Fabrication of Drug-Loaded Hydrogels with Stereolithographic 3D Printing

Pamela Robles Martinez[1], Alvaro Goyanes[2], Abdul W. Basit[1,2] and Simon Gaisford[1,2,*]

[1]UCL School of Pharmacy, University College London, 29-39 Brunswick Square, London, WC1N 1AX, UK

[2]FabRx Ltd., 3 Romney Road, Ashford, Kent, TN24 0RW, UK

* Corresponding author

Email: s.gaisford@ucl.ac.uk

Tel: +44(0) 207 753 5863

Fax: +44(0) 207 753 5942

Abstract

3D printing (3DP) technologies have been attracting much recent interest as new methods of fabricating medicines and medical devices. Of the many types of 3DP available, stereolithographic (SLA) printing offers the unique advantage of being able to fabricate objects by cross-linking resins to form networked polymer matrices. Because water can be entrapped in these matrices, it is possible in principle to fabricate pre-wetted, drug-loaded hydrogels and devices. Here, SLA printing was used to prepare ibuprofen-loaded hydrogels of cross-linked polyethylene glycol diacrylate. Hydrogels containing up to 30% w/w water, and 10% w/w ibuprofen, were successfully printed. Dissolution profiles showed that drug release rates were dependent on water content, with higher water content hydrogels releasing drug faster. The conclusion is that SLA 3DP offers a new manufacturing route to pharmaceutical hydrogels.

Key words

3D printing; stereolithography; SLA; hydrogels; ibuprofen; riboflavin

1. Introduction

Tablets (first patented in 1843) and two-piece capsules (first patented in 1846) have dominated formulation strategy for oral delivery since their invention; in part this is because both these dosage forms lend themselves to large-scale mass production. This reduces unit cost but at the expense of dose flexibility and so most products are available in a limited number of dose strengths. However, the advent of newer, more potent actives with narrow therapeutic indices and the increasing drive towards personalisation of medicines (in terms of dose strength and/or drug combinations) (Alomari et al., 2015) are changing the landscape of pharmaceutical manufacturing and forcing the pharmaceutical industry to consider new methods of pharmaceutical production.

The recent development of 3D printing (3DP) technologies has resulted in a new era of additive manufacturing approaches in which material is deposited layer-by-layer to fabricate solid objects (Dimitrov et al., 2006). 3DP offers many qualities ideally suited to meet the challenges facing the pharmaceutical sector; small production runs, broad versatility in dose and/or drug combinations and the possibility to use a wide range of excipients to solubilise, target or control drug release (Goyanes et al, 2017a; Khaled et al., 2015; Rowe et al., 2000; Sadia et al., 2016).

The first 3DP technology for pharmaceuticals used an ink-jet printer to jet a liquid binder onto a powder bed, adhering particles together to form an agglomerated mass (Rowe et al., 2000; Wu et al., 1996). In this technology, objects are fabricated by stacking agglomerated layers on top of each other and tablets are comprised primarily of powders, so are compositionally similar to powder compacts, but have the advantage that they can be fast disintegrating (this is the approach used to make Spritam®, the first 3D printed tablet approved by the FDA). More recently another powder bed technology using a laser to sinter and agglomerate the powder has been

reported, selective laser sintering (SLS) (Fina et al., 2017). An alternative technology, the use of fused-deposition modelling (FDM) for printing tablets has been demonstrated (Goyanes et al., 2014; Goyanes et al., 2015a; Goyanes et al., 2015b; Goyanes et al., 2015e) and acceptability of the medicines evaluated (Goyanes et al, 2017b). FDM 3DP is particularly suited to the use of polymeric excipients, as it uses extruded filaments as a primary feedstock, and so offers a manufacturing route to controlled-release 3D printed tablets (Printlets^{TM}). Being comprised of extruded filaments, FDM printlets have good porosity and high surface area and their drug release profiles are easily controlled by varying factors such as geometry, polymer selection and degree of infill during printing. One challenge for FDM 3DP currently is the limited choice of commercially available thermoplastic materials with good extrusion properties for printing; while it is possible to formulate polymer blends with good printable properties oneself, this adds complexity and an extra development step. Another is the significant risk of degrading thermally labile drugs during printing (Goyanes et al, 2016); in a previous study, approximately 50% of 4-ASA was degraded during 3D printing process (Goyanes et al., 2015a).

