Fused-filament 3D printing of drug products: microstructure analysis and drug release characteristics of PVA-based caplets

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Abstract

Fused deposition modeling (FDM) 3–Dimensional (3D) printing is becoming an increasingly popular technology in the pharmaceutical field, since it allows the manufacture of personalized oral dosage forms by deposition of thin layers of material. Here, a filament extruder was used to obtain filaments of polyvinyl alcohol (PVA) containing paracetamol or caffeine appropriate for 3D printing. The filaments were used to manufacture caplets for oral administration by FDM 3D printing in order to evaluate the effect of the internal structure (micropore volume), drug loading and composition on drug dissolution behaviour. Micropore volume of the caplets was primarily determined by the presence of large pores due to gaps in the printed layers/net while printing, and the porosity of the caplets was 10 fold higher than the porosity of the extruded filament. Dynamic dissolution drug release tests on the caplets in biorelevant bicarbonate media revealed distinctive release profiles, which were dependent on drug solubility and drug loading. Porosity of the caplets did not help to predict the different drug release profiles. This study confirms the potential of 3D printing to fabricate caplets and helps to elucidate which factors influence drug release from this type of new dosage forms.

1. Introduction

3D printing (3DP) is an increasingly popular manufacturing technique that allows creation of solid objects by deposition of many thin layers. 3DP is nowadays used as a production tool or for rapid prototyping in many areas, from research to industry. It is destined to be the next industrial revolution because it is changing the way objects are created, transported and stored (Barnatt, 2013).

The pharmaceutical sector has embraced 3DP. The claimed advantages of the *in situ* fabrication of unit dosage forms with doses and/or drug combinations personalised to the patient may lead to a change in the way medicines are designed and manufactured. It is predicted that 3DP will herald a change from limited dose-range unit forms manufactured in big industries to medicines tailored to the patient, prepared in community pharmacies or hospitals (Alomari et al., 2015).

3DP could also be used as a standard manufacturing technology instead of tableting or capsule filling, even facilitating patient compliance to the treatment. For instance, in 2015, the first 3D printed medicine (Spritam®) received approval from the U.S. Food and Drug Administration (FDA) for oral use in the treatment of seizures in patients with epilepsy (Aprecia_Pharmaceuticals, 2015). The 3DP system (ZipDose®) allows manufacturing fast disintegrating formulations incorporating high drug dose, facilitating intake in patients with difficulty swallowing.

Several commercially available 3DP systems are in current usage in the pharmaceutical arena (Goyanes et al., 2015b; Goyanes et al., 2016; Jonathan and Karim, 2016; Khaled et al., 2015; Wang et al., 2016; Yu et al., 2009). One of the barriers to the wider use of the technology is the need to adapt the printers to the specific needs of the pharmaceutical field and the high quality standards demanded and regulated by the pharmaceutical industry.

Fused-deposition modeling (FDM) is possibly the most common and affordable printing technology with the greatest potential for unit dose fabrication. In FDM 3DP a polymer filament is passed through a heated nozzle that partially melts the polymer and it is then deposited on a build plate, in the x-y dimensions, creating one layer of the object to be fabricated (previously designed with computer-aided design (CAD) software). The build plate then moves down and the next layer is deposited. Thus, the object is fabricated in three dimensions and in a matter of minutes. Since the printer feedstock is an extruded polymer filament, FDM 3DP makes it possible to blend drug and polymers into a solid dispersion prior

to extrusion, to print drug-loaded dosage forms. FDM 3DP technology in pharmaceutics allows printing, at a relatively low cost, with different materials, polylactic acid (PLA) or polycaprolactone (PCL) for medical devices (Goyanes et al., 2016; Sandler et al., 2014; Water et al., 2015) or mainly polyvinyl alcohol (PVA) in the case of oral dosage forms (Goyanes et al., 2014; Goyanes et al., 2015a; Goyanes et al., 2015e; Melocchi et al., 2015; Skowyra et al., 2015).

