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Designing peptide hydrogels for localised therapeutics in treating Glioblastoma

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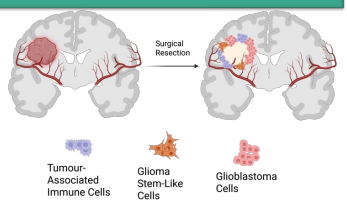
INTRODUCTION & AIM

Glioblastoma & Current Treatment



- Grade IV brain tumour, which is highly malignant with **a very poor prognosis.**
- Patients suffer from:
  - **High tumour recurrence** rates
  - **Inoperable** cancer cell population.
- **Temozolomide,** as standard systemic chemotherapy, faces primary limitations of **low Central Nervous System (CNS) bioavailability** and **myelosuppression**

Promising Approach : Self-Assembled Peptide Hydrogels

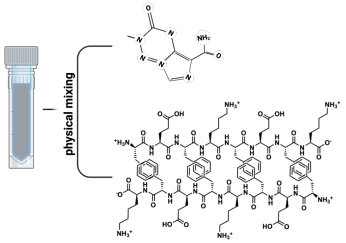
- Are **peptide-based,** which self-assemble into a β-sheet network
- **SAPHs** are **soft** and **injectable**.
- They have increasing traction for *in vivo* **drug delivery.**
- Their **biocompatibility** and ability to encapsulate diverse therapeutics make them ideal candidates for **localising chemotherapy** at post-resection sites

Aim :

- Developing an injectable peptide-based drug delivery system for post-resection
- Validating preservation of relevant small molecule drug (**TMZ**) in SAPH
- Employing relevant pathophysiological models to validate the therapeutic efficacy

METHOD

1. Formulation of TMZ in SAPH of different gelation pH

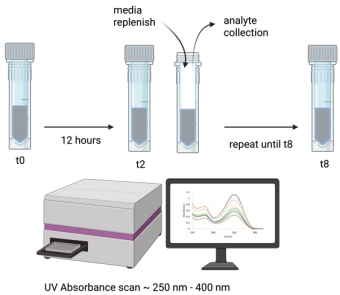


Peptide Sequence	Peptide Concentration	Gelation pH
F8	30 mg/mL	~3
KF8K	30 mg/mL	~7.4
$E_2(FKFE)_2E$	30 mg/mL	~7

2. Investigating TMZ release from SAPH

i. pH 3 buffer was applied as supernatant on top of TMZ-loaded hydrogel

ii. In 12-hour intervals, the analyte was gently stirred, and aliquots were scanned



3. Drug and Peptide Toxicity Profile

i. Peptides were co-incubated with U251 Malignant Glioblastoma, Human Microglia and Human Astrocyte cell line.

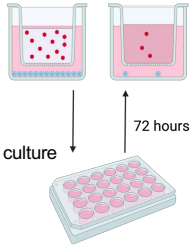
ii. Varying concentrations of peptide were tested.

iii. Metabolic activity was used as an indicator of cell health.

4. In-Vitro Release of TMZ from SAPH against U251 MG

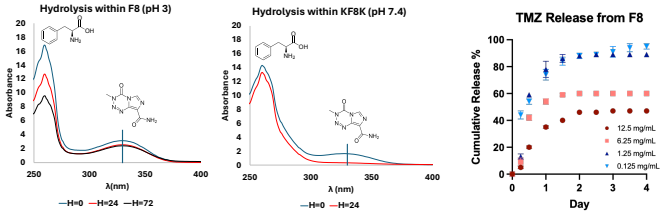
i. Transwell® was used to study the efficacy of formulation in 2D cell culture system of U251 MG.

iii. Metabolic activity was measured after 72 hours.



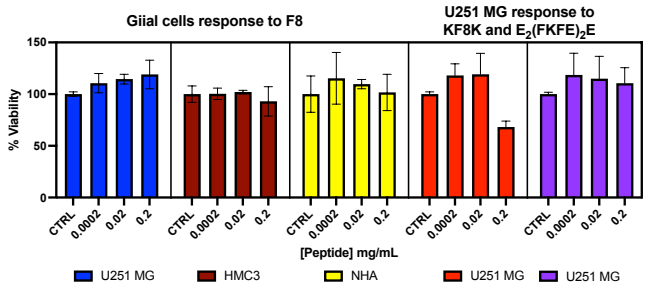
RESULTS & DISCUSSION

F8 effectively preserves and releases '*unstable TMZ*' at brain temperature



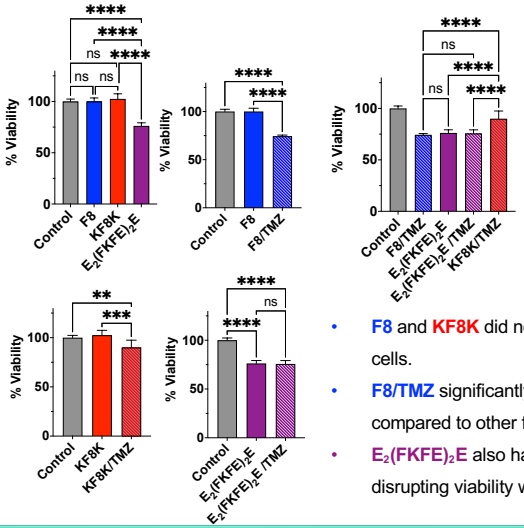
- TMZ was stable in F8 compared to its variant, KF8K, due to less prodrug hydrolysis occurring at lower pH.
- In F8 (pH3), **TMZ** was released followed a burst release profile, followed by a lower release fraction subsequently compared to KF8K (not shown)
- Additionally, higher loading seems to significantly retain the unreleased fraction

F8 and $E_2(FKFE)_2E$ do not disturb metabolic activity of U251 MG, HMC3 and NHA



- Peptide is core component of SAPH
- At low concentrations, F8 and $E_2(FKFE)_2E$ does not disturb metabolic activity
- KF8K starts to show trend (~0.2 mg/mL) for disrupting cell viability

F8 preserved and released TMZ thus reducing viability of U251 MG significantly



- F8 and KF8K did not disrupt viability of cells.
- F8/TMZ significantly reduced viability compared to other formulations.
- $E_2(FKFE)_2E$ also have similar potency in disrupting viability with F8/TMZ

CONCLUSION & FUTURE WORK

- Significant potential of F8 as effective TMZ delivery system
- Investigating the therapeutic efficacy of F8/TMZ against **Human Glioblastoma Tissue** to provide highly relevant pre-clinical evidence for disease-targeting potential.
- Characterisation of the F8 *'physiological parameters'* using **an *in vivo* Glioblastoma model** for robust *proof-of-concept* towards clinical application

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