A third type of 3DP technology is stereolithography (SLA). In this approach, the 'printhead' is a laser beam, focused into a tank of liquid resin. The laser causes photopolymerisation of the resin, forming a cross-linked polymeric matrix and so production of a solid mass. Again, objects are fabricated by solidifying them in a layer-by-layer process. SLA 3DP has been widely used in the field of tissue engineering (Arcaute et al., 2010; Arcaute et al., 2006), tissue scaffolding (Kim et al., 2017; Lee et al., 2017) and more recently to make microparticles (Raman et al., 2016; Yang et al., 2015), but its use in fabricating unit doses for oral delivery is less common. Partly, this is because of the limited number of photo-crosslinkable monomers that are available, although over the last few years more systems have been developed, such as polyethylene glycol diacrylate (PEGDA) (Chan et al., 2010;

Vehse et al., 2014), poly-2-hydroxyethyl methacrylate (pHEMA) (Hanson Shepherd et al., 2011), polyethylene glycol dimethacrylate (PEGDMA) (Arcaute et al., 2006; Dhariwala et al., 2004) and polypropylene fumarate-diethyl fumarate (PPF-DEF) (Fisher et al., 2002). One of the big advantages of SLA printing is that the active ingredient and/or any excipients can be incorporated into the resin as long as they are miscible. It does not matter whether the drug or excipients have photopolymerisable functional groups; upon cross-linking of the resin, any extra components simply become trapped in the polymeric matrix. This is a highly convenient method of drug loading/functionalization suggested more than 20 years ago by West and Hubbell (1995) and more recently demonstrated by Vehse et al., (2014), who incorporated aspirin in cross-linked PEGDA matrices, and Wang et al., (Wang et al., 2016) who printed modified-release printlets containing paracetamol or 4-ASA.

Where PEG-based resins are used, water may be incorporated prior to printing in the photopolymerisable solution, leading to the intriguing possibility of printing pre-wetted hydrogels (Wang et al., 2015). This approach has been used to make extracellular microenvironments for cancer research (Park and Gerecht, 2015) but has not to our knowledge been explored for fabricating drug-loaded dosage forms. Because the degree of cross-linking will be influenced by the ratio of diluent/water to resin and/or the concentration of cross-linking agents, drug-loaded hydrogels should in principle be capable of being manufactured with tunable drug-release profiles. However, one concern with the use of photo-polymerised systems is that a photo-initiator (PI) is required in the formulation. The PI, which converts to reactive radicals upon exposure to light to catalyse polymerization of the resin, may be present in relatively high concentrations and so there are concerns as to potential toxicity (Ng et al., 2006). In this work, we explore the use of SLA printing to fabricate controlled-release drug-loaded hydrogels using a pharmacologically non-toxic PI, riboflavin (vitamin B2).

Riboflavin has been shown to be an effective PI in producing hydrogels of cross-linked dextran-methacrylate (Kim and Chu, 2009).

2. Materials & Methods

Polyethylene glycol diacrylate (PEGDA, average MW 700), polyethylene glycol (PEG300, average MW 300), riboflavin, triethanolamine (TEA), diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide (DPPO) and ibuprofen were purchased from Sigma Aldrich Ltd (UK). The salts for preparing the buffer dissolution media were purchased from VWR International Ltd., Poole, UK. All materials were used as received.

