aaps PharmSci 360 OCT 22–25 2023

Cisplatin/Hyaluronan film for Loco-Regional Chemotherapy: Technology and Preclinical Evidence of Activity

October 23rd, 2023

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Session Description and Objectives

- Pleural Mesothelioma (PM) is a rare tumor with frequent metastases. Its standard treatment is with cisplatin (cisPt).
- A cisPt-loaded hyaluronan (NaHA) film was developed for loco-regional chemotherapy of PM.
- Effectiveness in reducing metastases was proven *in vivo* and despite the high drug concentrations in blood, there was no sign of cisPt-related toxicity.
- This great result was due to cisPt complexation with NaHA.

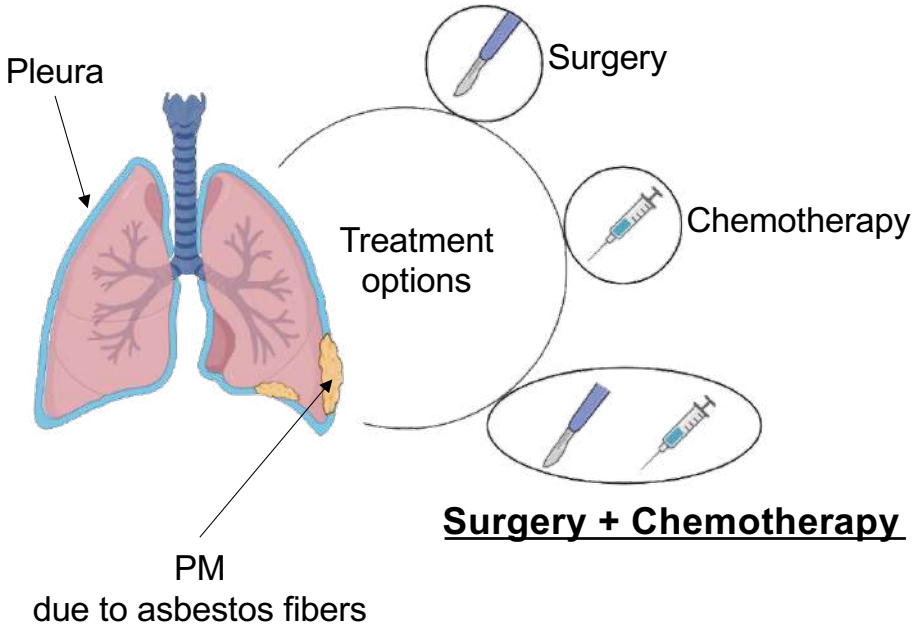
- To learn the film technology as drug delivery system.
- To understand efficacy and safety of cisplatin/hyaluronan complex.
- To appreciate the potential loco-regional chemotherapy.
- To show the cytotoxicity of cisplatin/hyaluronan complex.

Biography and Contact Information

- **2019 – 2022** PhD project focused on an innovative delivery system for anticancer drug delivery in loco-regional treatments.
- **2022** - Visiting scholar at St. John's University (New York, USA) for 10 months (supervisor: Prof. Abu Serajuddin), where she worked on solid amorphous dispersions, hot melt extrusion, 3D printing technologies, 3D cell models for drug testing.
- **2023** - PhD degree in Chemistry Sciences (Pharmaceutical technology) at University of Ferrara.
- **2023** - Patrick DeLuca Emerging Researcher Award by IPEC.

How did the idea come about?

1 A scientific discussion with thoracic surgeons about the treatment and management of **Pleural Mesothelioma** (PM), a rare cancer.



Surgery + Chemotherapy

Surgery + Chemotherapy

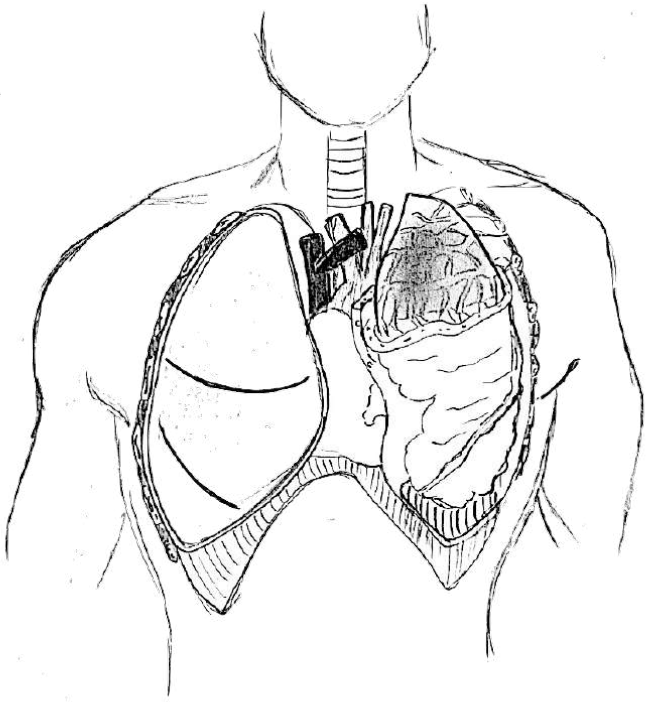
✖ Cisplatin (cisPt) solution applied in the pleural cavity