The creation of drug-loaded filaments suitable for 3D printing medicines has been demonstrated with different drugs by soaking water-soluble filaments in concentrated alcoholic solutions of drug: e.g. for fluorescein (Goyanes et al., 2014), 4-aminosalicylic acid (4-ASA) and 5-aminosalicylic acid (5-ASA) (Goyanes et al., 2015a) and prednisolone (Skowyra et al., 2015). However, hot melt extrusion (HME), a widely used technique in pharmaceutics, has been evaluated to produce better drug-loaded 3D printable filaments with higher percentage of drug (Goyanes et al., 2015e; Goyanes et al., 2015f). In HME, the raw materials are forced to mix in a rotating screw at elevated temperatures before being extruded through a die to produce a strand of uniform characteristics (Repka et al., 2012).

The microstructure of the extruded filament and the 3D printed solid dosage forms and its effects on drug dissolution rate have not been investigated previously. The porosity of the printed material, a measure of the void spaces in the material, is a parameter that may control drug release rates of oral dosage forms, especially in matrix formulations such as uncoated pellets (Goyanes et al., 2010). Porosity is relevant also in HME, where changes in the porosity of the extrudates by different methods (e.g. CO_2 injection) have been evaluated and used to modify the drug release rate (Verreck et al., 2006).

The aims of this study therefore are to (a) manufacture different filaments containing paracetamol or caffeine (used as model drugs) in a water soluble polymer (polyvinyl alcohol, PVA) suitable for printing pharmaceutical dosage forms (caplets) and (b) to evaluate the effect of the internal structure (micropore volume was determined using mercury intrusion porosimetry), drug loading and composition of the 3D printed caplets on the drug dissolution behaviour in biorelevant media.

2. Materials and methods

Commercial PVA filament was purchased from Makerbot Inc., USA (1.75mm diameter, print temperature 190-220°C, batch No: 20140509-1,). Paracetamol (Melting point 169ºC, MW 151.16, solubility at 37ºC: 21.80 g/L (Yalkowsky and He, 2003)) and caffeine (Melting point 238ºC, MW 194.19, solubility at 37ºC: 37.07 g/L (Yalkowsky and He, 2003)), both USP

grade, were purchased from Sigma-Aldrich, UK. The salts for preparing the buffer dissolution media were purchased from VWR International Ltd., Poole, UK.

2.1 Preparation of PVA filament loaded with drug

PVA filaments were prepared as detailed previously (Goyanes et al., 2015f). Briefly, the PVA filament was cut into small pieces (~1 mm) using a Pharma 11 Varicut Pelletizer (Thermo Fisher Scientific, UK) was milled in a Wahl ZX789 grinder (Wahl store, UK) and sieved through a 1000 µm mesh. The milled PVA was mixed in a mortar and pestle with the drug (paracetamol or caffeine, selected due to their thermal stability and their different solubilities), and then placed for 10 minutes in a Turbula® T2F shaker-mixer (Glen Mills Inc., USA). The mixture of drug and PVA (theoretical drug content of 5 or 10% w/w for each drug) was then extruded using a single-screw filament extruder, Noztec Pro hot melt extruder (Noztec, UK) in order to obtain a drug-loaded filament (temperature 180 °C, nozzle diameter 1.75 mm, screw speed 15 rpm). The extruded filaments were protected from light and kept in a vacuum desiccator until printing. The drug-loading of the filaments was determined by HPLC analysis.

2.2. 3D Printing of caplets

A standard fused-deposition modeling 3D printer, MakerBot Replicator 2X (MakerBot Inc, USA) was used to fabricate the oral dosage forms from the drug-loaded filaments. The templates used to print the formulations were designed with AutoCAD 2014® (Autodesk Inc., USA) and exported as a stereolithography file (.stl) into the 3D printer software (MakerWare v. 3.7.0, MakerBot Inc., USA). The printer settings were as follows: standard resolution with the raft option deactivated, extrusion temperature (200 °C), infill percentage (100%, in order to produce solid dosage forms of high density), speed while extruding (90mm/s), speed while traveling (150mm/s), number of shells (2) and layer height (0.20mm). The basic selected 3D geometry was a size 4 capsule-shaped tablet (caplet), 14.30mm length x 5.30mm diameter (Figure 1).

2.3 Imaging

Surface and cross-section images of the filaments were taken with a scanning electron microscope (SEM, JSM-840A Scanning Microscope, JEOL GmbH, Eching, Germany). All samples for SEM testing were coated with carbon (~30–40nm). The physical dimensions of the caplets were measured using a digital calliper. Pictures of the devices were taken with a Nikon CoolpixS6150 with the macro option activated.