2.1 3D printing: All printlets (3D printed tablets) were printed with a Formlabs 1+ SLA printer (Formlabs Inc, USA). The printer is equipped with a 405 nm laser and can fabricate objects with a resolution of 300 microns and a layer thickness of 25, 50, 100 or 200 microns. The template used to print the printlets (a cylinder, 10.5 mm diameter, 3.5 mm height) was designed with Autocad and exported as a stereolithographic file (.stl) into the 3D printer software (Preform Software v. 1.9.1, Formlabs, UK). PEGDA was used as the photopolymerisable monomer while PEG300 and water were used to alter the crosslinking density of the hydrogel. PEG300 was added to PEGDA in a ratio of 6:4 (v/v) and the water content of the formulations was varied. Two PI systems were used; DPPO (a commercially available PI which absorbs light between 380-425 nm (Arikawa et al., 2009) supplied by the manufacturer for cross-linking commercial printable resins), and riboflavin with triethanolamine (RT), riboflavin acting as the PI and triethanolamine as a coinitiator. Exact compositions of the formulations are given in Table 1. To print, a solution of PEGDA, PEG300 and water (where applicable) was mixed for 10 min, then ibuprofen (10% w/w) was added with constant stirring until complete dissolution. Riboflavin and

triethanolamine or DPPO were added next, keeping the solution protected from light and with constant stirring until complete dissolution (approximately 25 min for riboflavin/triethanolanine and 8h for DPPO). The mixture was then poured into the resin tray of the printer and printing initiated.

2.2 Physical properties: 3D printed hydrogels were blotted with filter paper to remove any uncured liquid formulation on the surface right after fabrication, they were weighed and measured (width and height) using a digital calliper. The measurements were done in triplicate.

2.3 Determination of drug concentrations in the hydrogels: Printed hydrogels were crushed using a mortar and pestle with 50 mL of ethanol to enhance extraction of ibuprofen. The solution was diluted to 1 L with deionized water and kept with constant magnetic stirring for 24 h. Samples of the solutions were filtered through 0.45 µm filters (Millipore Ltd., Ireland) and the amount of drug in solution was determined using HPLC (Hewlett Packard 1050 Series HPLC system, Agilent Technologies, UK). The validated high performance liquid chromatographic assay consisted of a mobile phase of phosphate buffer, pH = 6.8 (65%) and acetonitrile (35%), pumped through an Eclipse 5 µm C18 column, 4.6 x 150 mm (Agilent) maintained at 30 °C at a flow rate of 0.7 mL/min. The eluent was screened at a wavelength of 222 nm. All measurements were made in duplicate.

2.4 Determination of swelling ratio (SR) and water content (WC): 3D-printed hydrogels were blotted with filter paper to remove any uncured liquid formulation on the surface immediately following fabrication, then they were weighed (W_i). The hydrogels were then placed into deionized water for 24 h, after which time the excess water was carefully wiped off and the hydrogels were weighed again (W_s). Hydrogels

were also allowed to dry in an oven at 60 °C for 24h to reach complete dryness (W_d). The SR and WC were calculated using the following equations:

$$SR = \frac{W_s}{W_i}$$

Equation 1

$$WC = \frac{W_i - W_d}{W_i} \times 100$$

Equation 2

2.5 Differential scanning calorimetry (DSC) analysis was performed for the liquid formulations and the 3DP hydrogels using a Q2000 DSC (TA instruments, Waters, LLC, USA) calibrated with indium (Tm = 156.6, ∆Hf =28.71 J/g) according to the manufacturer instructions. The samples were placed in TA aluminium pans with hermetic lids. The purge gas used was Nitrogen at a flow rate of 50 ml/min for all the experiments. Data were collected with TA Advantage software for Q series (version 2.8.394), and analysed using TA Instruments Universal Analysis 2000. Melting temperatures are reported as extrapolated onset unless otherwise state. All the experiments were performed with a standard DSC method at a heating rate of 10 °C/min. All the measurements were done in triplicate.

