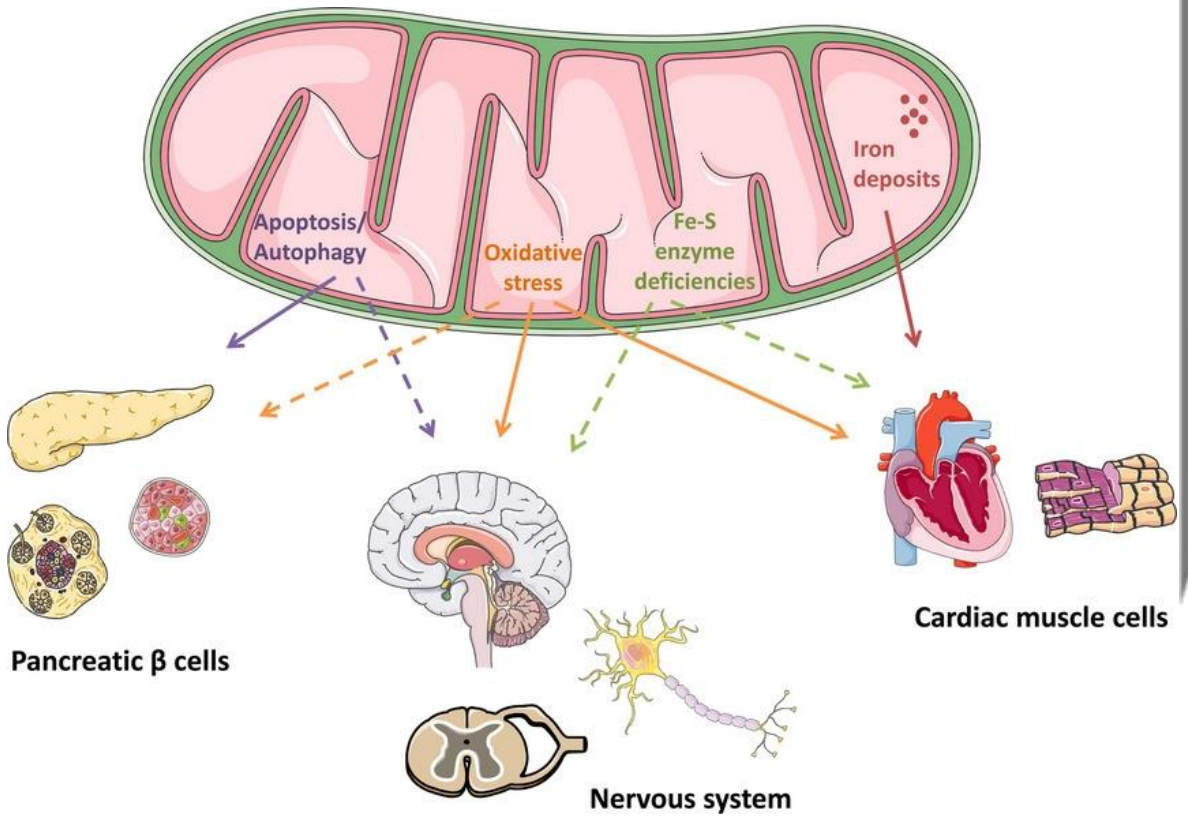
Prognosis
10-15 years after symptom onset most individuals require a wheelchair
Better prognosis with later symptom onset

Life expectancy
Reduced



Friedreich's ataxia (FRDA)





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The Friedreich's Ataxia Treatment Pipeline is a visual tool for communicating the progress of research and development on lead therapeutic candidates.

https://www.curefa.org/research/research-pipeline

FRIEDREICH'S ATAXIA TREATMENT PIPELINE

	DISCOVERY (Finding Potential Therapies/Drugs)	PRE-CLINICAL DEVELOPMENT (Testing in Laboratory)	IND FILED (Investigational New Drug; FDA filing)	PHASE I (Human Safety Trial)	PHASE II (Human Safety And Efficacy Trial)	PHASE III (Definitive Trial)	NDA FILED (New Drug Application; FDA filing)	AVAILABLE TO PATIENTS
Improve Mitochondrial Function & Reduce Oxidative Stress	SKYCLARYS™ (omaveloxolone) – Nrf2 Activator → Reata							
	Vatiquinone (PTC-743) - 15 LO inhibitor → PTC Therapeutics							
	Elamipretide → Children's Hospital of Philadelphia							
	NAD+ and Exercise in FA (ExRx in FA) → Children's Hospital of Philadelphia							
	MIB-626 → Metro International Biotech, LLC							
Modulation of Frataxin Controlled Metabolic Pathways	Leriglitazone → Minoryx Therapeutics							
	IMF & Dimethyl fumarate → Ixchel Pharma & University Federico II, Naples, Italy							
Frataxin Replacement. Stabilizers or Enhancers	CTI-1601, frataxin replacement → Larimar Therapeutics							
	Etravirine → Fratagene Tx & IRCCS Eugenio Medea							
Increase FA gene Expression	DT-216, Gene-TAC → Design Therapeutics							
	Oligonucleotides → University of Texas Southwestern, Univ of Massachusetts							
Gene Replacement and Editing	LX2006 → Lexeo Therapeutics							
	AAVrh.10hFXN, cardiac → Crystal/Cornell							
	CNS & Systemic, AAV approaches → CRISPR, Lacerta, Neurocrine/Voyager, Prime Medicine, Solid Biosciences, Tune Therapeutics							

FARA Friedreich's Ataxia Research Alliance

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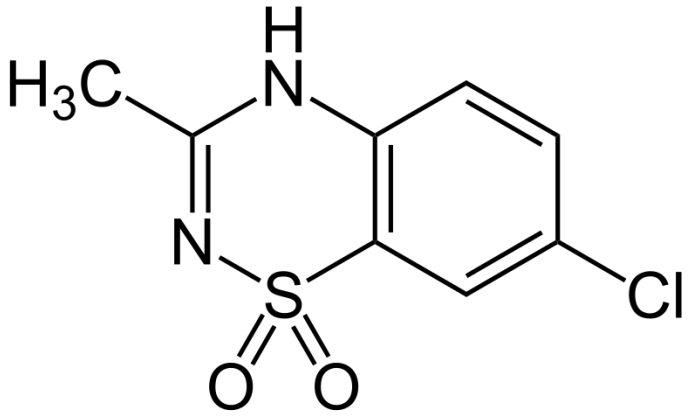
Drug Repositioning in Friedreich's Ataxia: Diazoxide



