Desktop 3D printing of controlled release pharmaceutical bilayer tablets

Shaban A. Khaled, Jonathan C. Burley, Morgan R. Alexander, Clive J. Roberts

ABSTRACT

3D printing was used as a novel medicine formulation technique for production of viable tablets capable of satisfying regulatory tests and matching the release of standard commercial tablets. Hydroxypropyl methylcellulose (HPMC 2208) (Methocel™ K100M Premium) and poly (acrylic acid) (PAA) (carbopol® 974P NF) were used as a hydrophilic matrix for sustained release (SR) layer. Hypromellose® (HPMC 2910) was used as a binder while microcrystalline cellulose (MCC) (Pharmacel® 102) and sodium starch glycolate (SSG) (Primojel®) were used as disintegrants for immediate release (IR) layer. Guaifenesin Bi-layer Tablets (GBT) were used as a model drug (Mucinex®) for this study. There was a favourable comparison of release of the active guaifenesin from the printed hydrophilic matrix compared with the commercially available GBT. The printed formulations were also evaluated for physical and mechanical properties such as weight variation, friability, hardness and thickness as a comparison to the commercial tablet and were within acceptable range as defined by the international standards stated in the United States Pharmacopeia (USP). All formulations (standard tablets and 3D printed tablets) showed *n* values between 0.27-0.44 which indicates *Fickian diffusion* drug release through a hydrated HPMC gel layer.

Key words

GBT, 3D printing, guaifenesin, controlled release, personalized medicine

Chemical compounds studied in this article

Guaifenesin (PubChem CID 3516).

1. Introduction

It is widely believed that a key factor for future improvements in disease treatment will be driven by point-of-care and home-based diagnostics linked with genetic testing and emerging technologies such as proteomics and metabolomics analysis (Malandrino and Smith, 2011). This has led to the concept of personalized medicine, which foresees the customization of healthcare to an individual patient (Holmes et al., 2010; Scoutaris et al., 2011). However, how are the requisite 'unique' medicines for each patient to be manufactured on a routine basis? Currently no viable method used in manufacturing of solid dosage forms, such as tablets, is suitable. Tablets for oral administration are by far the most common dosage form, and are generally prepared by either single or multiple compressions (and in certain cases with molding) processes (Sastry et al., 2000; Jivraj et al., 2000; Rosca and Vergnaud, 2008). This popularity is essentially because of their ease of manufacture, good patient compliance, pain avoidance (compared to injection), and accurate dosing (Sastry et al., 2000; Jivraj et al., 2000). Powders are prepared for tablet compression via many well-established unit processes such as milling, mixing and granulation (dry and wet) (Parmar and Rane, 2009; Davies, 2009). Each one of these steps can introduce difficulties in the manufacture of a medicine (e.g., drug degradation and form change), leading to possible batch failures and problems in optimization of formulations (Price et al., 2002; Surana et al., 2003; Taylor and Zografi, 1998; Yoshioka and Stella, 2000). Tablets are almost universally manufactured at large centralized plants via these processes using tablet presses essentially unchanged in concept for well over a century. This route to manufacture is clearly unsuited to personalized medicine and in addition provides stringent restrictions on the complexity achievable in the dosage form (e.g., multiple release profiles and geometries) and requires the development of dosage forms with proven long-term stability (Scoutaris et al., 2011). We have previously demonstrated the use of ink-jet printing for the production of a formulation in a 2D array of small deposits containing the poorly soluble drug felodipine, an antihypertensive, with polyvinylpirrolidone (PVP) as an excipient (Scoutaris et al., 2011; Scoutaris et al., 2012). And also the actives captopril and thiazide (both are diuretics) with poly (lactic-*co*-glycolic acid) to mimic its commercial formulation (Capozide®) at much reduced dosages (Scoutaris, Ph.D.

Thesis, 2011). In these cases the drug release was altered through control of the drug loading in the printed spots or the inclusion of excipients that slowed release. It was proposed that this demonstrated the potential of this approach to print practical dosage forms (e.g., as an array of many thousands of spots with different release profiles and different drugs) (Scoutaris et al., 2011). However, this work was based on an array of micro-deposits, limiting the dosage that could be achieved and hence confining this approach to only the most active drugs.

