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Development of Implants for Prolonged Drug Delivery

Sarah Stewart*, Ryan. F. Donnelly, Eneko Larrañeta,

School of Pharmacy, Queen's University Belfast, 97 Lisburn Road, Belfast, BT9 7BL

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*Corresponding author.
Tel.: +44 (0)28 9097 2333
Fax: +44 (0)28 9024 7794
E-mail: sstewart35@qub.ac.uk

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SUMMARY

Despite being a popular and convenient route of drug delivery, the oral route has several disadvantages. Polymeric sub-dermal implants offer an alternative delivery route that may circumvent many of these challenges. In this study, implants were designed using computer-aided design (CAD) software and fabricated using 3D printing. The impact of implant design on the rate of drug release was investigated using methylene blue as a model. It was found that drug release could be extended from 2 days to over 40 days as a result of changing the implant design. Future work will focus on optimisation of implant design with the aim of producing degrading polymeric rate-controlling membranes to further control drug release and to conduct further *in vitro* investigation with a drug compound.

INTRODUCTION

The oral drug delivery route remains the most popular and convenient method of drug delivery, with many advantages. However, it also presents several challenges. Many drugs are unsuitable for delivery *via* the oral route. This may be as a result of: drug degradation in the acidic conditions of the stomach (Kumar et al., 2001); first pass metabolism; or compliance issues. Therefore, there is a necessity for improved drug delivery systems for delivery of existing drug compounds, and to allow delivery of newly discovered drugs that are unsuitable for oral drug delivery. The development of new drug delivery systems should aim to optimise effectiveness and tolerability of drug compounds while ideally simplifying their administration (Wei et al., 2009).

A promising alternative delivery method is the use of polymeric implants to deliver drug compounds sub-dermally. Implantable, sub-dermal drug delivery systems may achieve a therapeutic effect with lower concentrations of drug (Dash, 1998; Rajgor, 2011) . As a result, they may minimise potential side-effects of therapy, whilst increasing patient compliance (Fialho, 2005). Implants have the potential to deliver drugs which would normally be unstable when delivered orally (Dash, 1998) because they would avoid first pass metabolism and chemical degradation in the stomach, thus, increasing bioavailability. Another advantage of sub-dermal implants is that they offer the opportunity for early removal if adverse effects require termination of treatment (Rabin et al., 2008; Schlesinger et al., 2016).

Sub-dermal implants can be used for a range of applications including: management of diabetes; contraception; treatment of human immunodeficiency virus (HIV); treatment of cancer; or treatment of central nervous system disorders (Dash, 1998).

This project aims to develop implants made from biodegradable and biocompatible polymers in which the rate of drug delivery is controlled by the implant design and through the use of dissolving poly(vinyl alcohol) (PVA) membranes.

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MATERIALS AND METHODS

Implant design: Five implants (A-E), shown in Fig.1 were designed using computer-aided design (CAD) software and printed using an Ultimaker3 3D printer equipped with poly(lactic acid) (PLA) and poly(vinyl alcohol) (PVA) filaments.

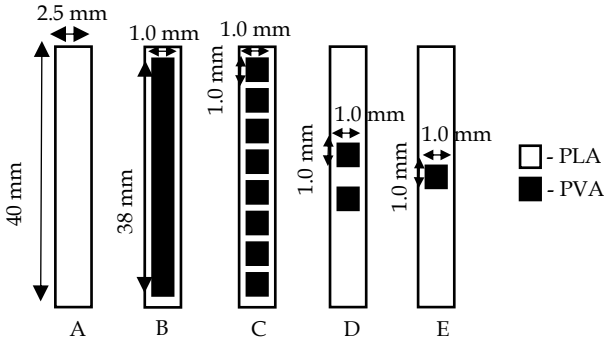

***Fig. 1**. An illustration showing the 5 designed implants*

Implant characterisation: The prepared implants were characterised using environmental scanning electron microscopy (SEM) and digital microscopy. Each implant was loaded with methylene blue (MB) and *in vitro* drug release from the designed implants was modelled. Implants were placed in PBS (500 mL) at 37°C, and samples were taken at pre-determined time points for analysis by UV spectroscopy at 668 nm.

RESULTS AND DISCUSSION

Polymeric implants were easily designed and rapidly produced using these methods, with each implant being produced in less than 6 minutes. Each implant was loaded with 70.48 (± 7.15) mg of MB. Implant design influenced the release rate from the designed implants. The *in vitro* release of MB from each of the designed implants is shown in Fig.2.

Implants made entirely from PVA (implant A) had the most rapid drug release, with 100% of drug being released within 24 hours. As expected, implants B and C showed significantly extended release in comparison with implant A, with release being extended to over 6 days. Implants D and E showed extended release in comparison to that of other implant designs. Implant E showed significantly prolonged release, with 100% of drug release only being achieved after 44 days.

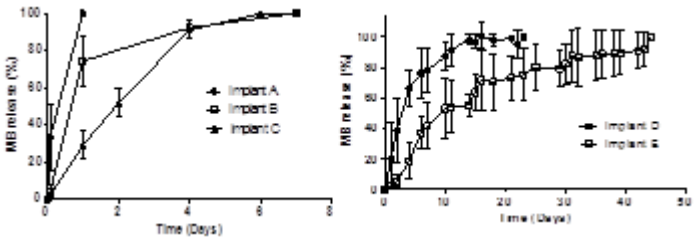

***Fig 2**. Graphs showing the release of MB from the designed implants*

CONCLUSIONS

These results demonstrate the impact of implant design on drug release. Future work will focus on further developing and improving the implant design and developing degrading polymeric membranes which will replace the dissolving PVA membranes, to create a long-acting implant with defined release properties.

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