2.6 Dynamic dissolution testing conditions: Drug dissolution profiles for the printlets were obtained with a USP-II apparatus (Model PTWS, Pharmatest, Germany). The hydrogels were placed in 750 mL of 0.1 M HCl for 2 h to simulate the gastric compartment, and then transferred into 950 mL of modified Hanks (mHanks) bicarbonate physiological medium for 35 min (pH 5.6 to 7); 3) and then in modified

Krebs buffer (1000ml) (pH 7 to 7.4 and then to 6.5). The modified Hanks buffer based dissolution medium (Liu et al., 2011) forms an in-situ modified Kreb's buffer (Fadda et al., 2009) by addition of 50 mL of pre-Krebs solution to each dissolution vessel. These conditions mimic transit through the small intestinal and colonic environments. The buffer capacity and ionic composition of the physiological bicarbonate buffers also closely match the buffer capacities of the intestinal fluids collected from different parts of the gut in humans (Fadda et al., 2009; Goyanes et al., 2015c; Goyanes et al., 2015d; Liu et al., 2011). 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 formulations was determined using HPLC, using the same method as described above.

3. Results and Discussion

Hydrogels are useful delivery devices when controlled-release of a drug is required. They are typically loaded with drug by immersing the dry hydrogel (termed a zerogel) into an aqueous solution of drug and allowing swelling to occur; drug solution enters the hydrogel matrix via passive diffusion. The hydrogel is then dried, removing water but entrapping drug. The potential to print drug-loaded hydrogels already containing water would appear to offer at least two tangible benefits. Firstly, it is inherently difficult to know how much drug has been incorporated into the matrix by passive diffusion; printing traps a known quantity of drug. Secondly, water imbibition may take several hours, so if a zerogel is swallowed it may well reach the small intestine relatively dry; since the water content in the GI tract is very low, administration of a pre-swollen hydrogel would ensure sufficient water for solubilisation and release of the drug at all times.

Figure 1 shows 2 hydrogels printed with DPPO as the PI system. It is apparent that the hydrogels are irregular in shape and that DPPO in this case is not capable of ensuring good print resolution. These qualitative observations are reinforced with the dimensional data provided in Table 2. Given that the pharmacological safety profile of DPPO is not known, we chose not to formulate any further hydrogels with it.

Riboflavin and triethanolamine, conversely, are widely used pharmaceutically. Initially hydrogels were printed comprising predominantly PEGDA, but these were found to be brittle (corresponding to earlier work on SLA printlets that showed higher ratios of PEGDA reduced the dissolution rate while higher concentrations of PEG300 promoted drug release (Wang et al., 2016). Hence, PEG 300 was added to the resin formulation as it is commonly used as a plasticizer and is chemically similar to PEGDA (the only difference is that is does not have photopolymerisable terminal groups).

Photographs of printed hydrogels using this photoinitiator/plasticizer combination are shown in Figure 2 (hydrogels appear yellow because of the riboflavin). It is evident that all formulations could be printed and that the consistency in shape of the hydrogels was good, even as the water content increased to 30% w/w. Again, the data in Table 2 confirm these observations. Riboflavin/triethanolamine showed good properties as a PI system for use in 3DP (including high solubility, compatibility with the polymer and high reactivity to the laser so fast polymerization is achieved). Furthermore, it has been demonstrated that it is more biocompatible than other commercial PIs like Irgacure 2959 and Irgacure 369 (Nguyen et al., 2013). Thus, one immediate outcome is that it is entirely feasible to use SLA 3DP to print water-loaded hydrogels.

The data in Table 3 show the uniformity of mass of a number of printed hydrogels. Here the outcome is less satisfactory, as the variation in mass became greater than 10% RSD for hydrogels containing 20% or more water. This is perhaps not surprising as the printer is optimized to print objects from pure resin, which has a high viscosity. Addition of water dilutes the resin and reduces viscosity and so, it appears, reduces the reproducibility of printing. Hence, while it is possible to print water-loaded hydrogels directly, more understanding of the effect of excipients on the printability of the formulation is required if hydrogels of uniform mass are to be fabricated.