Previous research by other workers has also shown that printed formulations are a potential route to personalized medicines. Sandler et al employed inkjet printing to deposit caffeine, theophylline and paracetamol onto a variety of surfaces (including paper) (Sandler et al., 2011). However, the amounts of drug deposited were small, with a maximum of 270 μg of drug deposited. For comparison, typical drug loadings in tablets are of the order of 500 mg (e.g. paracetamol, aspirin, and ibuprofen) (Sandler et al., 2011). In addition, Katstra et al., Yu et al. and Rowe et al. imported a complex multistep 3D printing process to produce a solid dosage forms (Rowe et al, 1999; Katstra et al., 2000; Yu et al., 2009). To address the issues of low drug loading in 2D printed formulations and complexity in 3D printing process, we used a single step 3D printing process using a low cost (less than $ 1000) desktop 3D printer to produce viable tablets capable of sustained release. This approach has the potential for producing medicines which would allow patients to be given an accurate and personalized treatment regime, which could include multiple active ingredients, either as a single blend or potentially as layers in a multi-layer printed tablet. For example, in the future patients suffering from chronic diseases such as cancer and kidney failure could have their treatment and dosage determined using identified genetic markers. Their individual, personalized medicines could potentially then be manufactured for them at the point of care. Patients would be administered an accurate and personalized dose given in a single tablet which may otherwise be a challenge using conventional centralized tableting processes (Kommanaboyina and Rhodes, 1999). Furthermore, 3D printers would eliminate the previously identified problematic unit processes used in the tablet production process. This could be important for many drugs, for example 1,2,3-trinitroxypropane (nitroglycerin), a drug used to treat angina pectoris, is among many noted for its tendency to degrade on storage but if

produced for immediate use this issue is reduced in significance (Kommanaboyina and Rhodes, 1999).

For our 3D printing approach, we aim for the first time to demonstrate the 3D pharmaceutical printing principle by producing a printed tablet using excipients selected based on their potential to mimic the commercially available dosage form in terms of drug release profile. The printer employed is a room-temperature extrusion system, therefore feedstock for printing took the form of a viscous paste.

2 Materials and methods

2.1. Materials

Guaifenesin and hydrochloric acid (HCL) 37 % Ph. Eur., were purchased from VWR international Ltd. (Leicestershire, UK). Trisodium phosphate dodecahydrate (TSP.12 H_2O) and hydroxypropyl methylcelloluse (HPMC 2910) (hypromellose®) were supplied by Sigma-Aldrich (Gillingham, UK). Poly (acrylic acid) (PAA) (Carbopol® 974P NF), hydroxypropyl methylcelloluse (HPMC 2208) (Methocel™ K100M Premium) were obtained as a gratis from Surfachem Group Ltd. (Leeds, UK), and Colorcon Limited (Dartford Kent, UK), respectively. Microcrystalline cellulose (MCC) (Pharmacel® 102) and sodium starch glycolate (SSG) (Primojel®) were kindly supplied as a gift from DFE Pharma. Guaifenesin Bi-layer Tablets (GBT) (Mucinex®) were purchased from Reckitt Benckiser Group (Berkshire, UK).

2.2. Methods

2.2.1. Printing of guaifenesin tablets

2.2.1.1. Preparation of hydroxypropyl methylcellulose gel

Two HPMC gels were prepared using different viscosity grades of HPMC; HPMC 2910 (1 % w/v) for the immediate release (IR) layer and HPMC 2208 (1 % w/v) for the sustained release (SR) layer. The following steps were used to prepare HPMC 2910 gel (Fig. 1). 1 g of HPMC 2910 powder was added into 30 ml of hot water (90 °C) and thoroughly mixed until a good dispersion was formed. 70 g of ice or cold water was added and stirred for half an hour to increase polymer solubility. The gel was stored in a refrigerator for 24 hrs until a smooth homogenous gel with good consistency, free from air

bubbles and aggregates was formed (Abd-Allah et al., 2010). The other gel, HPMC 2208 (1 % w/v), was prepared using the same above method.

