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Design and evaluation of an oral 3D printed chemotherapeutic delivery system

Clark, Karin

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ABSTRACT

Cancer is one of the prevalent diseases that continues to give physicians, scientists and researchers challenges in the delivery of oral chemotherapeutic agents. Conventional chemotherapeutics with fixed doses may lead to minimal concentrations reaching cancer targeted sites that are severe. Nanoparticles (NPs) are used as drug carriers that offers many advantages in chemotherapeutics such as targeted therapy, controlled release, increased stability, increased shelf life and high carrier capacity. Three-dimensional (3D) printing further offers a unique solution to the several limitations in cancer patients. 3D printing can print biodegradable oral delivery systems which can be customised to patients. This study aimed to design and develop a novel drug delivery system employing methotrexate-loaded nanoparticles encapsulated in alginate-gelatine 3D printable ink hydrogel to form a solid 3D printed tablet for oral chemotherapeutic delivery. A biodegradable polymeric nanoparticulate system was formulated using d-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS) and poly (lactic-co-glycolic acid) (PLGA) for methotrexate (MXT) entrapment. The oral chemotherapeutic tablet was then formed using the 3D bioplotter from nanoparticle formulation incorporated with sodium alginate-gelatine hydrogel ink. Fourier-transform infrared spectroscopy (FTIR), Scanning Electron Microscopy (SEM), and Thermal Gravimetric Analysis (TGA) confirmed polymer combinational synthesis of MTX polymeric nanoparticles. The MTX polymeric nanoparticles were 186 nm in size, with a zeta potential of -31.4 mV, (PDI ≤ 0.5), and a percent drug entrapment efficiency (DEE%) value of >85%. The SEM indicated that MTX polymeric nanoparticles were well distributed and had a regular orbicular shape. FTIR displayed comparable peaks to PLGA and MTX displaying MTX polymeric nanoparticle's similar chemical composition suggesting that there was no significant chemical interaction between the functional groups of MTX and PLGA during formation of the nanoparticles. Overall, results demonstrated that the MTX polymeric nanoparticles were successfully synthesized. The results also indicated that the high accuracy of the 3D printed hydrogel/nanocomposite system (including 15 sec pauses between layers) was achieved using a 25 G needle with inner diameter of 25 mm, optimal printing pressure was1400 kPa and 95% printing accuracy. The 3D Bioplotter parameters were optimised and validated. The oral 3D printed hydrogel/nanocomposite system for the targeted delivery of methotrexate was produced. *In vitro* drug release profiles were investigated at pH 7.4 and pH 1.2 to simulate the gastrointestinal environment. The *in vitro* release profile of MTX loaded nanoparticles displayed constant release of MTX over 24 hours. The development of this 3D printed drug delivery tablet

may have potential to overcome the chemotherapeutic challenges experienced with conventional therapies.