- Used to treat acute hypertension
- Increase frataxin levels in FRDA lymphoblastoid cell lines

Drug	Research status	Mechanism of action in FRDA	Category
PPARγ agonists	Phase II placebo-controlled clinical trial (Leriglitazone, 36 patients) – Completed	Increases frataxin mRNA and protein.	Chemical drug
Dyclonine	Proof of concept trial in patients (8 patients) – Completed	Increases frataxin mRNA and protein. Activates Nrf2	Chemical drug
Src inhibitors	*In vitro* studies Patients' cells	Increases frataxin protein.	Chemical drug
Methylprednisolone	Phase II open-label clinical trial (11 patients) – Completed	Unknown.	Chemical drug
Diazoxide	Preclinical	Increases frataxin mRNA and protein. Activates Nrf2	Chemical drug
Dimethyl fumarate	Preclinical	Increases frataxin mRNA and protein. Activates Nrf2. Promotes mitochondrial biogenesis.	Chemical drug
Etravirine	Phase II open-label clinical trial (30 patients) – Ongoing	Increases frataxin protein. No effect on frataxin mRNA levels.	Chemical drug
Artesunate	Phase I-II open-label clinical trial (20 patients) – Ongoing	Decreases iron overload.	Chemical drug
Erythropoietin and derivatives	Phase II placebo-controlled clinical trials – Completed	Increases frataxin protein. No effect on frataxin mRNA levels.	Biological drug
Interferon-γ	Phase III placebo-controlled clinical trial (92 patients) – Completed	Increases frataxin mRNA and protein.	Biological drug
G-CSF	Phase II open-label clinical trial (7 patients) – Completed	Increases frataxin mRNA and protein.	Biological drug
Exenatide	Phase II open-label clinical trial (16 patients) – Completed	Increases frataxin protein. No effect on frataxin mRNA levels.	Biological drug
Nicotinamide	Phase II open-label clinical trial (10 patients) – Completed. Double-blind, placebo-controlled phase II trial (225 patients) – Ongoing	Increases frataxin mRNA and protein.	Natural product
NAD + precursor (Nicotinamide riboside)	Phase II placebo-controlled clinical trial (72 patients) – Ongoing	Enhances mitochondrial metabolism.	Natural product
NAD + precursor (MIB-626)	Phase II open-label clinical trial (10 patients) – Ongoing	Enhances mitochondrial metabolism.	Natural product
Acetyl-L-Carnitine	Phase II open-label clinical trial (20 patients) – Completed	Enhances mitochondrial metabolism.	Natural product
Resveratrol	Phase II open-label clinical trial (27 patients) – Completed. Double-blind, placebo-controlled phase II trial (40 patients) – Ongoing	Increases frataxin mRNA and protein.	Natural product
Thiamine	Phase II open-label (34 patients) – Completed	Unknown.	Natural product
Sulforaphane	*In vitro* studies Patients' cells	Increases frataxin mRNA and protein. Activates Nrf2.	Natural product

Santoro A, Anjomani Virmouni S, Paradies E, Villalobos Coa VL, Al-Mahdawi S, Khoo M, Porcelli V, Vozza A, Perrone M, Denora N, Taroni F, Merla G, Palmieri L, Pook MA, Marobbio CMT. Effect of diazoxide on Friedreich ataxia models. Hum Mol Genet. 2018 Mar 15;27(6):992-1001. doi: 10.1093/hmg/ddy016. PMID: 29325032.

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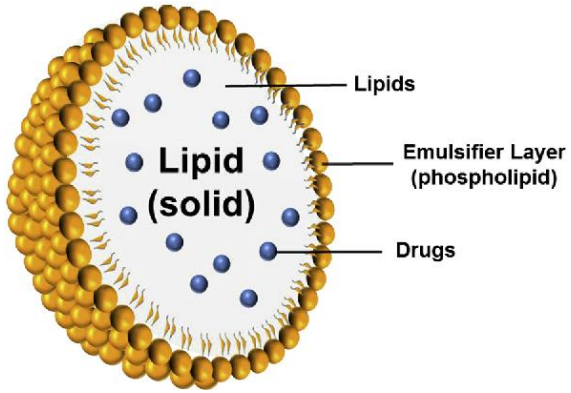
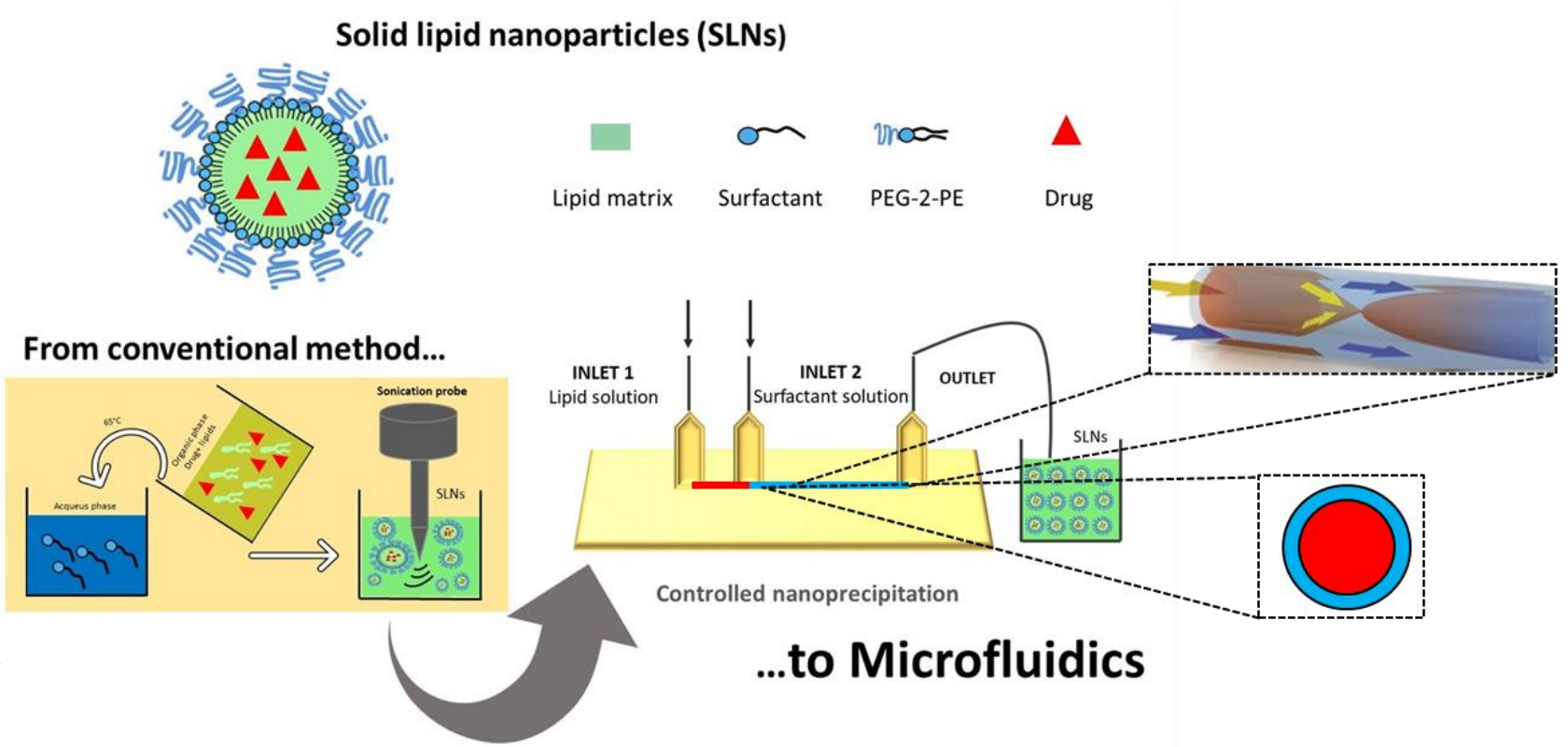
Diazoxide-loaded Solid Lipid Nanoparticles for the mitigation of oxidative stress in Friedreich's ataxia