2.4 Porosity

The micropore volume of the filaments and the printed caplets was determined as the total volume of pores >0.1 µm in diameter. Mercury intrusion porosimetry was performed, in duplicate, over the pressure range 0.01–14.00 MPa using an Autopore IV 9500 apparatus (Micromeritics, USA). Mercury porosimetry was selected to characterize the pore structure of the solid dosage forms because this method enables the determination of porosity and pore size distribution, revealing better information about the microstructure.

2.6 Dissolution test conditions

The drug release performance from the caplets was evaluated using a USP-II apparatus (Model PTWS, Pharmatest, Hainburg, Germany) as detailed previously (Goyanes et al., 2015f) and dissolution settings simulate the environment conditions of the fasted GI tract (Goyanes et al., 2015c; Goyanes et al., 2015d). Briefly, the devices were placed for 1 h into 900 mL of 0.1 M HCl, which simulates gastric residence time; and subsequently into 950 mL of modified Hanks (mHanks) based dynamic physiological dissolution medium for 35 min (pH 5.6 to 7); then in 1000 mL of modified Krebs buffer (pH 7 to 7.4 and then to 6.5). The modified Hanks buffer based dissolution media (Liu et al., 2011) (136.9 mM NaCl, 5.37 mM KCl, 0.812 mM $MgSO_4.7H_2O$, 1.26 mM $CaCl_2$, 0.337 mM $Na_2HPO_4.2H_2O$, 0.441 mM KH_2PO_4, 4.17 mM $NaHCO_3$) forms an in-situ modified Kreb's buffer (Fadda et al., 2009) by addition of 50 mL of pre-Krebs solution (400.7 mM $NaHCO_3$ and 6.9 mM KH_2PO_4) to each dissolution vessel.

The conditions of 3.5 h in bicarbonate buffer (pH 5.6 to 7.4), followed by a drop in buffer pH (6.5), were selected to simulate typical intestinal transit and pH values a formulation would experience moving through the small and large intestines. The buffer capacity and ionic composition of the physiological bicarbonate buffers representing the different regions of the GI tract closely match the buffer capacities of the intestinal fluids collected from the different parts of the gut in humans (Fadda et al., 2009; Goyanes et al., 2015c; Goyanes et al., 2015d; Liu et al., 2011).

The medium is primarily a bicarbonate buffer in which bicarbonate (HCO_3^-) and carbonic acid (H_2CO_3) co-exist in equilibrium, along with CO_2 (aq) resulting from the dissociation of carbonic acid. The pH of the buffer system can be can be decreased by purging CO_2 (g) in the solution, which promotes the formation of carbonic acid. Similarly, an inert gas (such as Helium), which removes the dissolved CO_2 from the solution, increases the pH of the media. The purging of gases is controlled by an Auto pH System™ (Merchant et al., 2014), which consists of a pH probe connected to a source of carbon dioxide gas (pH reducing gas), as

well as to a supply of helium (pH increasing gas), controlled by a control unit. The control unit is able to provide a dynamically adjustable pH during testing (dynamic conditions) and to maintain a uniform pH value over the otherwise unstable bicarbonate buffer pH.

The paddle speed of the USP-II was fixed at 50 rpm and the tests were conducted at 37 +/- 0.5 °C (n=3). The percentage of drug released from the caplets was determined using an in-line UV spectrophotometer (Cecil 2020, Cecil Instruments Ltd., Cambridge, UK) at 244 nm (paracetamol) or 274 nm (caffeine). Data were processed using Icalis software (Icalis Data Systems Ltd, Berkshire, UK). Profiles were characterized in terms of percentage of drug released in 270min (D_{270}).

2.7 Statistical analysis

The experimental assay was adapted to the structure of a two factorial experimental design based on drug solubility (paracetamol or caffeine) and drug content. Stepwise multiple regression was used to quantify the effects of the variables study on the properties of the 3D printed caplets and to construct the corresponding response surfaces (SPSS, v.22).

3. Results and discussion

Four filaments were successfully extruded, containing paracetamol or caffeine with different drug loadings. Figure 2 shows the surface and cross-section images of the drug-loaded filaments at the highest loading for each drug. The surfaces were smooth with no appreciable pores. Filaments were not significantly different from the commercial PVA filament in terms of size (diameter), physical appearance and mechanical behaviour.

