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A prolonged release in situ reconfiguring device for the delivery of drugs to solid tumors

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ABSTRACT

The poor response of patients to high-dose chemotherapy commonly associated with the treatment of solid tumors has led to research efforts in the development of implants for the delivery of drug directly to solid tumors. In order to prevent surgical complications associated with the placement of an implant at the site of the tumor, efforts have been made to develop implants which form at the site of the tumor.

This study aimed to develop an *In Situ* Forming Implant (ISFI) which was responsive to temperature and able to form an implant when injected into the body and to release drug over a period exceeding one month. To this end, a thermoresponsive polymer, poly(methyl vinyl ether) was selected and following preformulation studies to assess release and gelation temperature, a Design of Experiments approach was utilised to formulate an optimal formulation.

Fourteen formulations were prepared according to a Face-Centred Central Composite Design selected and were assessed for gelation temperature, ease of injectability and Mean Dissolution Time. Utilising the experimental values obtained, regression models for each of the outcomes were generated. The optimal formulation was then determined by selecting the appropriate targets for each of the responses in the design. The optimal formulation was able to gel at body temperature, could be injected into the body and showed release of entrapped chemotherapeutic, methotrexate for a period exceeding one month.

pH-responsive microparticles were also formulated and optimized using a Face-Centred Central Composite Design. Optimized particles were then loaded into the optimized ISFI and displayed faster release of the entrapped drug than with the dispersed drug.

In vitro testing of the ISFI was conducted against solid tumor forming cells and *in vivo* testing was conducted in healthy Sprague-Dawley rats. A few rats developed toxicity to methotrexate after 6 days, however, low quantities of drug were found in the plasma. In addition, drug was present in the surrounding tissue in a high concentration even after 10 days.