British Journal of Pharmacy

https://doi.org/10.5920/bjpharm.596

British Journal of Pharmacy

www.bjpharm.hud.ac.uk

Proceedings of the 9th APS International PharmSci 2018

Hot-melt co-extrusion technology as a manufacturing platform for anti-hypertensive fixed-dose combinations

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ARTICLE INFO

Received: 25/05/2018
Accepted: 11/06/2018
Published: 03/04/2019

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KEYWORDS: Fixed-dose combinations; hot-melt co-extrusion; hypertension

SUMMARY

This work focused on development of a concentric multi-layered fixed-dose combination via an advanced manufacturing technique, hot-melt co-extrusion. The dosage form was designed to offer differing release behaviour; immediate and sustained release from the coat and core, respectively. Hydrochlorothiazide and losartan potassium were incorporated as anti-hypertensive drugs. Solid-state characterisation revealed that both were transformed into their amorphous forms. *In-vitro* dissolution testing showed desirable release performances offering both immediate and modified release.

INTRODUCTION

The anti-hypertensives have been clinically proven to be effective in the treatment of hypertension (HYP), their full benefits are often not realised due to poor medication adherence (Brown et al., 2011). There are several factors which exist for poor medication adherence including those related to the patient i.e. increased age or a lack of understanding of their disease state (Ryan, 2017). However, it is generally accepted that adherence becomes poorer as the number of medicines prescribed is increased. This is a particular problem in the treatment of HYP, as it generally requires multiple drugs for a positive clinical outcome, with poor adherence leading to sub-optimal clinical outcomes. Therefore, the industry has attempted to overcome this burden by combining various APIs into a single pill, which are commonly referred to as fixed-dose combinations (FDCs). Recently, hot-melt (co)-extrusion (HMCE) has received considerable attention from the pharmaceutical industry for the production of FDCs, due to its ability in designing multi-layered FDCs in a single processing step. Furthermore, HMCE products are capable of independently modulating the release of the incorporated APIs. This investigation utilises HMCE to manufacture a multi-layered FDC providing an immediate release (IR) of hydrochlorothiazide (HCTZ) and an immediate and sustained release (SR) of losartan potassium (LK) as it has a very short half-life, i.e., 2 hours (Ripley et al., 2010) These APIs are recommended to be used in combination once-a-day for the treatment of HYP, as they have been shown to be well tolerated and more efficacious in lowering blood pressure (BP) than monotherapy (Saruta et al., 2007).

MATERIALS AND METHODS

HCTZ (Alfa Aesar, Heysham, England), LK (Tokyo Chemical Industries, Japan), Eudragit® EPO, RSPO and RLPO (Evonik Industries, Germany), Kollidon® VA46 and Soluplus® (BASF, Germany) were used. All other chemicals were of analytical grade or equivalent. Thermal stability was investigated using

https://doi.org/10.5920/bjpharm.2019.XX

thermogravimetric analysis (TGA, Q50 TA Instruments, Leatherhead, UK) and solid-state characterisation was performed using; differential scanning calorimetry (DSC, Q20 TA Instruments, Leatherhead, UK) and powder x-ray diffraction (PXRD, Mini-Flex II, Rigaku™, Japan). HME was performed using a co-rotating twin-screw extruder (Microlab, Rondol, UK) with full conveying elements for all examined formulations. Screw speed was varied from 10-100rpm, and feed rate was set at 1g/min. HMCE was carried out by connecting two identical Microlab extruders via an in-house designed side-feeding annular co-extrusion die, set to the mid-point temperatures of both extruders. *In-vitro* drug dissolution testing was performed using USP type II dissolution apparatus (paddle) with extrudates manually cut (width 2mm and diameter 4mm). The testing temperature was maintained at 37±0.5°C and the stirring speed set to 100rpm. Samples were tested over a period of 2 hours in 0.1N hydrochloric acid (HCl) pH1.2, and a further 22 hours in phosphate buffered saline (PBS) pH6.8. 3mL aliquots were withdrawn at pre-determined time intervals and analysed using a validated high-performance liquid chromatograph (HPLC) method.

RESULTS AND DISCUSSION

HMCE was successfully employed to produce a concentric coat-core FDC containing two anti-hypertensive drugs, HCTZ and LK. Eudragit® EPO was used a coat matrix, while a blend of Soluplus® and Eudragit® RSPO (10% (w/w)) was used as a matrix for the core. Solid-state characterisation of both (co)-extrudates using PXRD showed halo-like diffractograms indicating the lack of crystalline drug in both layers. Likewise, both layers were analysed via DSC and revealed a single glass transition temperature (Tg). This single Tg, which lay between the respective API and polymer Tgs, indicates the presence of a molecular dispersion. During *in-vitro* drug dissolution testing, co-extrudates offered bi-phasic release behaviour. HCTZ release was deemed IR as at least 75% was released within 45 minutes while LK delivery offered dual release characteristics. This included a burst release (a loading dose of LK, 50%, was included in the coat layer) followed by an extended release (ER) from the remaining LK dose in the core layer. This release is most desirable as this would allow for a rapid onset of action followed by a prolonged anti-hypertensive effect, achieved by maintaining the plasma concentration of the drug. This would prevent fluctuation in drug concentration in the bloodstream and therefore minimise episodes of underexposure to or toxicity from LK.

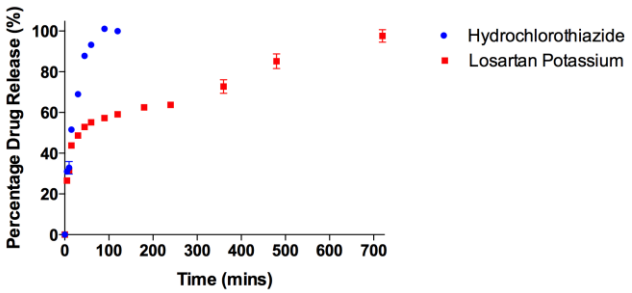

Fig. 1. *In-vitro drug dissolution for the hot-melt co-extrudate over a period of 2 hours in 0.1N HCl pH1.2 followed by a by 12 hours in PBS pH6.8. Dissolution testing was performed at 37±0.5°C and a stirring speed of 100rpm. Values represent an average (±SD, n=3).*

CONCLUSIONS

HCTZ was successfully formulated into the coat layer with LK. The remaining LK was formulated into the core layer. *In-vitro* drug dissolution confirmed the coat layer offered an IR of HCTZ and LK. The remaining core layered offered a SR of LK. Solid-state characterisation revealed that both HCTZ and LK were molecularly dispersed in the coat layer. LK was transformed into its amorphous form in the core layer. This study contributes to the possibility of HMCE being used in the pharmaceutical industry for the production of FDCs for the treatment of HYP.

ACKNOWLEDGEMENTS

This investigation was conducted with the financial support of both the Department for the Economy of Northern Ireland and Science Foundation Ireland (SFI) under Grant Number 14/IA/2559.

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