The drug loadings of the four PVA filaments were 4.3% and 8.2% for paracetamol and 4.7% and 9.5% for caffeine. The values were slightly lower than calculated, most likely due to adhesion of the fine drug powder to the container during the mixing process and to the walls of the barrel of the HME during the extrusion process. The extrusion temperature was 180 °C and was independent of the drug incorporated in the formulation or its loading.

The manufacture of the caplets by 3D printing with the loaded filaments was readily achieved with appropriate resolution and size (Table 1 and Figure 3). The geometry of the 3D printed caplets was selected to recreate the characteristics of size and shape of a size 4 capsule. The capsule-shaped geometry of the tablets makes them easier to swallow than flat round tablets (Liu et al., 2014), although they are more difficult to print due to the smaller surface in contact with the build plate, which reduces adherence of the caplets to it.

Drug loading in the caplets showed similar values to those in the drug–loaded filaments, indicating no degradation during the 3DP process. The different melting points of the drugs has no effect on the printing process, even when the printing temperature (200°C) is higher than the melting point of paracetamol (169°C) and lower than the melting point of caffeine (238°C).

Porosity determination of the filaments and the caplets reveals an interesting feature of the structure of the formulations. As expected from the SEM images (Figure 2) the filaments exhibited very low porosity, with micropore volumes <0.008 cm^3/g (Table 2). This low porosity of the filaments compares with the more than 10 fold higher porosity of the caplets (micropore volume 0.07-0.1 cm^3/g, Table 1). While the 3D printing process itself may increase the micropore volume of the melted filament deposited, the data show that 70-85% of the cumulative micropore volume of the caplets is actually as a consequence of pores bigger than 10µm (Figure 4).

This suggests that it is the space between the deposited material after printing which creates a porous structure, rather than any change in the polymer structure itself from melt-extrusion during printing. The gaps between the different deposited filaments observed in the SEM photomicrographs corroborate this viewpoint (Figure 5). This effect is similar to a skein of yarn, where the total porosity would depend on the porosity of the yarn itself and the disposition of the yarns to form the skein. A closer setup will lead to a lower porosity and could create empty spaces were the mercury cannot penetrate. The pictures of the cross-section of caplets after the analysis of the porosity show white spots where the mercury is not able to enter and black/grey areas where the mercury is retained.

None of the parameters evaluated (drug solubility, drug content on interaction of both) significantly influenced the micropore volume of the caplets or the filaments, indicating that there is no relationship between these variables (Figure 6).

Dissolution tests of the different formulations performed under biorelevant conditions are shown in Figure 7. All the caplets released 100% of the drug dose in less than 480 min. Drug release starts in the gastric phase (acid medium) and continues in the intestinal phase (biorelevant bicarbonate buffers), independent of the nature or pH of the dissolution media. Drug release profiles from caffeine formulations were slightly faster than those from paracetamol formulations; this may be attributable to the higher aqueous solubility of caffeine. For formulations incorporating the same drug, the release is faster when the drug

loading is higher. The increment of the drug loading reduces the percentage of the PVA matrix that is in charge of effectively controlling drug release.

Drug release was evaluated in terms of percentage of drug released at 270min (D_{270}) because it is at this point in the test that the formulation leaves the small intestine and moves into the colon. Furthermore after 270min, the fastest formulation releases 100% of the dose and the parameter D_{270} shows good discrimination among the other formulations. Response surface analysis reveals the effects of the variables, percentage of drug loading and drug solubility on the D_{270} parameter (Figure 8). The equation obtained by stepwise multiple regression [D_{270} = 78.127 + 0.059 x Solubility x Drug loading; R =0.928] indicates the existence of a synergistic effect between solubility and drug content, which significantly increases the value of D_{270}.

The comparison of the response surfaces of micropore volume and percentage of drug released (Figures 6 and 8) shows that there is no relationship between the microstructure of the caplets and the drug release rate. This indicates that the porosity of this type of formulation does not have an effect on drug release, since drug release depends on the combination of the effect of the parameters drug content and solubility. One possible explanation of why the porosity of the tablets did not affect the drug dissolution rate may be that the swelling layer of the PVA hinders the penetration of water through the pores, culminating in the drug dissolution process being ultimately controlled by diffusion/erosion mechanisms.