The production of SLNs by bulk methods involves:

- Long preparation time;
- High lipids and surfactants concentrations;
- Batch to batch variability (size and PDI);
- Difficulties in obtaining nanoparticles with sizes under 200 nm, which are desirable due to their ability to cross spontaneously different biological barriers.

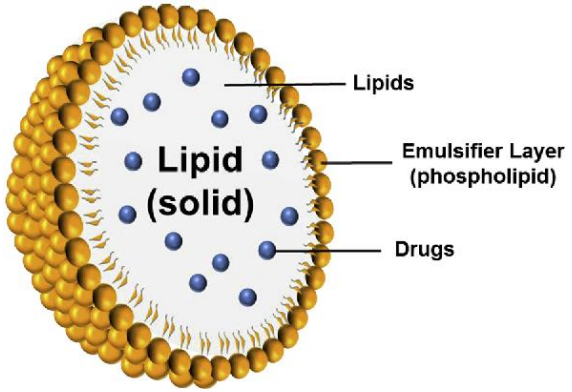
3D glass capillary co-flow microfluidic nanoprecipitation platform



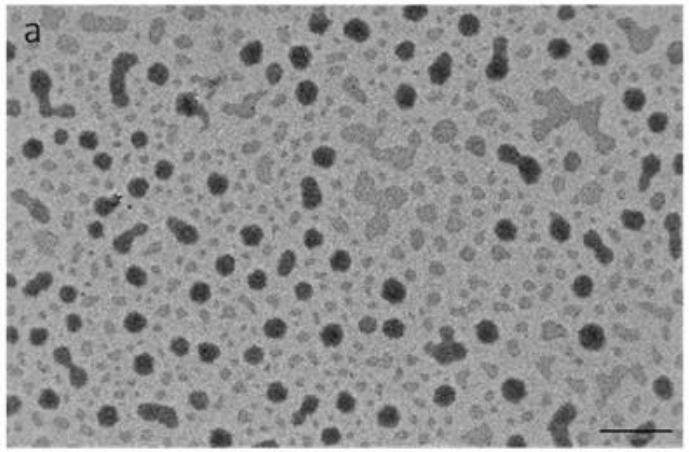
FONDAZIONE PER LA RICERCA FARMACOLOGICA GIANNI BENZI ONLUS

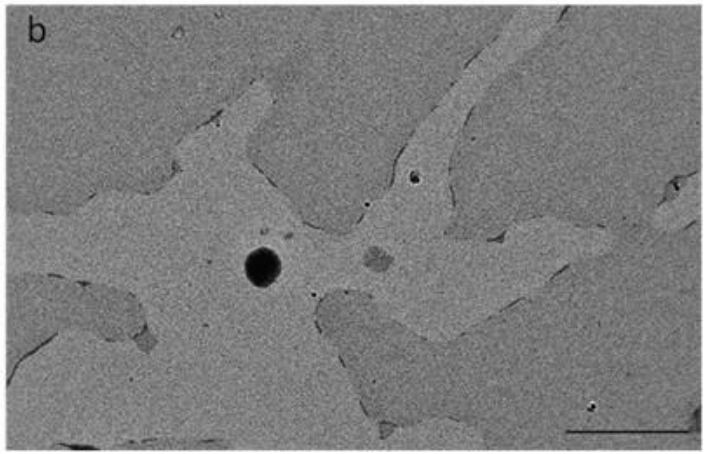
UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