- Rapid clearance from the site of application
- High systemic toxicity

2 An **IDEA**: How could we apply the anticancer drug directly onto the pleura more effectively?

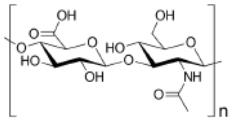
FILM TECHNOLOGY

- Big surface to treat
- Dose control
- Safer handling by surgical team
- Prolonged release of drug
- Biodegradation of the film
- Control of drug plasma concentration

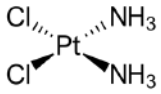


3 A **SOLUTION**: development of cisplatin-loaded hyaluronan film.

Sodium Hyaluronate (NaHA)

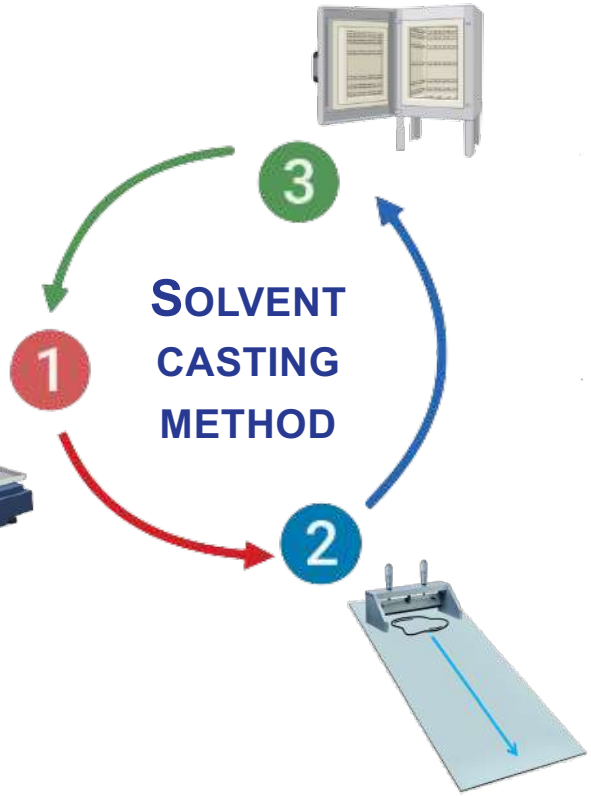


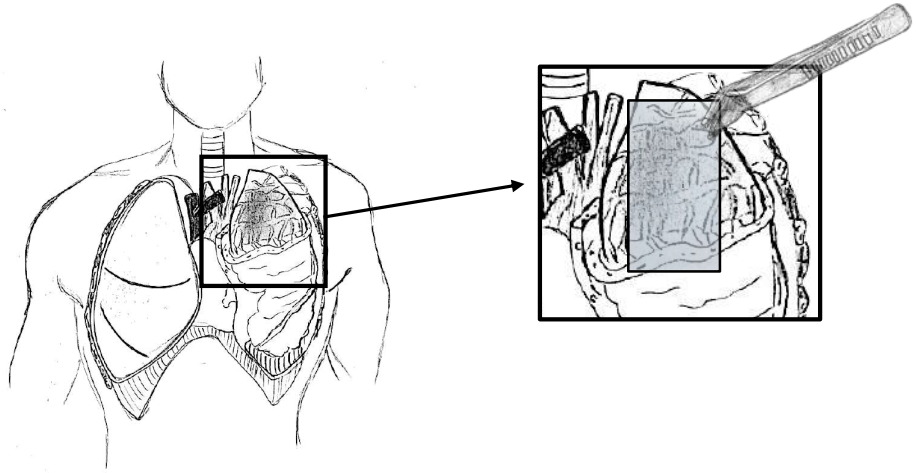
Cisplatin (cisPt)