Conclusions

Four filaments of PVA incorporating paracetamol (4.3 and 8.2%) or caffeine (4.7 and 9.5%) were successfully obtained using a filament extruder with appropriate characteristics for use in FDM 3DP. Drug release tests in biorelevant media showed different drug release profiles for each caplet type. Drug release was faster from formulations incorporating the drug with higher solubility and higher loading. An investigation into the porosity of the caplets did not help to explain the different drug release profiles. The selection of the percentage of drug loading and the characteristics of the drug itself influence drug dissolution profiles, so these aspects should be taken in to account in the rational design of 3D printed dosage forms.

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Table 1. Measured parameters of the 3D printed caplets

Formulation	Weight (mg)	Height (mm)	Width (mm)	Length (mm)	Filament micropore volume (cm^3/g)*	Caplet micropore volume (cm^3/g)*
4.3% Paracetamol	333.8 ±3.9	5.52 ±0.05	5.52 ±0.09	14.18 ±0.03	0.006 (6.5×10^{-4})	0.107 (1.7×10^{-2})
8.2% Paracetamol	291.6 ±5.5	5.39 ±0.02	5.07± 0.05	14.09 ±0.08	0.006 (1.0×10^{-3})	0.075 (2.0×10^{-2})
4.7% Caffeine	293.8 ±1.5	5.31±0.03	5.18 ±0.04	14.10 ±0.01	0.005 (2.0×10^{-3})	0.070 (1.7×10^{-2})
9.5% Caffeine	299.6 ±5.1	5.21 ±0.18	5.04 ±0.03	13.88 ±0.06	0.007 (2.8×10^{-3})	0.094 (7.3×10^{-2})

* SDs are shown in parenthesis

Figure captions

Figure 1. 3D representation of the printed caplets.

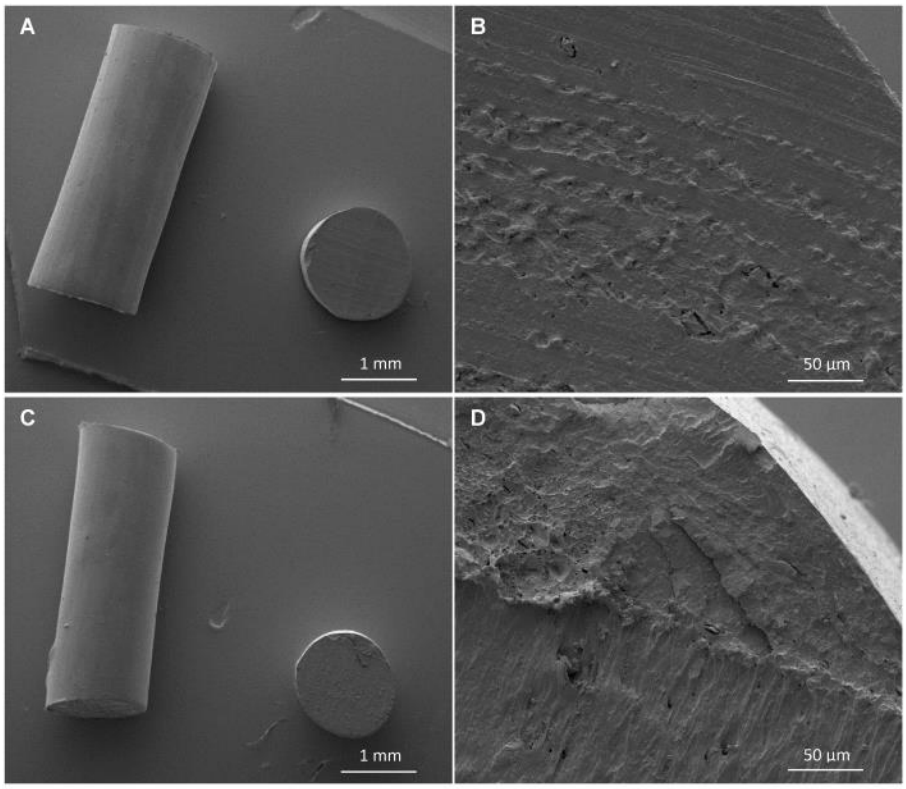

Figure 2. SEM images of (A, B) 10% Paracetamol-PVA filament and (C, D) 10% Caffeine-PVA filament.