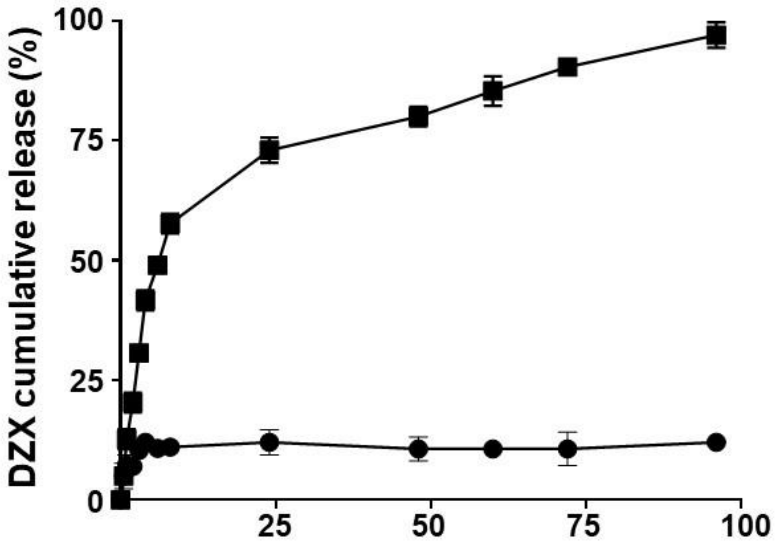
Diazoxide-loaded Solid Lipid Nanoparticles for the mitigation of oxidative stress in Friedreich's ataxia



Formulazions	Empty SLNs	SLN-DZX
d_{mean} (nm)	175.3 ± 1.2	180.1 ± 3.2
Polidispersity index (PdI)	0.129 ± 0.03	0.125 ± 0.02
ζ – potential (mV)	-42.5 ± 3.2	-31.8 ± 0.1
Encapsulation Efficiency (EE%)	/	85.6±10.2







In vitro release profiles of DZX from SLNs.

unpublished data

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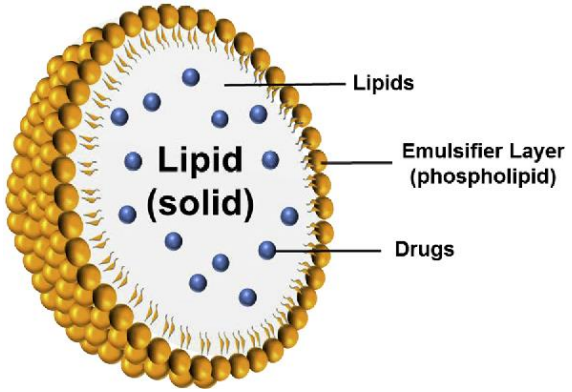

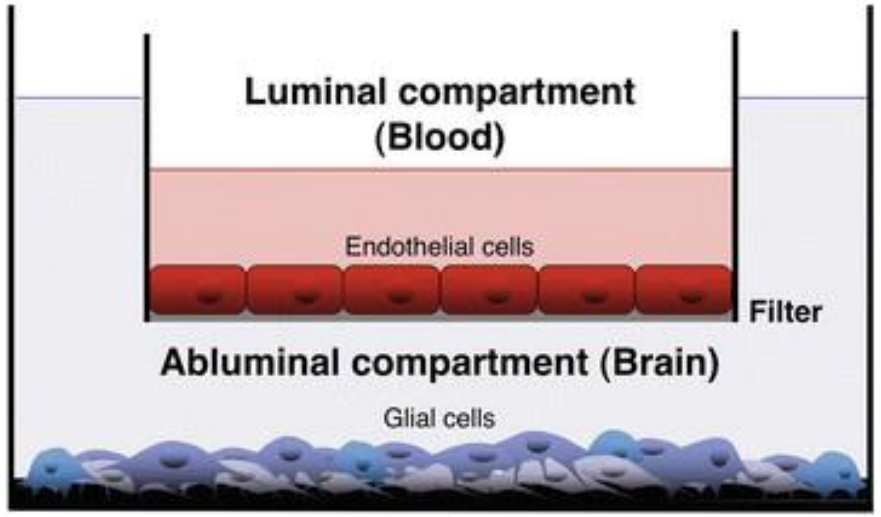

Compound	P_{app}AP cm/sec
DZX	9.3 ±1.2 E^{-05}
SLN-DZX	12.2 ± 0.6 E^{-05}
Diazepam	3.6 ± 1.1 E^{-05}
FD4	8.4 ±1.5 E^{-06}

Permeation experiments through hCMEC/D3 cells monolayer were performed by using concentration of DZX loaded into SLNs of 1 μM. The ability of SLNs to cross the in vitro BBB model was assessed at 3 h.