Table 3 also shows the measured water contents of the printed hydrogels. Surprisingly, the hydrogels printed from the formulation containing no water lost 4% mass on drying, which may imply that the resin itself is reasonably hygroscopic. For the remaining formulations, the mass losses on drying correlate broadly with the expected water content based on the resin composition. The swelling ratios for the hydrogels ranged between 1.2-1.3, Table 3, reflecting the degree of crosslinking caused by the PI.

Table 3 also shows the drug loading for the hydrogels. The theoretical drug loading for all formulations was 10% w/w, and it is clear that this is only approached as the water content reaches 30% w/w. Prior to printing the resin formulations were characterized with DSC (Figure 3). The data show a melting endotherm for PEGDA at ca. 10 ^{o}C when no water is present. With water present in the formulations no PEGDA melting is seen, implying the PEGDA is fully dispersed within the water phase at these concentrations. The broad endotherms in these data reflect water loss upon heating. No melt endotherms for ibuprofen are seen in any of the formulations, indicating that the drug dissolves in the polymer and/or the water. It has been demonstrated that the solubility of poorly soluble drugs like Ibuprofen is increased with the presence of solvents like PEG300, which decrease the polarity of

the aqueous solution. Since the actual drug loading only approaches the theoretical value at higher water contents, it may be the case that ibuprofen is not fully extracted from the hydrogels during analysis, an observation seen in SLA printlets (Wang et al., 2016).

Drug release profiles of ibuprofen from the hydrogels as a function of water content in the bicarbonate buffer system are shown in Figure 4. Dissolution is slowest from the formulation containing no water and gets faster as the water content is increased. Since the dissolution profiles for the hydrogels containing 20 and 30% w/w water are the same, it can be concluded that diffusion of ibuprofen through the cross-linked polymer matrix is limited at low water contents, but is unhindered once the formulation contains 20% w/w water. The main mechanism for drug release from this type of delivery device is drug diffusion through the swollen matrix of the hydrogel, and hence the drug release is highly dependent on the time taken for the hydrogel to swell upon contact with dissolution medium. It follows that the formulations with higher initial water contents are able to swell to their equilibrium extents faster, causing faster drug release. The non-crosslinkable components in the formulation act as “pore-forming” agents, as they diffuse and disperse on swelling. It has been shown that by decreasing the concentration of the crosslinkable polymer and increasing the non-crosslinkable components and water in the initial resin formulation that the final properties of the hydrogel, including pore size and water uptake, can be modulated (Wu et al., 2010). This phenomenon has been observed in hydroxyethyl methacrylate (HEMA) gels, where lidocaine diffusion becomes larger above 50% of water content in the liquid formulation (Gulsen and Chauhan, 2006). A further potential effect is that the more cross-linked the hydrogel, the higher the viscosity of the swelled matrix; this would also reduce drug diffusion rates.

Although this was not the primary aim of this proof-of-concept study, the implications are that by changing the ratio of components in the initial resin formulation, hydrogels with tailored release profiles can be fabricated. The dissolution data also show that less than 10% of the drug is released during immersion in the acidic phase, probably because of entrapment as well as the low solubility of ibuprofen at this pH, which means the formulations meet the criteria for being delayed-release in terms of US FDA regulations.

4. Conclusions

The aim of this study was to determine whether SLA 3DP was a suitable technique for fabricating drug-loaded hydrogels, and it is clear from the results that this is the case. It was possible to fabricate hydrogels from crosslinkable resins and, because non-crosslinkable components become trapped in the polymeric matrix after printing, to incorporate a significant amount of active. Further, it was shown that by adding water to the initial resin formulation that hydrogels could be printed that contained and retained the water. This has the effect of pre-swelling the hydrogels prior to dissolution testing, thus increasing the rate of drug release from the matrices. Thus, SLA printing would seem to offer potential as a new manufacturing route to pharmaceutical hydrogels.