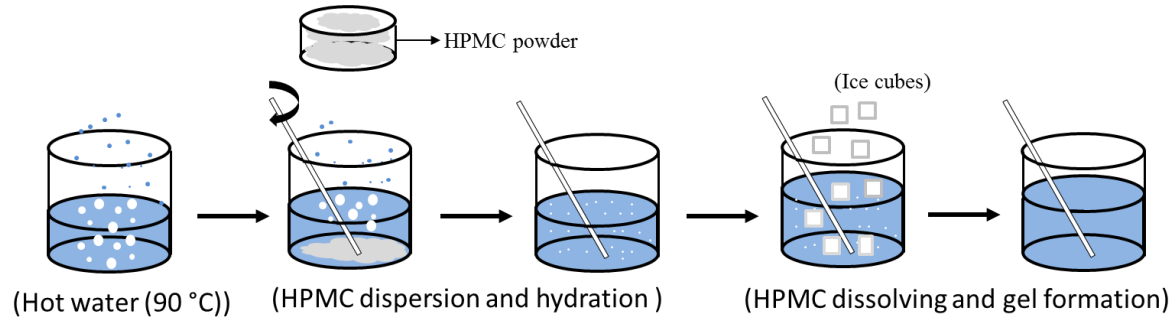

Fig.1. Schematic diagram of dispersion technique of hydroxypropyl methylcelloluse powder (HPMC 2910 and HPMC 2208).

2.2.1.2. Preparation of guaifenesin paste

The guaifenesin powder and required excipients for the IR layer (SSG and MCC) were mixed for 30 minutes. HPMC 2910 (1 % w/v) was used as a binder for the powder blend. A pre-adjusted volume of HPMC 2910 gel was added and mixed until homogenous paste without aggregates and separation was observed. For the SR layer, different excipients (HPMC 2208 at different percentages and PAA) were mixed with guaifenesin powder. HPMC 2208 (1 % w/v) was used as a binder to hold up the ingredients together and form guaifenesin paste. Each prepared paste was filled in a separate syringe tool and from the software (FabStudio), GBT were extruded through a 1.2 mm nozzles using desktop 3D printer. The IR functionality was studied using different disintegrants; MCC and SSG. The sustained release functionality was investigated using a hydrophilic matrix; HPMC 2208 and PAA, at four different HPMC 2208 percentages; *GBT-HPMC (6 % w/w)*, *GBT-HPMC (8 % w/w)*, *GBT-HPMC (10 % w/w)* and *GBT-HPMC (14 % w/w)* according to the formula shown in Tables 1& 2.

Table 1. The percentage composition of various ingredients in guaifenesin immediate release (IR) feed stock.

Ingredients	**(% w/w) per IR layer**
Guaifenesin (active ingredient)	81
HPMC 2910 (binder)	2
SSG type A (disintegrant)	7
MCC PH 102 (disintegrant)	10

Table 2. The percentage composition of various ingredients in guaifenesin sustained release (SR) feed stock.

Ingredients	GBT-HPMC (6 % w/w)	GBT-HPMC (8 % w/w)	GBT-HPMC (10 % w/w)	GBT-HPMC (14 % w/w)
Guaifenesin (active ingredient)	91	88	86	82
HPMC 2208 (hydrophilic matrix)	6	8	10	14
HPMC 2208 (binder)	2	2	2	2
PAA (hydrophilic matrix)	2	2	2	2

2.2.1.3. 3D based extrusion printer

To investigate the potential applicability of this concept an easily available desktop extrusion based 3D printer (Fab@Home) (Fig. 2 a& b) was used to formulate various sustained release (SR) guaifenesin bilayer tablets (GBT) containing the active guaifenesin, an expectorant used in the treatment of respiratory tract infections, and a range of excipients (Fig. 2 c). As a realistic model system, we chose to try to mimic the drug release of a commercial preparation of guaifenesin. It is available commercially as a bi-layer tablet (containing 600 mg guaifenesin), with IR and SR layers, in order to provide a rapid alleviation of symptoms via the burst release, while maintaining therapeutic levels of drug release over an extended time-scale.

