3D Printed Praziquantel Formulations via Direct Powder Extrusion for the Treatment of Schistosomiasis

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INTRODUCTION

A disorder caused by parasitic worms, schistosomiasis, affects around 250 million people worldwide and results in the highest mortality rates in developing countries [1]. The current standard treatment, praziquantel (PZQ), has no licensed formulation on the market for paediatric patients [2,3]. PZQ treatment for children involves the off-label use and dose adjustment via tablet splitting, resulting in dosing errors and dangerous side effects or absence of medicine effectiveness, and the bitter taste of PZQ is also rejected by many patients when taste buds are exposed due to the splitting of tablets [2,4].

AIMS

To prepare and analyse amorphous solid dispersions (ASDs) of PZQ, a BCS class II drug, using a novel three-dimensional (3D) printing (3DP) technology, direct powder extrusion (DPE) in the form of paediatric Printlets™ (3D printed tablets).

METHODS

Different compositions were tested and printed: powder from milled HME pellets (M) consisting of crystalline racemic PZQ (Fiocruz, Brazil) and Kollidon® VA 64 (KOL), Kolliphor® SLS Fine (SLS) (BASF, Ludwigshafen, Germany), or Span™ 20 (Span) (Croda International, UK) (Table 1).

Table 1. Printlet compositions and DPE printing parameters used

Formulation code	Composition (%wt)				Printing Parameters		
	PZQ	KOL	SLS	Span	Printing temp (°C)	Flow rate (%)	Feed rate (%)
M 50	50	50	-	-	135	75	100
M 35 Span	35	60	-	5	130	75	100
M 35 SLS	35	60	5	-	130	75	100

The prepared milled extrudates were printed using the M3DIMAKER™ pharmaceutical 3D printer with a DPE nozzle attachment (FabRx Ltd., UK) (Fig 1).

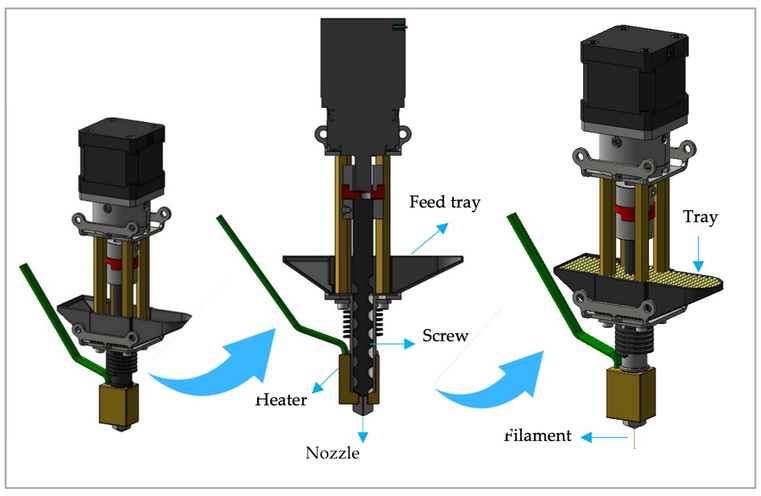

Fig 1. Single-screw direct powder extruder design in the FabRx M3DIMAKER™.

RESULTS & DISCUSSION

Two different PZQ dose printlets (100 and 150 mg) were successfully printed from 35 and 50 %wt loaded ASDs, respectively, with satisfactory dimensional characteristics (Fig 2).

