Journal of Controlled Release 217 (2015) 308–314

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

3D printing of five-in-one dose combination polypill with defined immediate and sustained release profiles

Shaban A. Khaled [a], Jonathan C. Burley [a], Morgan R. Alexander [a], Jing Yang [b], Clive J. Roberts [a,*]

[a] Laboratory of Biophysics and Surface Analysis, School of Pharmacy, The University of Nottingham, Nottingham NG7 2RD, UK
[b] Division of Drug Delivery and Tissue Engineering, School of Pharmacy, The University of Nottingham, Nottingham NG7 2RD, UK

ARTICLE INFO

Article history:
Received 4 July 2015
Received in revised form 15 September 2015
Accepted 16 September 2015
Available online 25 September 2015

Chemical compounds studied in this article:
Aspirin (PubChem CID: 2244)
Hydrochlorothiazide (PubChem CID: 3639)
Atenolol (PubChem CID: 2249)
Pravastatin sodium (PubChem CID: 16759173)
Ramipril (PubChem CID: 5362129)

Keywords:
3D printing
Polypill
Sustained release
Immediate release
Personalised medicine

ABSTRACT

We have used three dimensional (3D) extrusion printing to manufacture a multi-active solid dosage form or so called polypill. This contains five compartmentalised drugs with two independently controlled and well-defined release profiles. This polypill demonstrates that complex medication regimes can be combined in a single personalised tablet. This could potentially improve adherence for those patients currently taking many separate tablets and also allow ready tailoring of a particular drug combination/drug release for the needs of an individual. The polypill here represents a cardiovascular treatment regime with the incorporation of an immediate release compartment with aspirin and hydrochlorothiazide and three sustained release compartments containing pravastatin, atenolol, and ramipril. X-ray powder diffraction (XRPD) and Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy (ATR-FTIR) were used to assess drug-excipient interaction. The printed polypills were evaluated for drug release using USP dissolution testing. We found that the polypill showed the intended immediate and sustained release profiles based upon the active/excipient ratio used.

1. Introduction

The use of multiple medications to control complex diseases such as cancer and heart diseases is an increasingly used therapeutic strategy [1,2]. Each active pharmaceutical ingredient is traditionally administered via a separate dosage form [2]. This is inconvenient, can lead to errors in medication and presents significant patient compliance issues [2,3]. Combining multiple actives into a single tablet with appropriate release profiles and doses (potentially optimised for individuals) is an attractive alternative [3–5].

The term "polypill" refers to a tablet that is composed of a combination of several medicines [5]. The polypill concept has been used to treat and prevent cardiovascular disease and high blood pressure [6–9]. This polypill (in fact a capsule) manufactured by Cadila Pharmaceuticals Limited under trade name of Polycap™ is currently the only polypill formulation commercially available [7,8,10]. Cardiovascular disease is the most common cause of death globally and requires managing as a chronic condition in many people during large portions of their lifetime [11]. Based on previous work, we suggest that additive manufacturing or 3D printing is potentially well suited to producing a multicomponent polypill formulation [4,8,9]. As an approach 3D printing also offers the opportunity to produce personalised medicines and is adaptable to a distributed manufacturing model [4]. The freedom to form specific geometries in comparison to the restrictions of traditional tableting via powder compression can be used to separate incompatible substances and to enable different release rates using shape and size as well as excipient manipulation [4,12]. Here we have designed a 5-component polypill based upon the currently available "polycap" commercial formulation with three sustained release compartments containing pravastatin, atenolol, and ramipril, which were physically separated by a hydrophobic cellulose acetate shell designed to act as a permeable carrier, and covered with an immediate release aspirin and hydrochlorothiazide compartment (Fig. 1.). Atenolol is a beta-blocker agent which is used to treat hypertension and also prevent and/or treat heart attack [13]. Hydrochlorothiazide is a thiazide diuretic used to prevent absorption of too much salt and to treat oedema or fluid retention in individuals with congestive heart failure, kidney disorder, and liver cirrhosis [14]. Ramipril is an angiotensin converting enzyme (ACE) used for treatment of hypertension and congestive heart failure which improves heart function after a heart attack [15]. Aspirin is an antiplatelet used to reduce the risk of blood clotting and reduce heart attacks or strokes [16]. Pravastatin is a 3-hydroxy-3-methylglutaryl–coenzyme A

* Corresponding author at: School of Pharmacy, The University of Nottingham, University Park, NG7 2RD, UK.
E-mail address: clive.roberts@nottingham.ac.uk (C.J. Roberts).