2.2.2. In vitro drug release

In vitro drug release studies of commercial GBT (the IR layer composed of 100 mg guaifenesin, SSG, magnesium stearate and MCC, the SR layer composed of 500 mg guaifenesin, carbomer 934P NF, FD&C blue No. 1 aluminium lake, hypromellose, USP, magnesium stearate NF) and 3D printed tablets were performed using a United States Pharmacopeial Convention (USP) Type I apparatus at 50 rpm (Dissolution-Erweka Dt600 Dissolution Tester) in acidic medium for 2 hrs (representative of the stomach) followed by addition of 0.2 M trisodium phosphate dodecahydrate (TSP.12 H_2O) solution to increase the pH to 6.8, for 10 hrs (representative of the small intestine) to mimic the gastrointestinal fluid pH. 6 tablets from each formulation were placed in acidic dissolution medium 675 ml of 0.1 M hydrochloric acid. 5.0 ml samples were withdrawn at 0.25, 0.5, 1, and 2 hrs time interval from each vessel (Blume et al., 2002). 225 ml of 0.2 M TSP.12H_2O was added to each vessel immediately after two hours to raise the solution pH 6.8 (Blume et al., 2002). The pH was adjusted by adding few drops

of 2.0 M HCl. 5.0 ml samples were subsequently removed at 4, 6, 8, 10 and 12 hrs. The dissolution samples were filtered using standard 20 µm filters (Copley Scientific, UK). 1 ml from each 5 ml sample was diluted by 9 ml of a suitable dissolution medium and analyzed with UV-Visible spectrophotometer (Cecil UV, Nottingham, UK) at a λ_{max} of 274 nm. The temperature of the dissolution medium was retained at 37 °C ± 0.5 ºC throughout the test. Two guaifenesin calibration curves were prepared using acidic medium (0.1 M HCl) and a phosphate buffer medium (pH 6.8) and used to identify concentration of unknown samples (Fig. S.1).