Acknowledgements

P Robles-Martinez is in receipt of a scholarship from Consejo Nacional de Ciencia y Tecnología (Mexico).

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Table 1. Compositions (% w/w) of the initial resins used to print the hydrogels

Name / Comp.	DPPO	RT (no PEG)	RT	RT + 10% water	RT + 20% water	RT + 30% water
PEGDA	89.95	86.90	53.45	48.45	40.14	34.14
PEG300	0	0	33.45	28.45	20.76	22.76
Riboflavin	0	0.1	0.1	0.1	0.1	0.1
TEOHA	0	3	3	3	3	3
DPPO	0.05	0	0	0	0	0
Water	0	0	0	10	20	30
Ibuprofen	10	10	10	10	10	10

Table 2. Width and height values for the printed hydrogels as a function of photoinitiator system and water content (n=3, expected values; width 10.5 mm, height 3.5 mm).

Hydrogel	Width (±sd, mm)	Height (±sd, mm)
DPPO	10.7 ± 0.7	4.2 ± 0.2
RT (no PEG)	10.6 ± 0.1	3.5 ± 0.1
RT	10.4 ± 0.1	3.4 ± 0.2
RT + 10% water	11.0 ± 0.2	3.6 ± 0.2
RT + 20% water	11.0 ± 1.0	3.3 ± 0.3
RT + 30% water	12.3 ± 0.7	3.1 ± 0.1

Table 3. Uniformity of weight, water content and swelling ratio data for the printed hydrogels (n= 3).

Theoretical water content (%)	Measured water content (WC, %)	Weight (mg) ± SD	Drug load (mg) ± SD	Swelling ratio (SR)
0	4.0	362.6 ± 29.7	8.4 ± 0.1	1.38
10	7.5	439.0 ± 31.5	8.3 ± 0.2	1.33
20	17.5	420.9 ± 57.2	9.6 ± 0.1	1.23
30	29.0	470.2 ± 80.2	9.9 ± 0.4	1.33