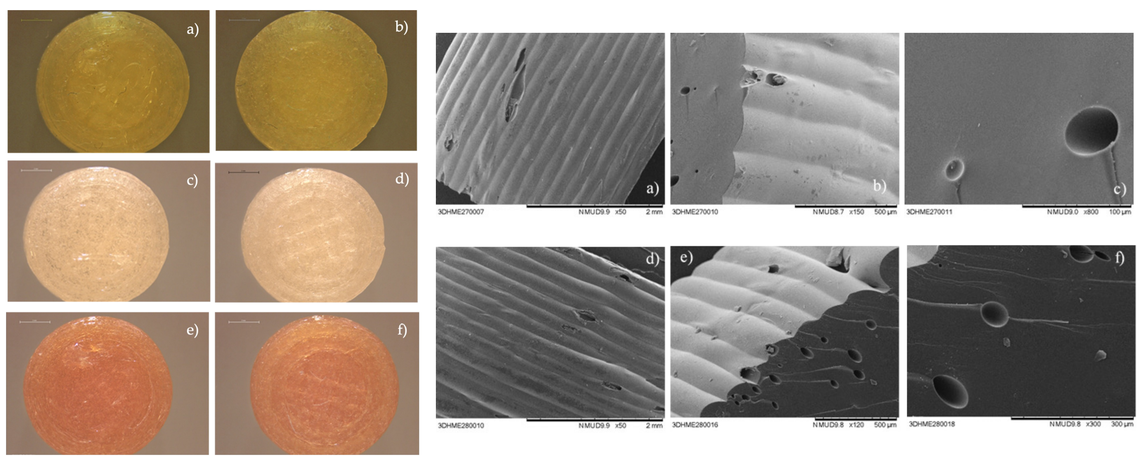

Fig 2. On the left; Top (left) and bottom (right) images of printlets obtained from: (a,b) M 50, (c,d) M 35 Span, (e,f) M 35 SLS. Scale refers to 2 mm. On the right; SEM images of (a-c) M 35 Span, and (d-f) M 35 SLS printlets.

Raman mapping results displayed an even distribution of PZQ within the polymer matrix, displaying the high stability of the printed ASDs (Fig 3).

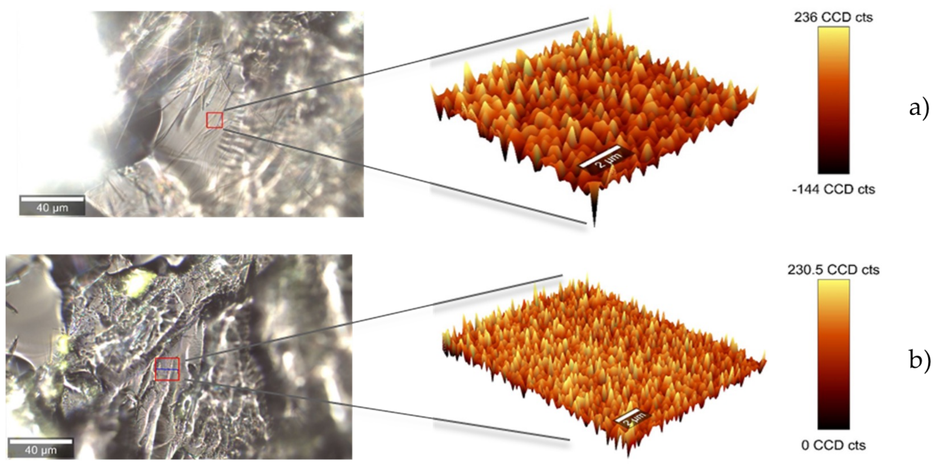

Fig 3. Raman 3D mapping of: a) M 50 printlet with an area of 10x10 microns, and b) M 35 Span printlet with an area of 15x15 microns.

When compared to the crystalline PZQ, the in vitro drug release profiles of the printlets with no additional excipients showed a greater than four-fold increase in drug release after 2 hours (Fig 4).