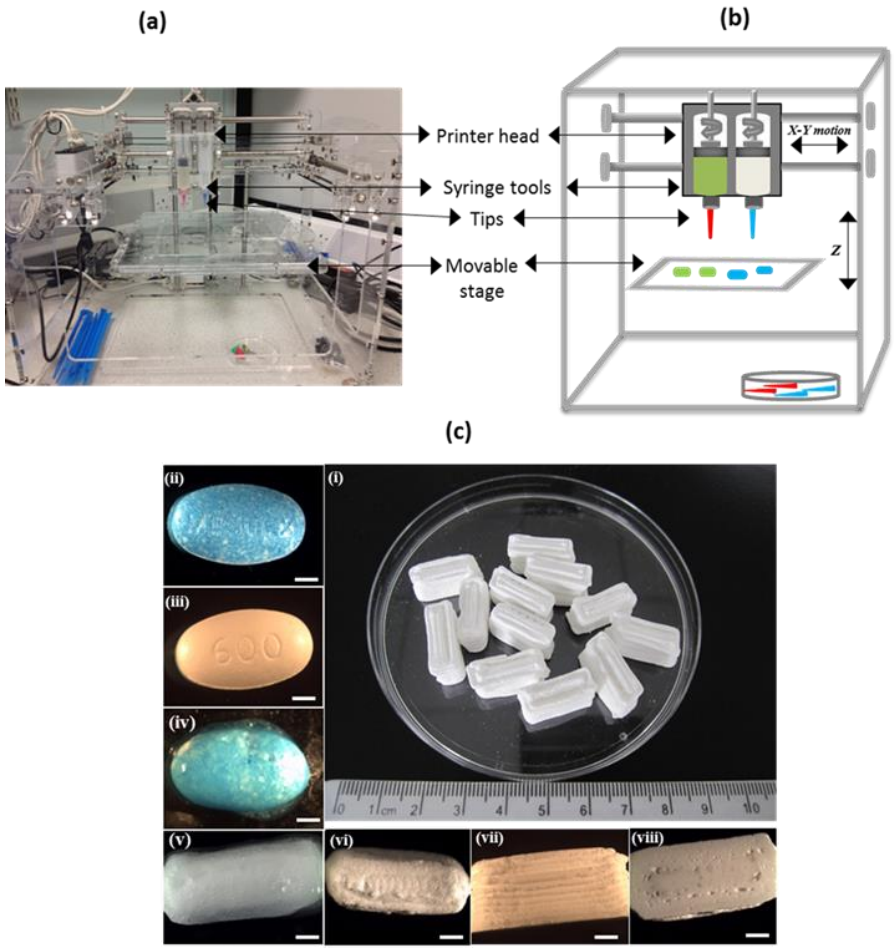

Fig. 2. (a) Photograph and (b) schematic diagram of the Fab@Home printer model 2. (c) Images at different scales of 3D printer produced guaifenesin bilayer tablets (H/W/L = 7 × 6.3 × 15.5 mm) and commercial GBT (H/W/L = 5.91 × 9.6 × 16.4 mm). (ii) Top view and (iii) underside view of commercial GBT. (iv) & (v) Gel barrier surrounding commercial GBT and 3D printed bilayer tablet after 2 hrs dissolution test, respectively. (vi)

Top view (vii) side view & (viii) underside view of individual 3D printed bilayer tablets. The scale bar (ii-viii) is 10 mm.

2.2.3. Physical characterization of guaifenesin tablets

2.2.3.1. Weight uniformity test

20 tablets were individually weighed and their average was calculated and compared with percentage of weight variation (Bushra et al., 2008; Remington and Beringer, 2006).

2.2.3.2. Hardness

Ideal tablets should have enough hardness to resist breaking during transportation, storage. However, tablets also should be soft enough to disintegrate and release drug (US Pharmacopoeia XXIV, 2000). 6 tablets were randomly selected and tested for hardness using hardness tester (Hardness tester C50, I Holland Ltd., Holland) (US Pharmacopoeia XXIV, 2000; Bushra et al., 2008).

2.2.3.3. Friability

20 guaifenesin tablets from each formulation were selected randomly and placed on a sieve. The loose dust found over tablets was removed with a soft brush. The tablets were accurately weighed. The tablets were placed in a friabilator (Friability tester, E-1851 Erweka) and rotated at a constant speed of 25 rpm for a period of 4 min (Bushra et al., 2008; Remington and Beringer, 2006; Folttmann and Quadir, 2008). The tablets were cleaned from loose dust and reweighed and the percentage weight loss calculated.

3. Results and discussion

3.1. Dissolution profiles

The dissolution data presented in Fig. 3 shows that all formulations displayed sustained release of guaifenesin over a period of 12 hrs as is required. An initial burst release (> 20 % in half an hour) of guaifenesin occurred from the IR layer of the formulations. This initial high amount of guaifenesin is attributed to the inclusion of the disintegrants; MCC and SSG. Disintegrants are designed to cause

tablets to break up on exposure to water and rapidly release any active ingredients. The initial release of guaifenesin from the formulations with low concentration of HPMC 2208 in *GBT-HPMC (6 % w/w)* and *GBT-HPMC (8 % w/w)* was high (> 75 % in two hours) compared to the drug release (65 % in two hours) and (57 % in two hours) from *GBT-HPMC (10 % w/w)* and *GBT-HPMC (14 % w/w),* respectively. This is mainly because of release of guaifenesin from the IR layer and also drug release from the surface of SR layer due to the small channels found underside of individual 3D printed bilayer tablets (Fig. 2c (viii)). The drug release of guaifenesin from *GBT-HPMC (14 % w/w)* was the closest to the *commercial GBT*. This is consistent with the increased amount of hydrophilic matrix material used (HPMC 2208) (14 % w/w). Finally, the release rate of guaifenesin release decreased as the concentration of HPMC 2208 was increased. This increase in concentration of HPMC is expected to lead to improved wettability, enhanced water uptake and greater swelling of the hydrophilic matrix and gel barrier formation which is all consistent with the observed reduction in drug release rate from the formulation with greater amounts of HPMC 2208 (Fig. 2c (iv & v)) and (Fig. S.2) (Folttmann and Quadir, 2008).