Figure 3. From left to right, Image of a size 4 HPMC capsule (VCAPS^{TM} Capsugel); 3D printed 8.2% paracetamol-PVA caplet and 3D printed 9.5% caffeine-PVA caplet (Scale in cm).

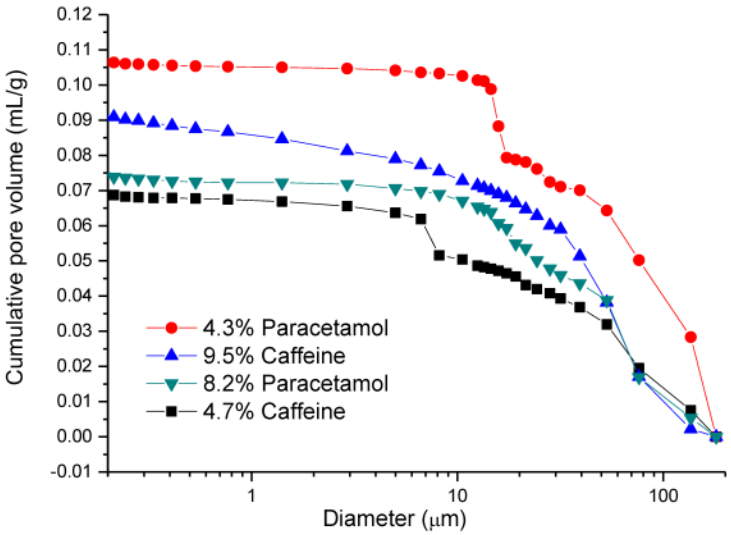

Figure 4. Cumulative volume pore-diameter distributions for the 3D printed caplets.

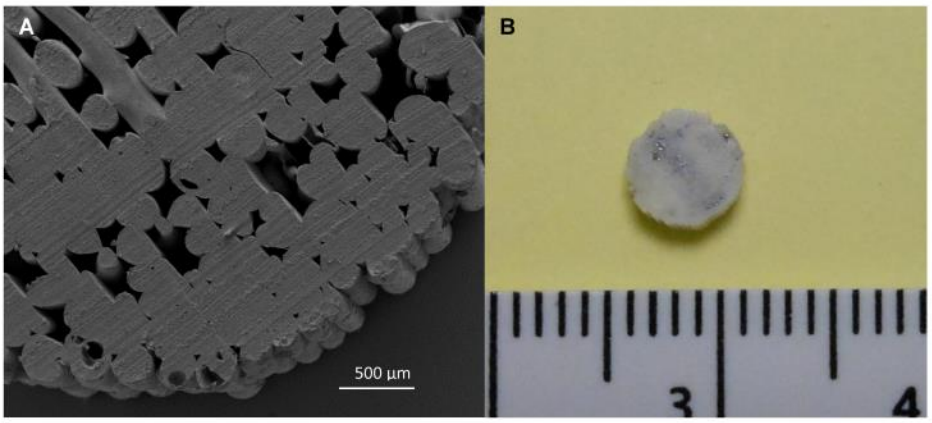

Figure 5. (A) SEM image of internal structure of cross-section of a 3D printed caplet and (B) image of the cross-section of a low dose paracetamol caplet after porosity analysis.