unpublished data

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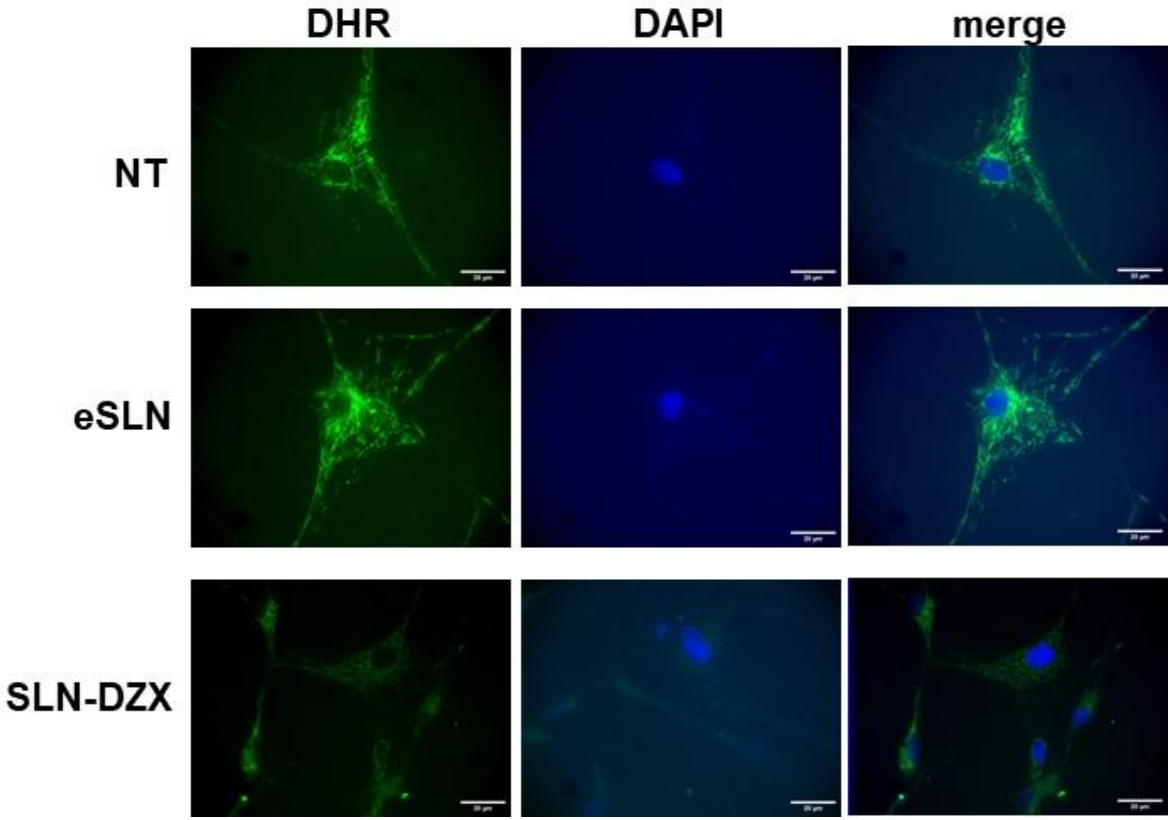
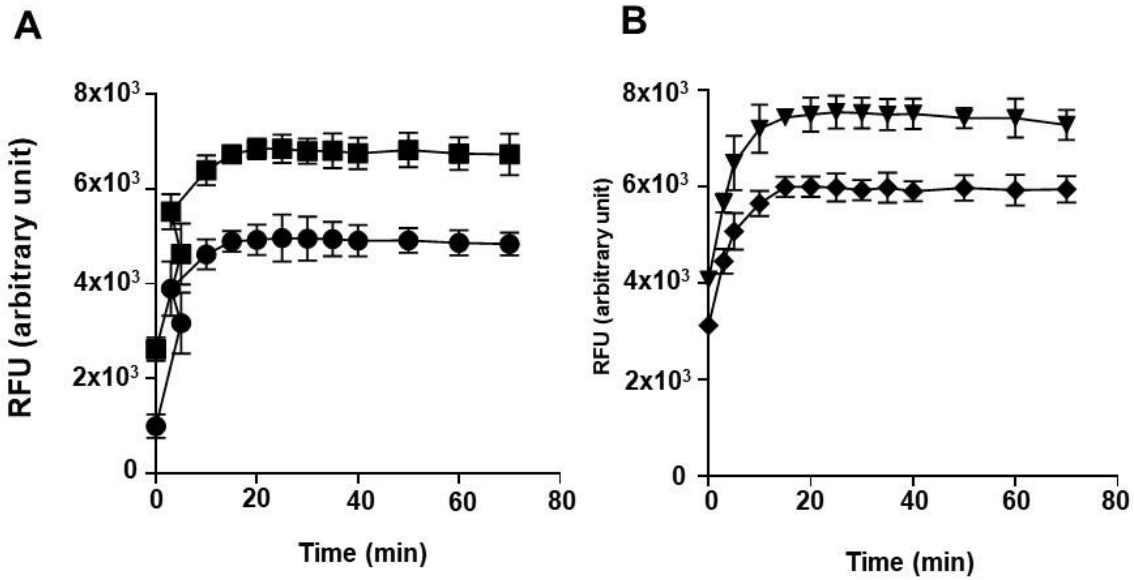


Fluorescence microscopy of FRDA fibroblast.



Effect of SLN-DZX on ROS production in FRDA fibroblast.

unpublished data

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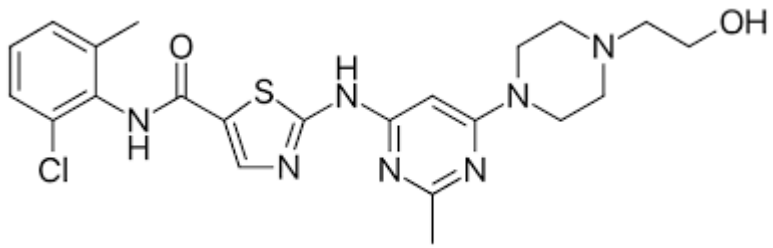
Dasatinib/HP-β-CD inclusion complex based aqueous formulation as a promising tool for the treatment of paediatric neuromuscular disorders

- Dasatinib (DAS) is the first-choice oral drug in the treatment of chronic myeloid leukemia (CML) for patients resistant or intolerant to imatinib;
- DAS may be applied in the treatment of Duchenne muscular dystrophy (DMD), a genetic muscle-wasting disorder, whose symptoms occur around the age of four years in boys and get worse quickly.

Disadvantages:

- low water solubility;

- no parenteral dosage form.