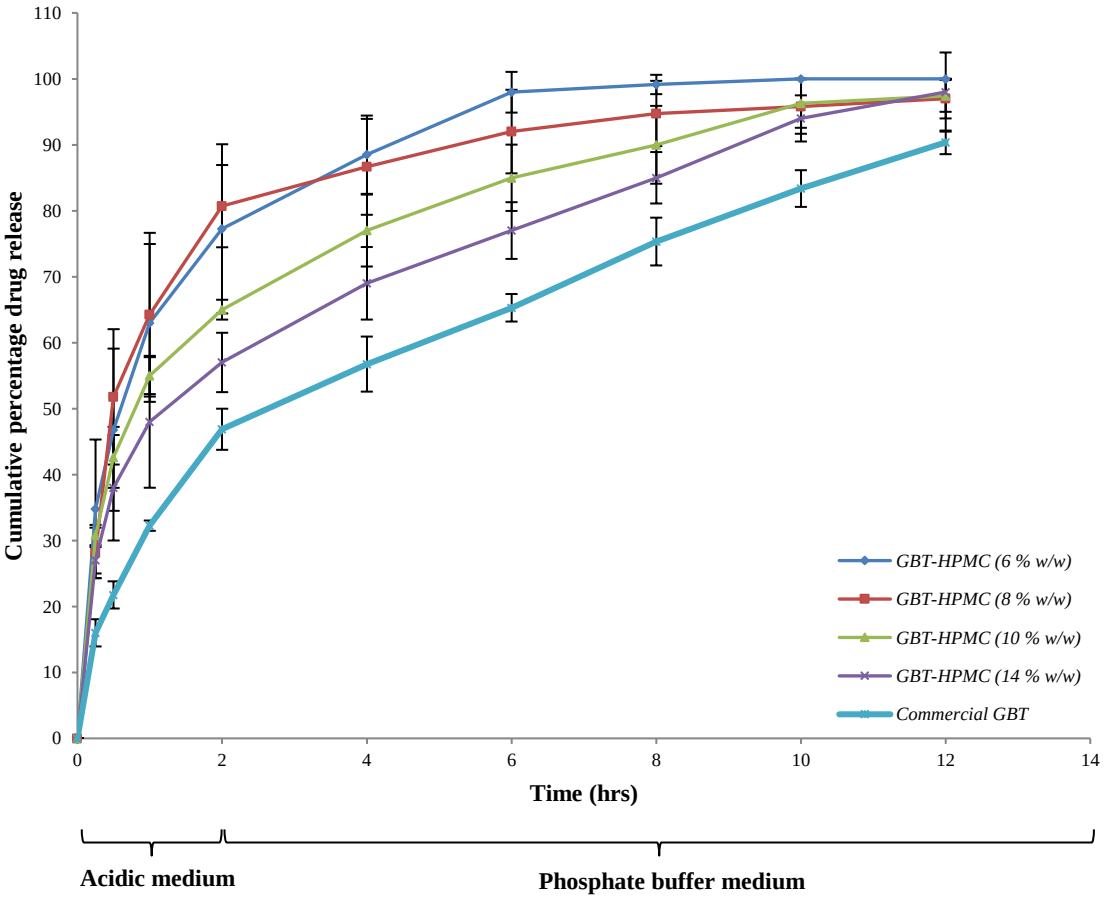

Fig. 3. Dissolution profile of guaifenesin tablets; *GBT-HPMC* (6 % w/w), *GBT-HPMC* (8 % w/w), *GBT-HPMC (10 % w/w)*, *GBT-HPMC (14 % w/w)* and commercial GBT. The error bars are the standard error in the mean where $n = 6$.