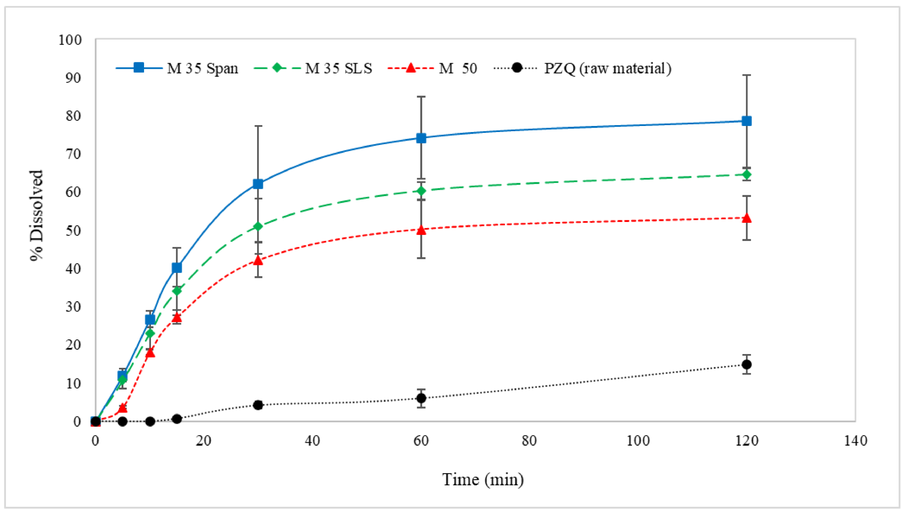

Fig 4. In vitro drug release of raw PZQ and the different printlets.

Two 35 %wt PZQ milled extrudate printlets (M 35 Span and M 35 SLS) were evaluated for their taste masking capabilities with an in vitro buccal dissolution method previously described by Keeley et al. (Fig 5.) [5]. Both printlets were below the PZQ tolerability threshold and further below the PZQ IC50 (0.06 mg/mL).

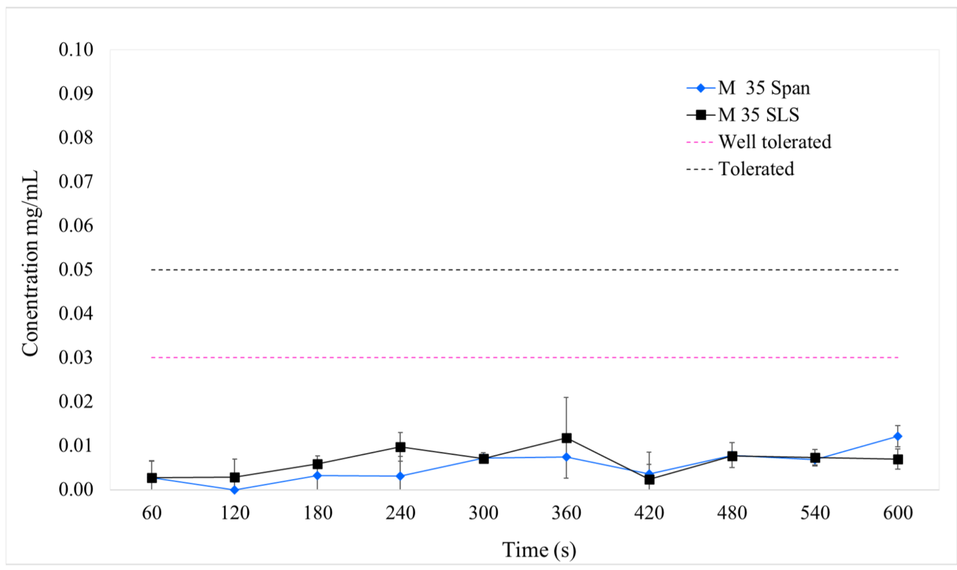

Fig 4. Details of the two 35 %wt PZQ printlet release in comparison to the taste thresholds of a previous study, represented by pink and purple dashed lines.

CONCLUSIONS

This study demonstrated for the first time the successful 3DP of both 35 and 50 %wt PZQ printlets using DPE, a novel single step technology, from various HME pellet extrudates. With a focus on paediatric patients, this work provides a viable manufacturing approach towards the efficient taste masking and improved drug release of low solubility BCS class II drugs such as PZQ.

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