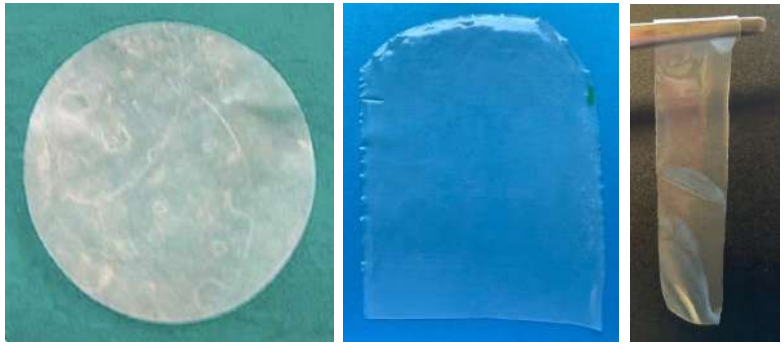


+

PVA
SORBITOL
PEG 200
PEG 1000S







Sonvico F. et al. Physicochemical and pharmacokinetic properties of polymeric films loaded with cisplatin for the treatment of malignant pleural mesothelioma. J Thorac Dis. **2018**

4 The **assessment** of film effectiveness in preventing tumor relapses.

1st preclinical study in an orthoptic rat model with PM

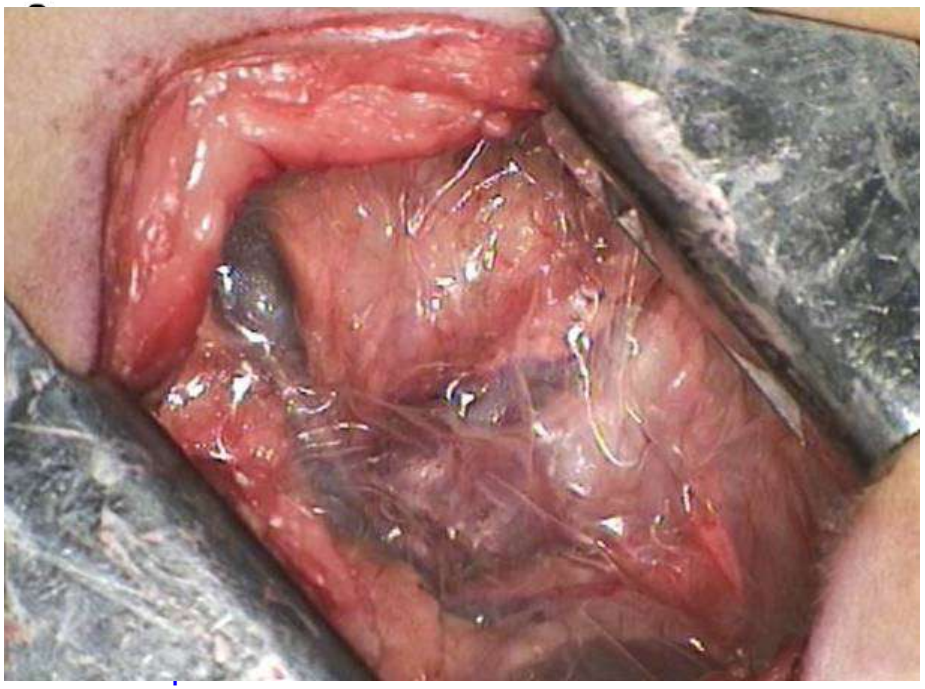
Ampollini L. et al. Intrapleural polymeric films containing cisplatin for malignant pleural mesothelioma in a rat tumour model: a preliminary study. *Eur J Cardiothorac Surg.* **2010**, *37*, 557-565.

cisPt solution group (intrapleural)

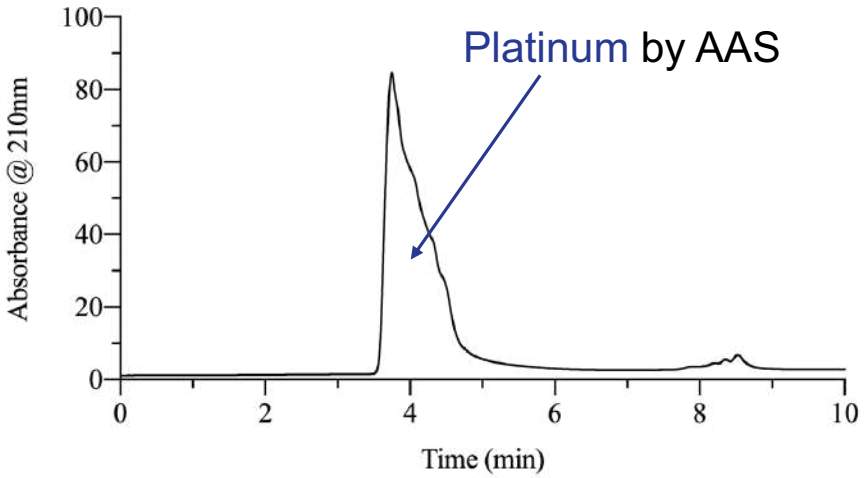
cisPt-loaded hyaluronan film group

2nd preclinical pharmacokinetic study in healthy sheep

Ampollini L. et al. Polymeric films loaded with cisplatin for malignant pleural mesothelioma: a pharmacokinetic study in an ovine model. J Thorac Dis. ***2018****, 10, S207-S220.*



5 The **investigation of cisPt/NaHA complex** in film-forming mixture and dry film.



SEC-HPLC chromatogram of the film-forming mixture.