3.2. Mechanical properties

The tablets were evaluated for weight variation, thickness, hardness and friability and all tablets complied with USP specifications (total weight loss is ≤ 1 % for friability, % deviation = ± 5 % for weight variation) (US Pharmacopoeia XXIV, 2000). The results of these standard pharmacopeial tests are presented in Fig. 4 (i to iv). The weight variations of the five formulations are shown in Fig. 4 (i). Although the absolute weights of the different formulations vary slightly between formulations, all tablets weight are from 650-730 mg, which is typical for many commercial bilayer formulations. The variation in tablet thickness is presented in Fig. 4 (ii). All formulations (commercial and printed) have similar average thicknesses. *GBT-HPMC (6 % w/w)* (printed) has by far the highest in-batch variation in thickness. The commercial formulation exhibited the narrowest variation in thickness, and this is in itself not unreasonable. Our 3D printing process is an experimental approach and is not expected at this stage to reproduce the very small variations seen in formulations manufactured using well-established tableting technology. The key point perhaps is that changing the formulation type for the 3D printed tablets allows a level of control to be achieved over the variation in thickness. The tablet hardnesses are shown in Fig. 4 (iii). The hardness of *commercial GBT* is more than twice that of the printed ones. Considering the nature of the manufacturing processes for the commercial (high pressure compression) versus the printed tablets, this difference seems entirely reasonable. With respect to the lower hardness exhibited by the 3D printed tablets, it should be noted that all the printed tablets can be handled readily without any loss of structural integrity. The parameter for which there is the greatest difference between commercial and printed tablets is the friability (Fig. 4 (iv)). This variation in friability (% in weight loss) was attributed to the low percentage of binder, low-viscosity grade HPMC 2910 (1 % w/w) in the IR layer, a binding agent which gives reasonable binding strength between active and non-active ingredients and form tablets with good mechanical properties (Nagadivya et al., 2012). However, the friability of *GBT-HPMC (14 % w/w)* was the closest to the

commercial GBT. The % in weight loss can be decreased by increasing the binder percentage which will also decrease the burst release of drug from the IR layer and decrease the overall drug release for the whole tablet and eventually shift the drug release rate to mimic the *commercial GBT*. From a subjective and qualitative assessment, the printed tablets appear to be quite robust and are able to withstand a reasonable amount of rough handling, including dropping onto a wooden table top from a height of six inches.