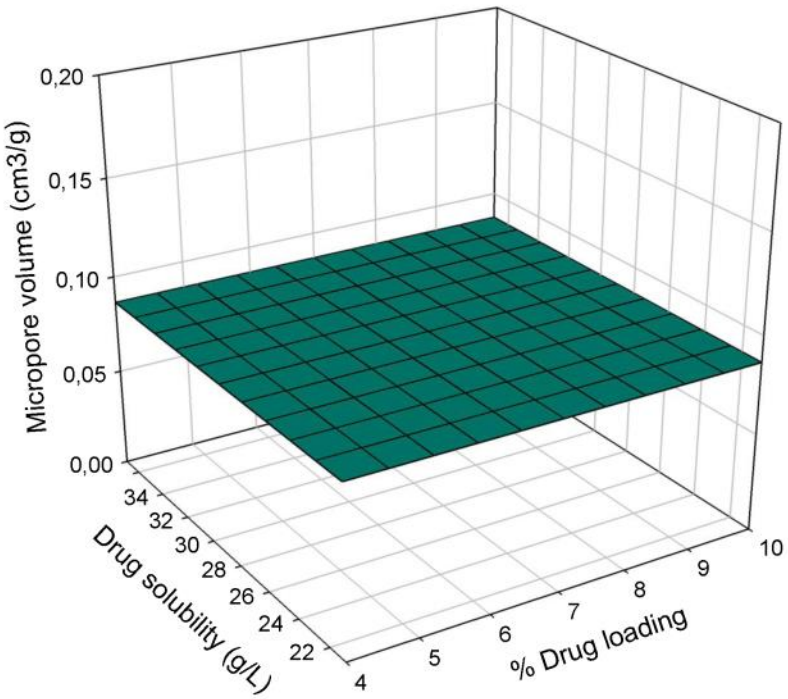

Figure 6. Response surface for micropore volume as a function of drug content and drug solubility.

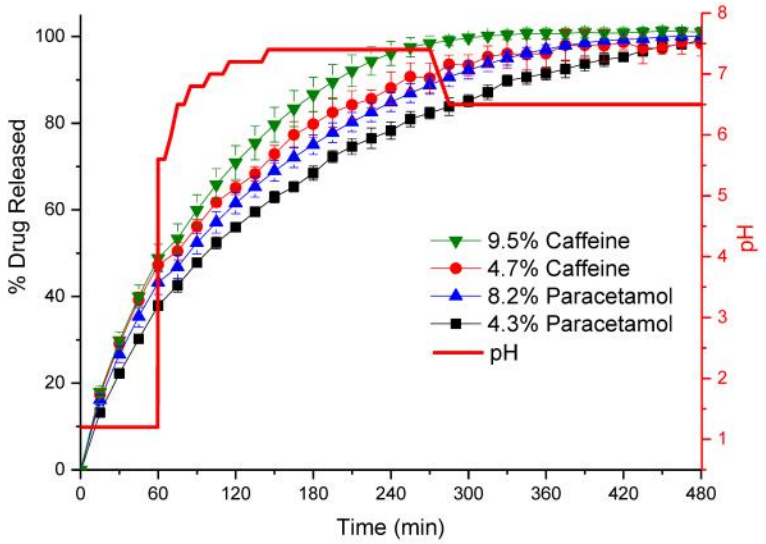

Figure 7. Drug dissolution profiles from 3DP caplets of paracetamol or caffeine. Red line shows the pH values of the medium.

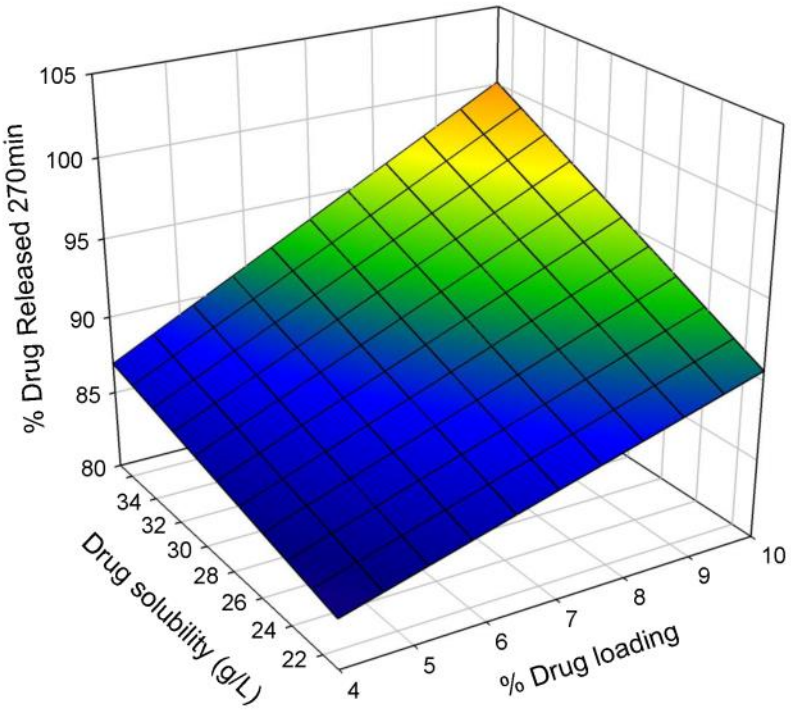

Figure 8. Response surface for percentage drug released 270min (D_{270}) as a function of drug content in the formulation and drug solubility.