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## 3-dimensional (3D) fabricated polymer based drug delivery systems

### Abstract

Drug delivery from 3-dimensional (3D) structures is a rapidly growing area of research. It is essential to achieve structures wherein drug stability is ensured, the drug loading capacity is appropriate and the desired controlled release profile can be attained. Attention must also be paid to the development of appropriate fabrication machinery that allows 3D drug delivery systems (DDS) to be produced in a simple, reliable and reproducible manner. The range of fabrication methods currently being used to form 3D DDSs include electrospinning (solution and melt), wet-spinning and printing (3-dimensional). The use of these techniques enables production of DDSs from the macro-scale down to the nano-scale. This article reviews progress in these fabrication techniques to form DDSs that possess desirable drug delivery kinetics for a wide range of applications.

### Keywords

3, fabricated, drug, polymer, 3d, systems, delivery, dimensional

### Disciplines

Engineering | Physical Sciences and Mathematics

### Publication Details

Moulton, S. E. & Wallace, G. G. (2014). 3-dimensional (3D) fabricated polymer based drug delivery systems. *Journal of Controlled Release*, 193 27-34.

## **3-dimensional (3D) Fabricated Polymer Based Drug Delivery Systems**

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### **Abstract**

Drug delivery from 3-dimensional (3D) structures is a rapidly growing area of research. It is essential to achieve structures wherein drug stability is ensured, the drug loading capacity is appropriate and the desired controlled release profile can be attained. Attention must also be paid to the development of appropriate fabrication machinery that allows 3D drug delivery systems (DDS) to be produced in a simple, reliable and reproducible manner. The range of fabrication methods currently being used to form 3D DDSs include electrospinning (solution and melt), wet-spinning and printing (3-dimensional). The use of these techniques enables production of DDSs from the macro-scale down to the nano-scale. This article reviews progress in these fabrication techniques to form DDSs that possess desirable drug delivery kinetics for a wide range of applications.

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## **Introduction**

Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals. Drug delivery systems (DDSs) can provide predetermined drug release profiles that ensure optimal distribution and absorption of drug to improve efficacy and safety, providing patient convenience and assisting compliance. Current efforts in the area of drug delivery include the development of targeted delivery (sometimes called smart drug delivery) in which the drug is only active in the target area of the body [1-4] (for example, in cancerous tissues), and sustained release formulations in which the drug is released over a period of time in a controlled manner from a formulation [5-7]. The materials inventory for use in drug delivery, particularly in the areas of targeted delivery and controlled delivery, continue to expand.

In parallel with developments in new materials for drug delivery, new material fabrication tools and protocols have emerged. These advances provide an alternative means of engineering release profiles by control of spatial distribution within a given polymer composition rather than creating a new host material.

There is a growing interest towards the fabrication of three dimensional (3D) macro-, micro- or nanoscale systems made from thermoset, [8] or thermoplastic polymers, [9] hydrogels, [10,11], powders, [12] or polyelectrolytes, [13] which may find potential applications in complex microfluidic networks, [14,15] tissue engineering scaffolds, [16,17] and drug delivery systems [18]. Several strategies have been employed to precisely assemble 3D structures, including photolithographic, [19] colloidal-epitaxy, [20] and direct write techniques. [21,22] Among these, direct-write is one of the most promising approaches as it offers flexibility in material selection, low cost, and ability to construct complex 3D

structures. [23] Direct-write assembly is a 3D printing technique which employs a computer-controlled translational stage that moves a pattern-generating device in order to achieve, layer by layer, the desired 3D microstructure. This enables composition to be varied throughout the 3D structure giving a degree of control not available with traditional fabrication [24] Different materials such as colloidal inks, [25,26] concentrated polyelectrolytes, [27] and bioinks (e.g., hydrogels with suspended cells) [28,29] have been employed in this technique to fabricate various microstructures for specific applications [30]. The added advantage of these types of 3D DDSs is that it does not rely on the use of a mold to form the structure as is the case for conventional DDSs such as tablets or inserts and devices that may be made from injection molding methods. The fact that molds are not required for the direct write 3D approach provides a high degree of flexibility in the structural design aspects of these direct write 3D DDSs.

This review will provide insight into the rapidly growing area of fabricating 3D drug delivery systems with a range of techniques such as wet-spinning, printing, melt extrusion and electrospinning technologies. A recent review by Kolakovic, *et al* [31] comprehensively detailed the use of 2-dimensional (2D) flexible roll-to-roll and inkjet printing technology to produce drug delivery systems. Therefore this review presented here will not discuss this area of research.