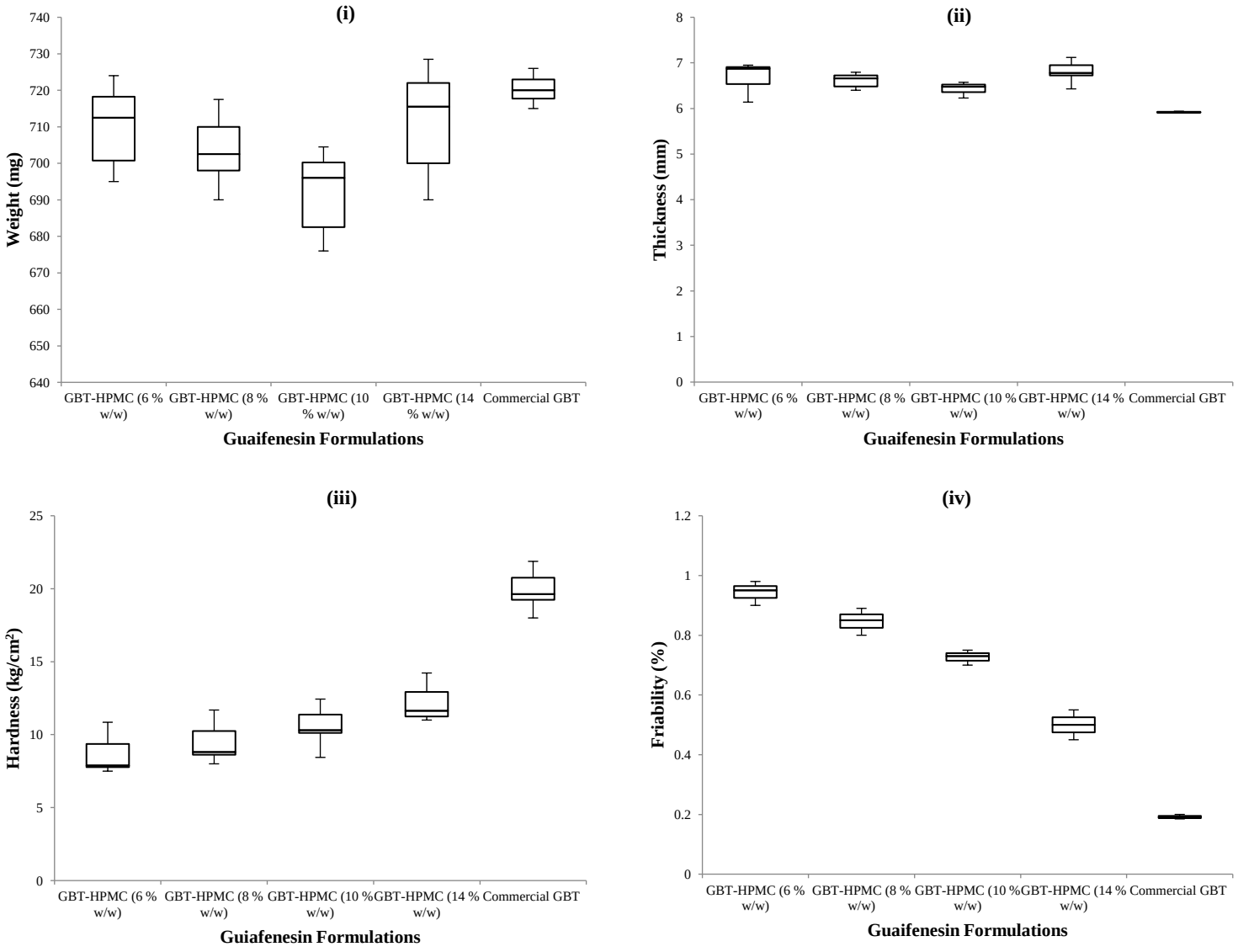

Fig. 4. Box plot summery of weight variation (mg) (i), thickness (mm) (ii), hardness (kg cm^{-2}) (iii) and friability (%) (iv) for *GBT-HPMC (6 % w/w), GBT-HPMC (8 % w/w), GBT-HPMC (10 % w/w), GBT-HPMC (14 % w/w) and commercial GBT.*

3.3. Drug release kinetics

Finally, so as to understand the drug release mechanisms displayed by the formulations, the modes of release of guaifenesin at acidic conditions (0-2 hrs), buffer conditions (2-12 hrs) and for both conditions (0-12 hrs) were modeled (Folttmann and Quadir, 2008; Patra et al., 2007; Pattanayak et al., 2011). For all formulations, the "best fit" model remained the same, irrespective of the dissolution conditions (Table S.1). The *commercial GBT* was best fitted by the *Higuchi equation* (i.e., cumulative percentage drug release is proportional to the square root of time) with an r^2 value of 0.99 and an *n* value of 0.44. This suggests that the drug is released primarily by diffusion through the hydrated HPMC gel layer for these formulations (Dash et al., 2010; Nep et al., 2010). *GBT-HPMC (10 % w/w)* and *GBT-HPMC (14 % w/w)* were best modeled using the *Korsmeyer–Peppas* model, Eqn. 1:

$$M_t/M_\infty = Kt^n \qquad (1)$$

Where M_t / M_∞ is the fraction of drug released at time t, K is the release rate constant and *n* the release exponent (Dash et al., 2010). They showed an *n* values of 0.29 and 0.32 fitted (r^2 = 0.99) which indicate *Fickian diffusion*, respectively *(Grassi and Grassi, 2005)*. *GBT-HPMC (6 % w/w)* and *GBT-HPMC (8 % w/w)* displayed *Fickian diffusion* having the same *n* value (0.27) and fitted (r^2 = 0.97) and (r^2 = 0.94), respectively. They were best modeled using the *first order* model (i.e., log cumulative percentage of drug remaining vs. time) where the drug release rate depends on its concentration (Dash et al., 2010). Overall, all formulations showed *n* values between 0.27-0.44 which that indicates *Fickian diffusion* drug release through the hydrated HPMC gel layer dominates for these formulations (Fig. S.3).

4. Conclusions

In this summary, we have demonstrated the production of relatively complex formulations printed into bilayer tablets using an inexpensive desktop 3D printer that can match the release of a *commercial GBT* (manufactured using conventional tablet compression methods). We believe that

there is clear potential for 3D printing to allow entirely new formulation types, such as new geometries, complex multi-layer or multi-reservoir tablets, and others. The potential for using 3D printing to develop new ways to treat many chronic conditions (e.g. asthma, arthritis and diabetes) is exciting. We believe that the present work is a significant step towards the demonstration and validation of simple, low-cost 3D printing for the tailored manufacture of medicines, which has the potential to play a crucial role in future developments in personalized care and treatment.

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