- ✓ SEC-HPLC: **qualitatively evidenced** the complex in the FFM.
- ✓ RP-HPLC: quantified the **5% of free cisPt**, hence the 95% was complexed with NaHA.
- ✓ DSC: the interaction of cisPt/NaHA displaced **water that evaporated at lower T**.
- ✓ Rheology: the complex **increased the viscosity** of the film-forming mixture due to cross-linking.
- ✓ FTIR-ATR: complex formation involved the **carboxylate group**.

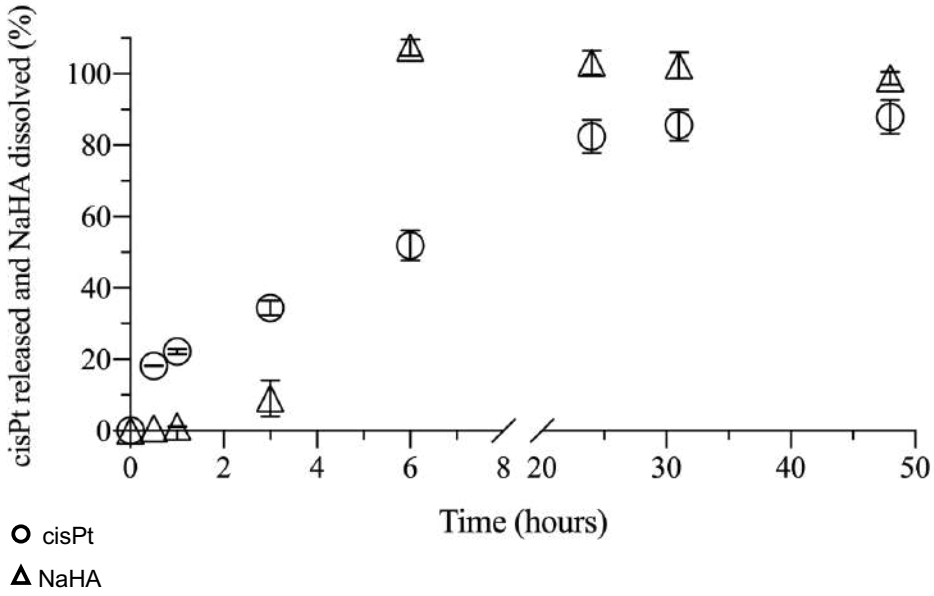
Banella, S. et al. Orphan Designation and Cisplatin/Hyaluronan Complex in an Intracavitary Film for Malignant Mesothelioma. Pharmaceutics. ***2021****, 13, 362.*

In vitro cisPt release from film and NaHA dissolution.

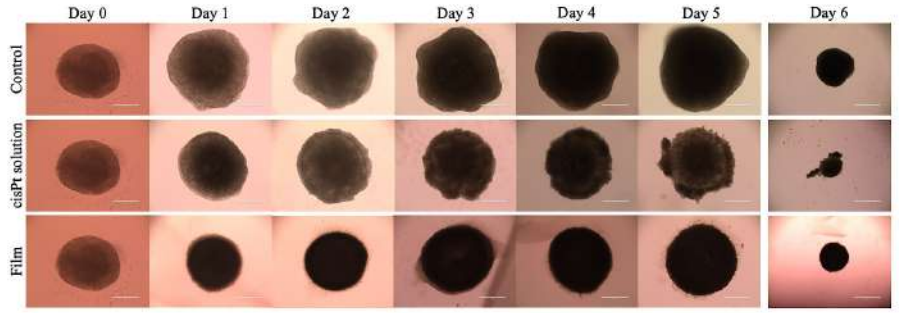
Conditions:

- 20 ml of **0.9% NaCl**
- 37 °C

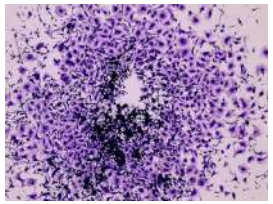
No cisPt release in water!!!



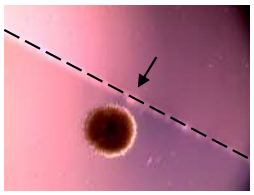
Film inhibited the formation of spheroid-derived cellular colonies.

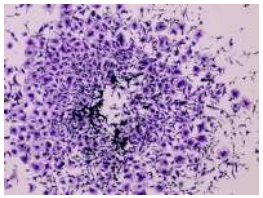


Control with no treatment



cisPt solution group





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