Utility of the Layer-by-layer Technique in Photodynamic Therapy to Enhance Photodynamic Efficacy

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INTRODUCTION

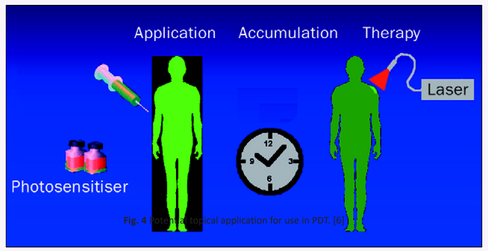


Fig. 1 Routes of administration, accumulation, and irradiation of a photosensitizer. [5]

- Irradiation of a photosensitizer at a specific wavelength causes it to undergo excitation and energy transfer, leading to the generation of singlet state oxygen and subsequently other reactive oxygen species (ROS). [1]
- This in turn leads to oxidative cell damage and cell death via:
  1) ROS mediated killing
  2) Vasculature damage
  3) Inherent stimulation of immune defense [2]

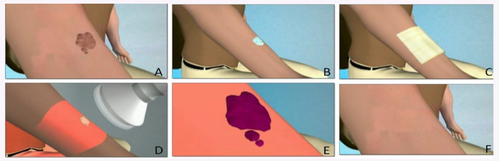


Fig. 2 Potential topical application for use in PDT. [6]

- We are attempting to design a Band-Aid like formulation with a loaded photosensitizer to be applied directly to a surface level melanoma.
- This should allow the slow and controlled release via the leaching of the photosensitizer into the cancerous cells.
- Due to its direct localization, when it is subsequently irradiated, this could mitigate one of the biggest drawbacks of PDT, i.e. off-target photosensitivity.

METHODOLOGY

- Utilizing layer-by-layer assembly, a variety of poly-L-lysine (PLL) and hyaluronic acid (HA) systems at a multitude of assembly pH's was constructed. [3]
- Photofrin dissolved in solution pH's ranging between 4-10 were loaded into each multilayer systems, and the quantities of absorption were compared.
- The release of Photofrin was monitored at different time points varying from 0.5, 1, 2, 4, 8, 24, and 48 hours in a solution pH of 5, which mimics the pH of the skin.

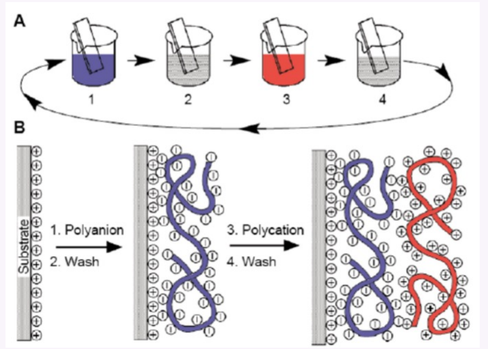


Fig. 3 LbL build-up for multilayer assembly. [7]

RESULTS

- The loading pH had no effect on quantity of Photofrin loaded at assembly pH's 4, 5, 6, and 10.
- Films constructed at pH's 7, 8, and 9 led to variability in loading of Photofrin.
- The system that led to the most Photofrin being loaded was assembly pH's of 8 and 9, with solution pH's of 6 and 7, respectively.

Fig. 4 Release of Photofrin from pH 6 Multilayered Films

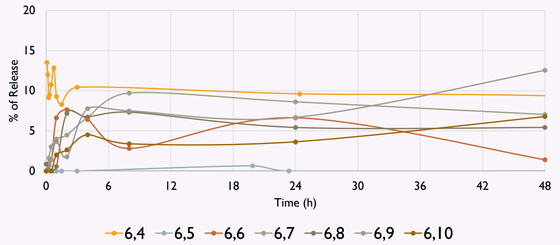


Fig. 5 Release of Photofrin from pH 8 Multilayered Films

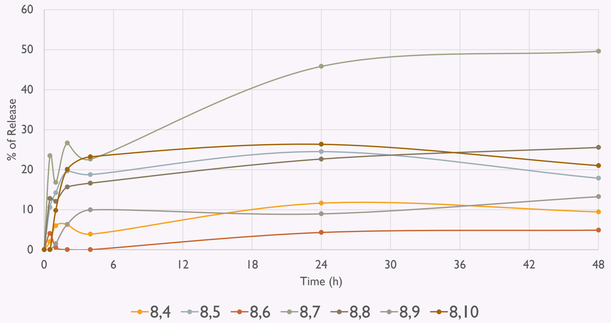
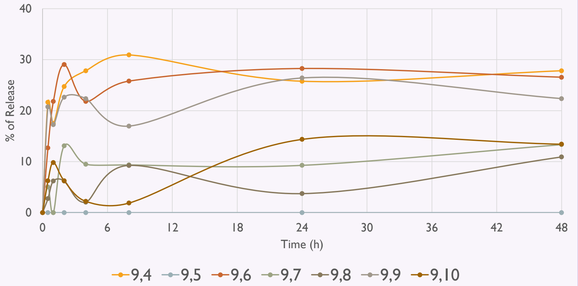


Fig. 6 Release of Photofrin from pH 9 Multilayered FIlms



CONCLUSIONS

- The films with assembly pH's of 8 and 9, with solution pH's of 6 and 7 respectively, demonstrated the best results and should be the films studied on different cancerous cell lines.
- Regardless, all systems demonstrated slow release, which is what we were targeting.
- In the future, we hope to see that a topical formulation for photodynamic therapy is explored.