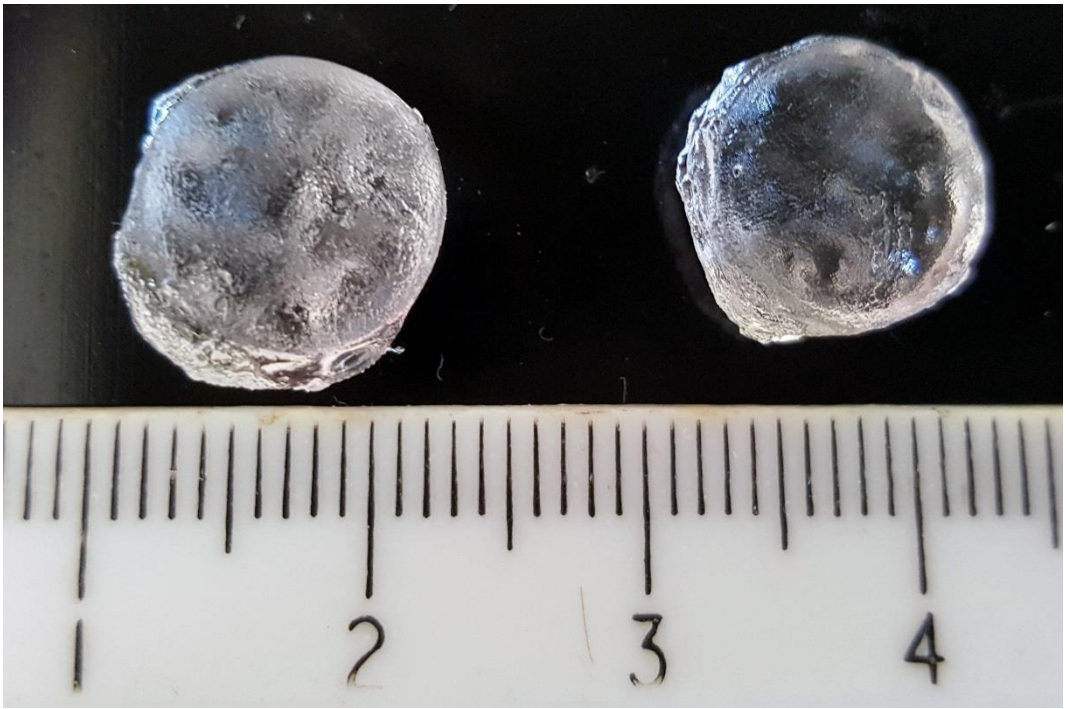

Figure 1. Hydrogels printed with DPPO as the photoinitiator, showing poor repeatability of size and shape. The scale is shown in cm.

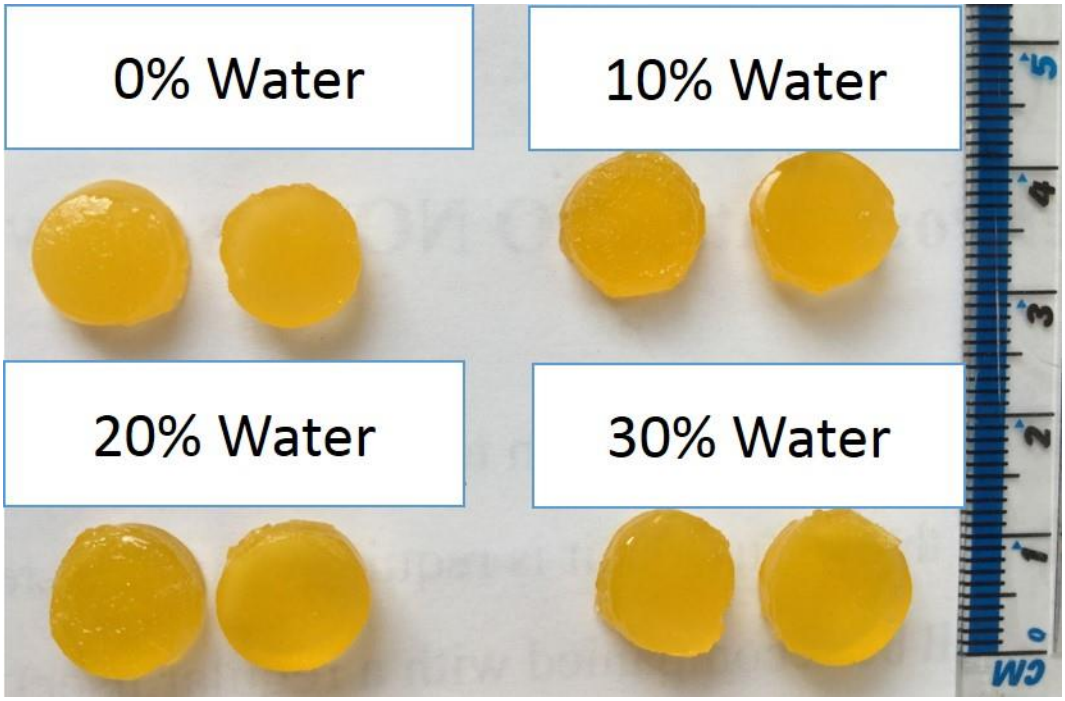

Figure 2. Hydrogels printed with riboflavin/triethanolamine as the photoinitiator with various water contents. The scale is shown in cm.

