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Three-dimensional printing of flexible polypill

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SUMMARY

Three-dimensional printing is getting a great deal of interest in recent years because of what it can offer to personalize medication in general and personalized polypill specifically. Fused deposition modelling (FDM) is one of the most studied technologies in 3dp because of its low cost and simplicity. However, this technique has some limitations among which are the high printing temperature and low drug load. In this work, an analgesic polypill with a flexible design that can be tailored according to patient needs after printing, will be formulated. This polypill will contain paracetamol, ibuprofen and caffeine. Paracetamol formulation in addition to having taste masking properties. It will have a high drug load and be printed at a relatively low temperature.

INTRODUCTION

Polypill is an oral dosage form that contains more than one active pharmaceutical ingredient (API). Polypills can improve patient compliance especially in chronic diseases that require multiple medications like hypertension, diabetes and HIV. Moreover, combining multiple medications in the same pill can decrease the cost of packaging and transportation(Tan et al., 2018). However, fixed polypill can target only a special group of patients(Sadia et al., 2018) who are prescribed with the same multiple regimens. In addition, sometime it is counterintuitive to combine more than one medication if their daily regimens are different.

3D printing is additive manufacturing techniques that form the desired structure layer by layer. Fused deposition modelling is of these techniques that depend on high temperatures to extrude thermoplastic material. In recent years, there have been multiple attempts to employ FDM to fabricate a personalized polypill(Gioumouxouzis et al., 2018). However, in all these attempts personalization was done during the printing stage or not at all. Personalization done at this stage will require the printing to be at a clinical level which will complicate the process and require vigorous regulations. Therefore, the aim of this work is to formulate a polypill that can be customizable after printing. In addition, printing temperature, drug load and specific API formulation requirements will be addressed.

MATERIALS AND METHODS

Paracetamol, ibuprofen, caffeine, Triethyl citrate, talc, ethyl cellulose and polyvinylpyrrolidone 40,000 M.W (PVP 40K) was purchased from Sigma-Aldrich Co. Ltd. (Dorset, UK). Eudragit EPO (E EPO) and Eudragit L100-55(E L100-55) were supplied from Evonik Industries AG (Darmstadt, Germany). Scotch blue painter's tape 50 mm was obtained from 3 M (Bracknell, UK).

Paracetamol and caffeine formulations were prepared using Eudragit EPO, PVP 40K, API and TEC. Extruded at 63° C using a single screw extruder (Noztec Pro hot melt extruder, Noztec, Shoreham-by-Sea, UK). Then, printed at 100° C using MakerBot replicator + (Makerbot Industries, LLC., USA).

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Ibuprofen was formulated using Eudragit L100-55, ethyl cellulose and ibuprofen. Extruded at 100° C and printed at 165° C using the same extruder and printer.

RESULTS AND DISCUSSION

Eudragit EPO and PVP 40K were chosen to be in a polymer mix because, although E EPO has low Tg -48° C- it usually needs high solid filler to produce printable filament(Sadia et al., 2016). On the other hand, PVP 40K besides having high Tg -93° C- it known to be hygroscopic which usually affects the integrity of the filament and the printlet(Pereira et al., 2019). E EPO is known to improve hygroscopicity and add taste-masking properties because its Catanionic nature(Wang et al., 2020). In the second formulation, E L100-55 was used as the release modifier with Ethyl cellulose and Ibuprofen because of its enteric coating capabilities(Dumpa et al., 2021).

All Three filaments produced had good mechanical properties and were printable. The units produced was assembled into different configuration and drug release was measured in both phosphate buffer 7.2 pH and 0.1 M hydrochloric acid.

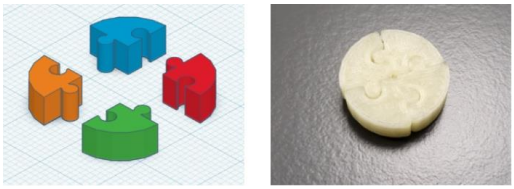

Fig. 1. *Flexible-pill design and Flexible-pill tablet after printing.*

Paracetamol had great release in the acidic media and less release in alkaline media giving it the desired taste masking effect. Ibuprofen had better solubility in alkaline media which will improve its safety since it is known to cause gastric irritation.

CONCLUSIONS

The flexible design allowed manipulation of the components doses by changing the units used to assemble the tablet. This can offer a great deal of personalisation at the clinical level. The formulation of Paracetamol had a high drug load of 55% at low printing temperature in addition to having taste masking abilities. Additionally, the Ibuprofen formulation had better drug release in the buffer compared to the acid media improving its safety and absorption.

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