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NCODA | PASSION FOR PATIENTS

Chrono-Chemotherapy

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INTRODUCTION

- The circadian rhythm is the 24-hour cycles that are a part of the body's internal clock which primarily carries out the sleep-wake cycle as well as other biologic, physiologic, and behavioral functions.[1]
- Disrupting circadian homeostasis has been linked to the development and progression of various diseases including cancer.[2]
- For example, in breast cancer there have been a distorted expression pattern of the core clock of profile ARNTL and PER2 genes, demonstrating that disrupting the circadian rhythm could be associated with a poorer cancer prognosis.[2]
- Circadian regulation has been employed in the treatment of several different therapeutic areas including peptic ulcers, allergic rhinitis, and diabetes to name a few. [2]
- The premise behind chrono-chemotherapy is to administer cytostatic drugs when optimal effects on the tumor can be achieved to reduce toxic side effects.[3]
- In vivo experiments in mice have shown that the toxicity of chemotherapy varies by 50% or more based on dose timing, which led to the development of chrono-chemotherapy, which depended on administering chemotherapy according to circadian rhythms.[3]
- For the same individual, drugs can be delivered at different times within the 24-hour timescale, and the difference in efficacy can be greater than 2 times, and difference of adverse reaction can be as much of a 10 times difference.[4]
- Time programmed pumps became a useful tool to test the hypothesis that chrono-chemotherapy could work.
- New oncology drugs could benefit from chrono-chemotherapy studies as it can increase drug effectiveness, as well as protect patients from unwanted toxicities and side effects. [3]

MECHANISMS

- According to a Chinese expert consensus on chrono-chemotherapy for oral squamous cell carcinoma, glutathione is an essential antioxidant in the body and can reverse the toxicity of many of the chemotherapy agents that are in use today, protecting normal cells from the side effects of chemo while not reducing efficacy of these cancerous drugs. [3]
- GSH is secreted according to circadian rhythm and during different times can be more than 3 times in a patient.[3]
- Peak GSH secretion is around 16:00 in the human body, so administration at this time can reduce the side effects experienced by the chemotherapy.[3]
- Thymidylate synthetase is a target for methotrexate and 5-FU, which also follows circadian rhythm.[3]
- Its activity is lower in the resting phase with lowest activity around 00:00 to 4:00, by administering chemotherapy during this time it can reduce the incidence of adverse events.[3]

CASE STUDY

- A 21-year-old patient had a rare and highly aggressive ovarian endodermal sinus tumor spilling into the peritoneal cavity, and using the principles of chrono-chemotherapy, was able to survive her illness.5
- CBCs, mood, vigor, nausea, and temperature were monitored to identify times of tolerance in laboratory animals and then extrapolated to the patient. 5
- The remaining treatment was administered according to these times of tolerance.

TRIAL

Side Effect	Study	Control	P-value
Nausea	66.7%	79.5%	< 0.05
Vomiting	47.9%	71.2%	< 0.05
Oral Mucositis	73.9%	87.7%	< 0.05

- 148 patients with biopsy-diagnosed Stage 3-4b nasopharyngeal carcinoma the two treatment groups are:
  - Two cycles of chronomodulated infusion, delivering peak infusion of cisplatin at 4pm [study]
  - A routine constant rate of cisplatin infusion (100mg/m^2 on Day 1 of a 21-day cycle) [control]
- After follow-up of 20 months the study group had better outcomes for adverse effects and immune functions.[6]
- However no significant difference between the groups in 2-year survival, progression-free survival, and metastases free survival. [6]

PHARMACOECONOMICS

- This study aimed to identify the cost between a single chronotherapy cycle and a single course of the FOLFOX regimen.[7]
- This study demonstrated in a European setting that a single course of chronotherapy was around 337/356 euros vs a FOLFOX cycle being 346 euros, which is quite similar.[7]
- Although this was not conducted in an American population, it does show us that both treatment regimens are fiscally similar.[7]

CONCLUSIONS

- Studies have suggested that circadian time-dependent efficacy of chemotherapy could increase patient survival outcomes, however clinical trials have yet to prove that chrono-chemotherapy is a technique worth integrating into oncology care.[3]
- Future studies should aim to discover what mechanisms cause circadian based cancer killing and aim to exploit and target these mechanisms.[3]

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