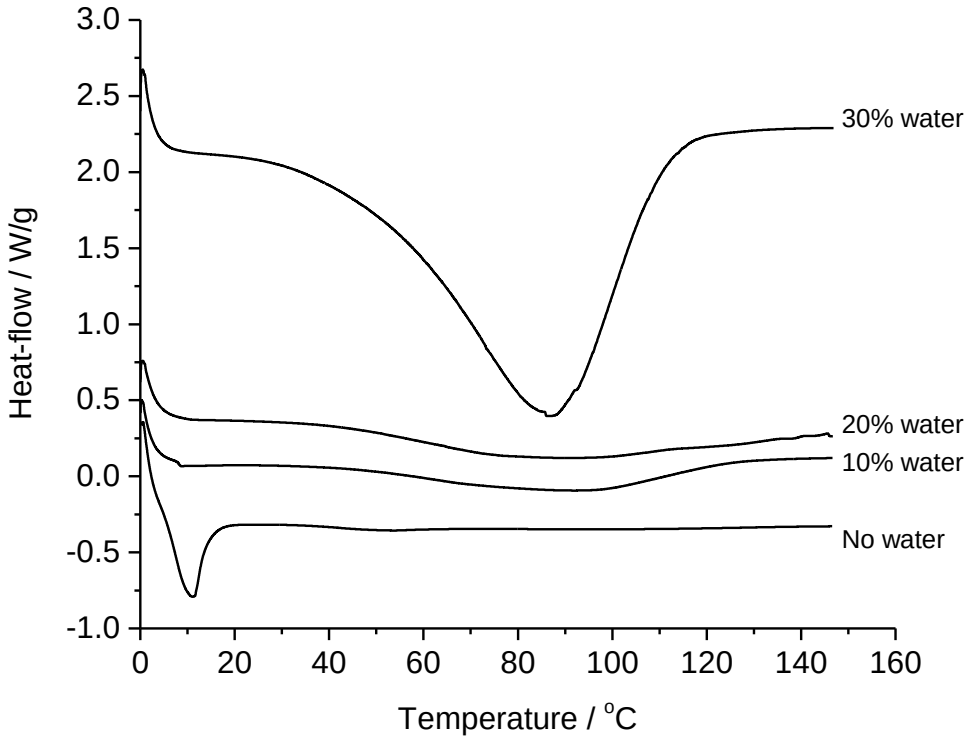

Figure 3. DSC data for the 4 liquid formulations prior to printing, showing melting of PEGDA at ca. 10 ^{o}C in the formulation with no water, and water loss in the other formulations.

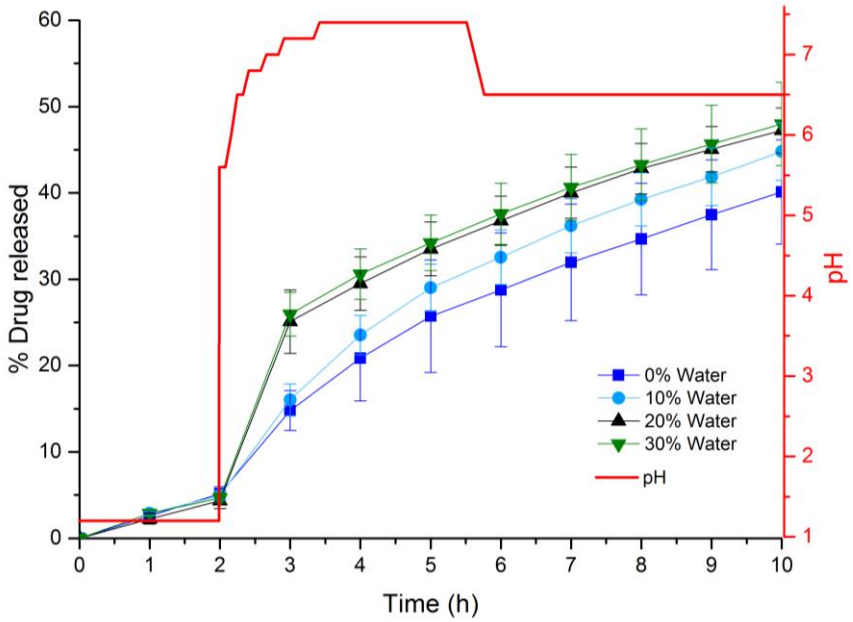

Figure 4. Dissolution profiles of ibuprofen from the four printed hydrogels in the dynamic dissolution system (n=3). Red line shows the pH values of the media