http://dx.doi.org/10.1016/j.jconrel.2015.09.028
0168-3659/

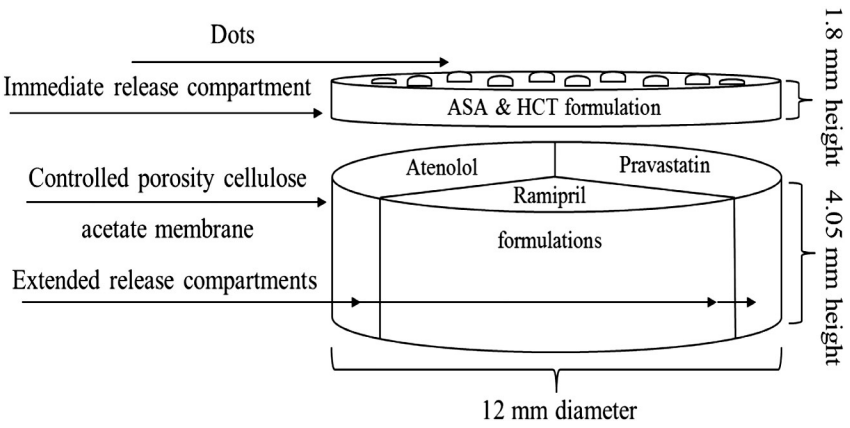

Fig. 1. Schematic structural diagram of the polypill design, showing the aspirin and hydrochlorothiazide immediate release compartment and atenolol, pravastatin, and ramipril sustained release compartments.

(HMG-CoA) reductase inhibitors used to reduce blood cholesterol and triglycerides in hyperlipidaemic patients and lower rates of strokes and heart attacks [17].

3D printing is a process used to fabricate 3D objects by laying down successive material layers in different shapes taken directly from a digital file [18]. There has been a significant recent growth in interest of 3D printing as a tool in pharmaceutics and personalised medicine [19–23]. For example, a heat based fused deposition modelling 3D printer (>200 °C) has been used to extrude 5-aminosalicylic acid (5-ASA, mesalazine), and 4-aminosalicylic acid (4-ASA) and prednisolone loaded poly (vinyl alcohol) (PVA) filaments and produce simple solid tablets [19,24]. However, this approach would not be suitable generally due to the possibility of heat induced degradation of thermally sensitive drugs. Also, there are not many reports of printing a single drug formulation with multiple release mechanisms [4,25]. Katstra et al. employed multi-steps 3D printing to deposit chlorphenaramin maleate (antihistamine used in the prevention of symptoms of allergic conditions such as rhinitis and urticaria) as a binder onto powdered excipients (the amount of drug deposited was 5.45 mg) [25,26]. However, issues such as ink bleeding, migration, and capillary effect due to drug/binder oversaturation are difficult to avoid for printing of larger drugs doses such as 500 mg of paracetamol or ibuprofen [25,26]. Problems with this approach include long drying times (in excess of 50 h) and high friability (>1%) of the resultant tablet [25,26].

To address the above mentioned issues of drug degradation and the complexity in published 3D printing processes we have employed a 3D extrusion system operated at room-temperature to manufacture a polypill capable of delivering the five drugs via two predictable release mechanisms. A hydrophobic cellulose acetate shell was first extruded then the active drugs atenolol, pravastatin, and ramipril were mixed with a hydrophilic matrix (HPMC) and extruded in to the segmented compartments of cellulose acetate to form sustained release compartments. Aspirin and hydrochlorothiazide were mixed with a disintegrant; sodium starch glycolate and other excipients and extruded directly on the top of the sustained release compartments, to give an immediate release compartment. A series of raised dots were also printed onto the top of the tablet to facilitate identification of the formulation both visually and by touch, the composition of these was the same as the upper "immediate release" layer. The printed tablets were tested for drug release and drug-excipients interaction using United States Pharmacopoeia Convention (USP) Type I apparatus dissolution tester, X-ray Powder Diffraction (XRPD), and Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy (ATR-FTIR).

Table 1
The weight percentage composition of various ingredients in the cellulose acetate shell feed stock.

Ingredients	Function	Coating (% w/w)
Cellulose acetate	Hydrophobic shell	22.64
D-mannitol	Filler	62.26
PEG (6000)	Plasticizer	15.10

2. Materials and methods

2.1. Materials

Ramipril and pravastatin sodium were supplied by Kemprotec Limited (Cumbria, UK). Atenolol, aspirin, and hydrochlorothiazide, polyvinylpyrrolidine (PVP) and lactose were supplied by Sigma–Aldrich (Gillingham, UK). D-mannitol 99% was purchased from VWR International Ltd. (Leicestershire, UK). Sodium starch glycolate (Primojel®) was kindly supplied as a gift from DFE Pharma. Hydroxypropyl methylcelloluse (HPMC K100M CR) (Methocel TM) was a gift from Colorcon®. Milli-Q water (resistivity 18.2 MΩ cm) was used for all formulations and solutions. All other reagents were of either HPLC or analytical grade.

Table 2
The weight percentage composition of various ingredients in atenolol, pravastatin, and ramipril formulation feed stock for the sustained release compartments of the polypill.

Ingredients	Function	ATEN-HPMC* (15% w/w)	PRA-HPMC** (15% w/w)	RAM-HPMC*** (15% w/w)
Atenolol	Active ingredient I	30.00	–	–
Pravastatin	Active ingredient II	–	20.00	–
Ramipril	Active ingredient III	–	–	15.00
HPMC 2208	Hydrophilic matrix	15.00	15.00	15.00
Lactose	Filler	55.00	65.00	70.00

* ATEN = atenolol.
** PRA = pravastatin.
*** RAM = ramipril.