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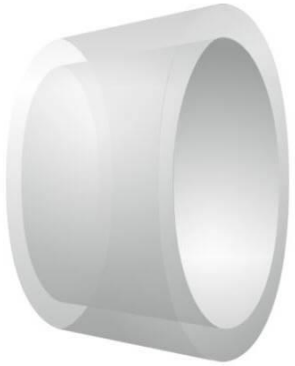
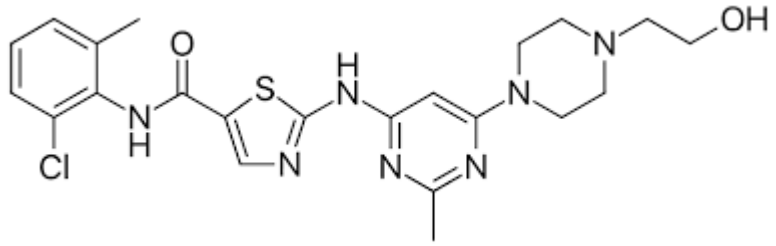
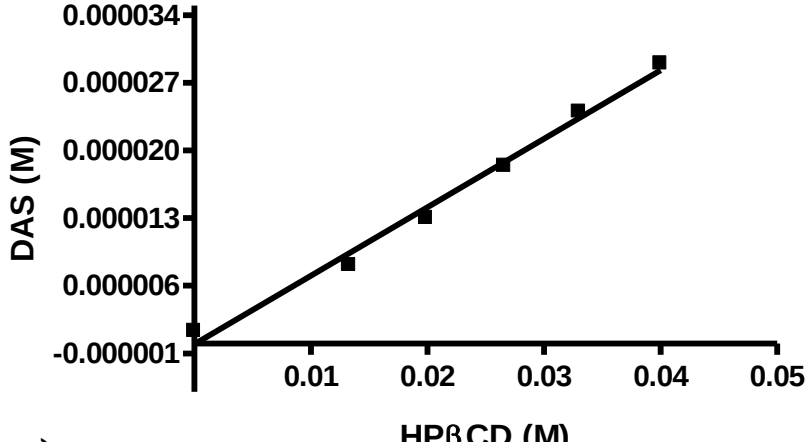
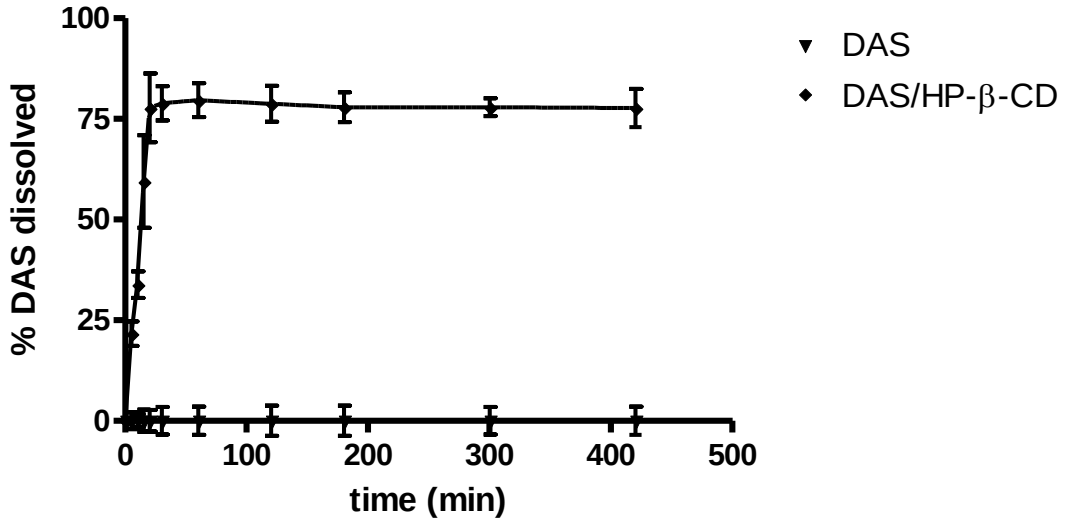
Dasatinib/HP-β-CD inclusion complex based aqueous formulation as a promising tool for the treatment of paediatric neuromuscular disorders









Dissolution profiles at 37 °C: pH 7.4 ▼) DAS alone, ♦) DAS/HP-β-CD complex;

Phase solubility and Job's plot diagrams of DAS and HP-b-CD in water at 25°C.

Cutrignelli A, De Luca A. et al. Int. J. Mol. Sci. 2019, 20, 591; doi:10.3390/ijms20030591

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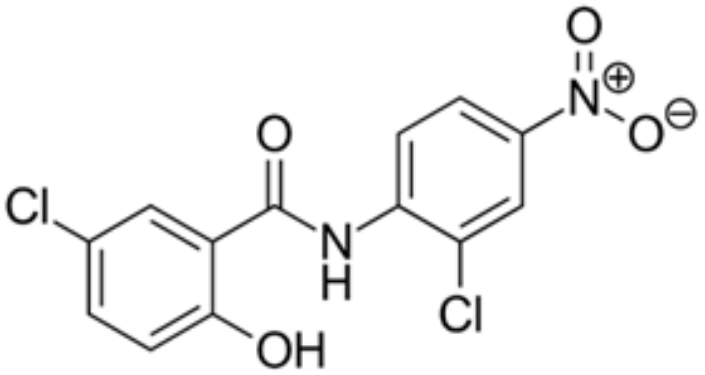
Direct cyclodextrin-based powder extrusion 3D printing for one-step production of the BCS class II model drug niclosamide



- ✓ Niclosamide (NCS) is a drug included in the World Health Organization's Model List of Essential Medicines and has been approved in 1982 by the FDA as an anti-parasitic and anthelmintic drug;
- ✓ Repurposed with a potential therapeutic indication for the treatment of tumor disease;
- ✓ NCS is BCS Class II drug.

AIM

Explore the use of 3DP DPE to directly extrude powders containing HP-β-CD, and to overcome the solubility limitations associated with NCS.

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Direct cyclodextrin-based powder extrusion 3D printing for one-step production of the BCS class II model drug niclosamide

The IDEA

Combining the **hot melt extrusion (HME)** process with the **3D printing** technique to generate from pharmaceutical grade powders or pellets customizable solid dosage forms.

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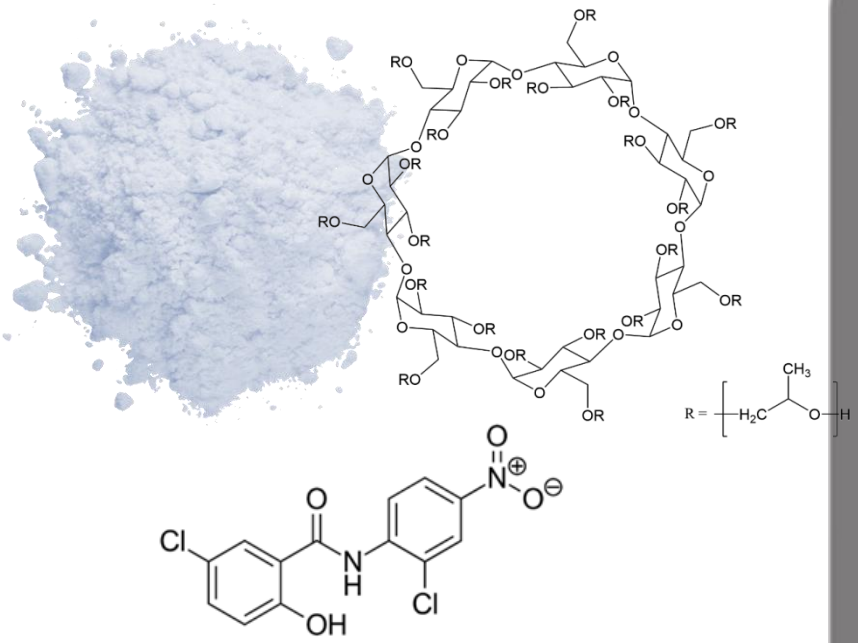
CASE STUDY - Niclosamide loaded tablets

Composition of powder mixtures

Samples	NCS	HPMC	PEG 6000	HP-β-CD
	(% w/w)			
Blend 1	10	90.00	/	/
Blend 2	10	85.50	4.50	/
Blend 3	10	42.87	/	47.13
Blend 4	10	40.73	2.14	47.13



- ✓ Hydroxypropyl methyl cellulose (HPMC) AFFINISOL™ HPMC HME 15 LV;
- ✓ PEG 6000;
- ✓ Hydroxypropyl-β-cyclodextrin (HP-β-CD) (Cavasol W7).

M. Pistone et al. Drug Delivery and Translational Research
https://doi.org/10.1007/s13346-022-01124-7

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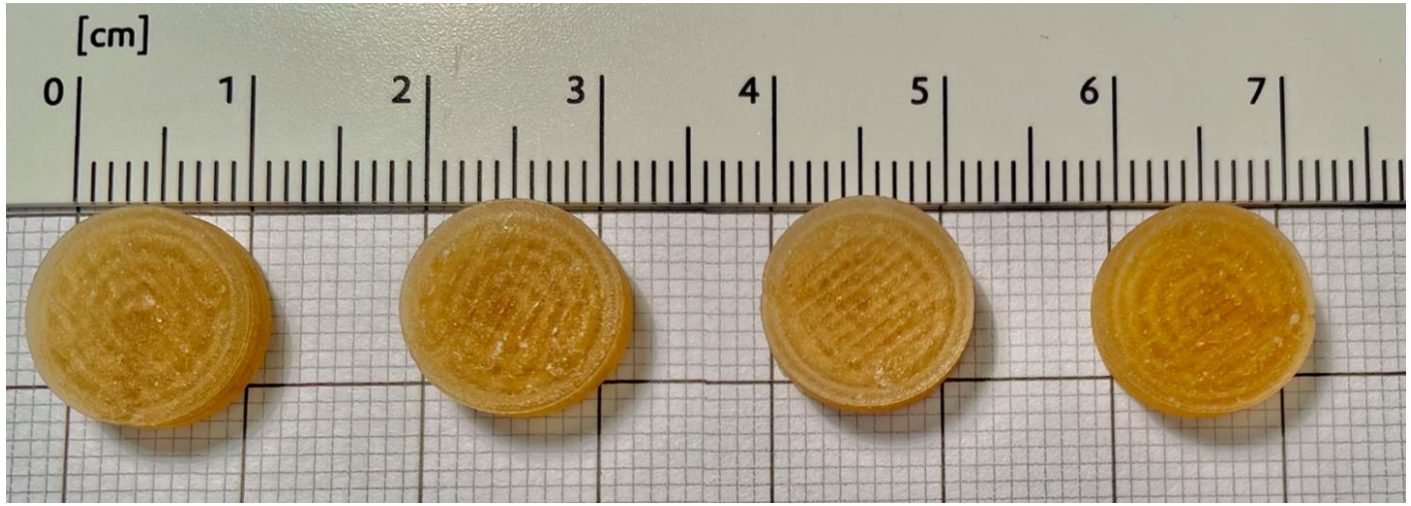

Printing parameters:

- Geometry: Cylindrical (12×3.7 mm)
- Printing Temperature: 180 °C (T_m 230 °C)
- Build plate temperature: 70 °C
- Print speed: 5 mm/s
- Infill pattern: Concentric
- Infill Density: 70 %

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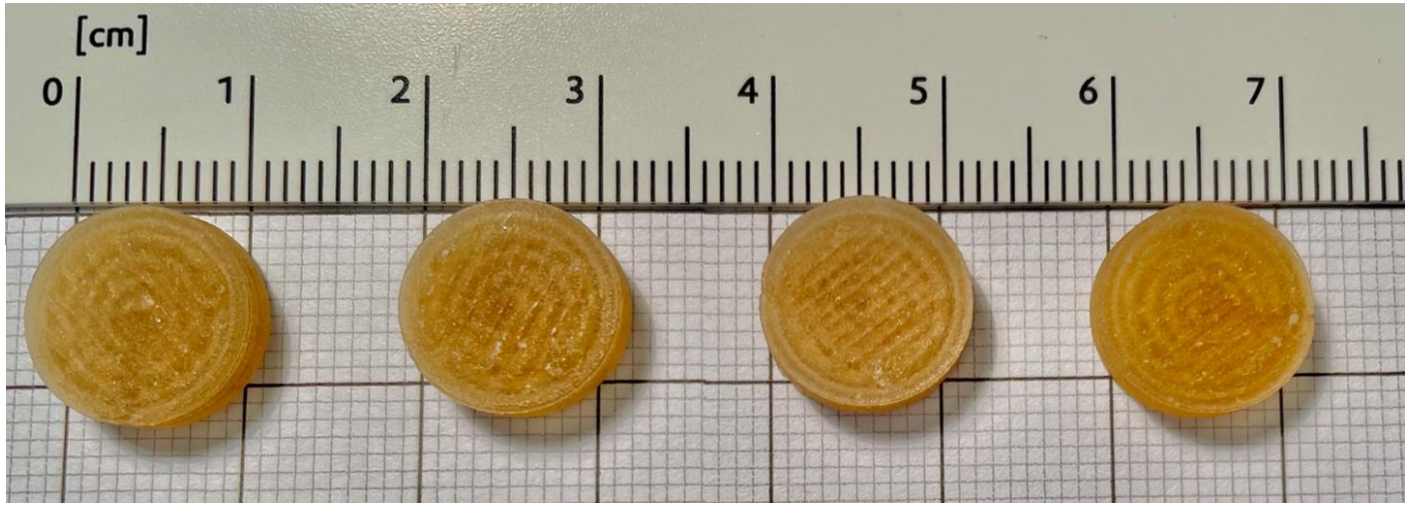

info:

- ✓ Tablets mass 500 mg, therapeutic dose 50 mg of NCS;
- ✓ All formulations comply with pharmacopoeia-required tests.

Characteristics of formulations printed by DPE

Formulation	Weight Uniformity* (mg)	Drug content* (%)	Friability* (%)	Breaking Force (N)*	Dimensions*	
					Diameter (mm)	Height (mm)
Formulation 1	414.00 ± 26.84	9.74 ± 1.85	0.060	416.80 ± 61.27	11.63 ± 0.20	3.74 ± 0.06
Formulation 2	480.30 ± 24.41	9.86 ± 0.50	0.000	484.00 ± 0.00	12.15 ± 0.24	3.66 ± 0.23
Formulation 3	506.80 ± 28.04	10.42 ± 0.37	0.099	429.40 ± 94.82	12.15 ± 0,65	3.49 ± 0,31
Formulation 4	494.70 ± 28.16	10.23 ± 0.40	0.038	226.40 ± 99.18	12.09 ± 0.75	3.65 ± 0.15

*The value is the average of 10 tablets. ± is the deviation standard

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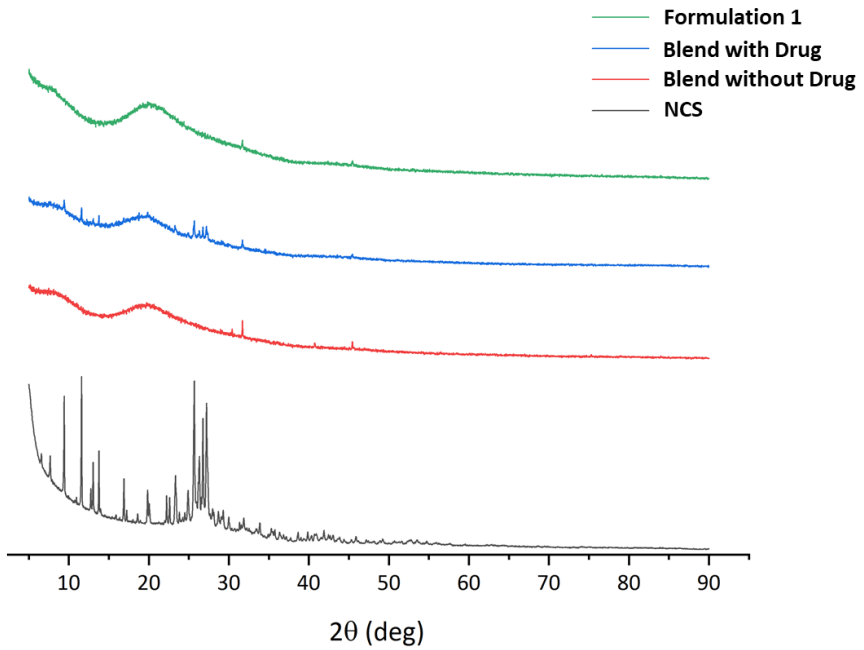
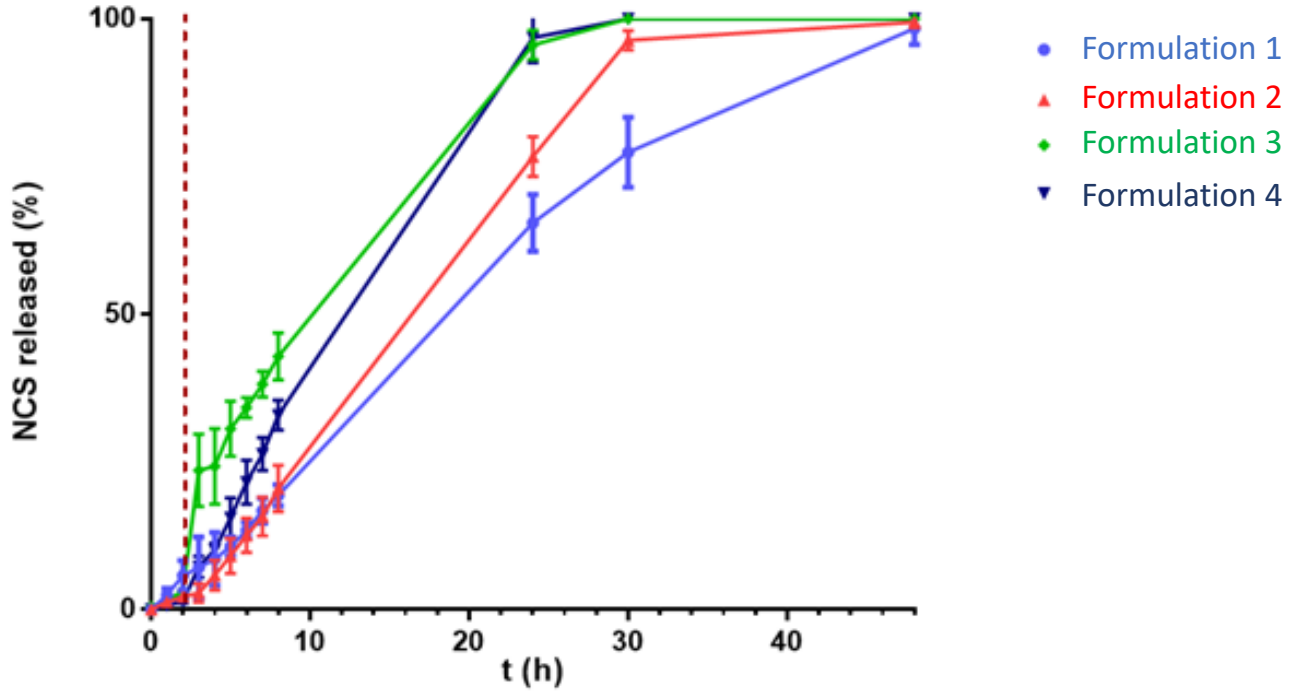
CASE STUDY - Niclosamide loaded tablets



Solid State Characterization

NCS amorphization during the printing phase.



Dissolution profiles in gastric (2 h) and enteric (46 h) fluids.

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CONCLUSIONS

- Pre-formulation and formulation studies allow to overcome repurposed drug limitations associated with the physical-chemical properties of the drug;
- Improve the drug stability and bioavailability;
- Generate tailormade formulations.

Acknowledgements

Permanent Staff
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PHARTECO LAB
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