### **Wet-spinning drug loaded fibres**

The wet-spinning technique (Figure 1a) uses polymers dissolved in a solvent (the spinning dope). The spinneret is submerged in a chemical bath that is of a composition such that this causes the fibre to precipitate, and then solidify, as it emerges. By incorporating a drug into

the spinning dope it is possible to form a drug-loaded fibre. This approach has been utilised for a number of pharmaceutical applications [32].

**Figure 1** Wet-spinning process (a). SEM images of the cross-section of medicated fibres with different HPMC contents: (b) 0 wt% and (c) 15 wt%. Cumulative TAM release profiles (d) with varying amounts of HPMC added to PAN (0, 10, 20 and 30 wt%). Experiments were carried out in triplicate and the results were reported as average values. (Reproduced from reference [33] with permission)

Nie et al [34] prepared Tamoxifen citrate (TAM)-loaded polyacrylonitrile (PAN) fibres using a wet-spinning technique. TAM was used as a model drug to evaluate the potential application of the loaded fibre system for drug delivery. PAN was first homogeneously dissolved in the N,N-dimethylacetamide (DMAc) solution containing TAM and then the co-dissolving solution was solidified to prepare the fibres using a wet-spinning method. The *in vitro* release experiment indicated that constant drug release from the fibre was observed over an extended period. Kinetic studies demonstrated that the system followed Higuchi kinetics. They did observe that at the beginning of the experiment a larger amount of TAM is released and concluded that this is possibly due to surface location and the physical binding of TAM to the fibres. Shen *et al* [33] later showed that the incorporation of the hydrophilic polymer hydroxypropyl methylcellulose (HPMC) with PAN reduced the initial burst release effects and increased the drug-loading (Figure 1b, c and d). The drug-release profiles of HPMC/PAN drug-loaded fibres were consistent and stable compared to those of the control PAN. With the increased ratio of HPMC to PAN the drug-release profiles became more stable on account of the hydrated viscous layer formed by HPMC in the composite fibres. The *in vitro* dissolution results also reflected the effect of HPMC on modulating the release rate of TAM in the composite fibres. A higher proportion of HPMC decreased the rate of drug release.

The biodegradable polymer PLGA has also been used to form biofactor loaded fibres using a wet-spinning process [35]. Crow *et al* [35] fabricated biodegradable fibres of poly(L-lactic acid) (PLLA) and poly(D,L-lactide-co-glycolide) (PLGA) that encapsulated the protein bovine serum albumin (BSA) using an approach that consisted of wet-spinning a water-in-oil emulsion. They also studied the drug release kinetics and changes in molecular weight over time. These fibres are 2.4% by mass of bioactive material, and showed slow release properties. Release kinetics demonstrated that BSA release rates and molecular weight degradation were influenced by the amount of aqueous phase added as an emulsion during fabrication. They concluded that the type of polymer used (PLLA or PLGA) determines the molecular weight degradation rates, but has little effect on drug release kinetics. This last finding suggests that diffusion processes, as opposed to degradation rates, are the driving force for BSA release from the degradable polymer structures.

More recently biodegradable PLGA fibres (diameters of 250–300  $\mu\text{m}$ ) were used for the controlled delivery of dexamethasone or levofloxacin [36]. Mack *et al* [36] performed a comprehensive study whereby the degradable polymer composition was varied (PLGA 75:25, PLGA 50:50 and poly(D,L-lactide)- PDLLA) as was the drug type (dexamethasone (Dex) or levofloxacin (Levo)) and loading (4.8 to 18.4 wt%). Their findings indicated several important factors influencing drug release kinetics (Figure 2);

- i. Drug release could be controlled by drug loading (Figure 2a)
- ii. Drug release could be controlled by polymer type (Figure 2b), and
- iii. Dex released more slowly than Levo and that, upon increasing the Dex concentration, release could be slowed (Figure 2c)

**Figure 2** The release profiles of a) filaments containing levofloxacin, dissolved and precipitated, PLGA 50:50, b) filaments made from different polymers, and c) filaments

formulated with dexamethasone (PLGA 50:50 at Levo 7 wt% loading given in each panel for comparison). Error bars represent one standard deviation (n=3). The table describes the wet-spinning conditions for each fibre in the release graphs. (Figure reproduced from reference [36] with permission, Table adapted from [36])

### **3-Dimensional (3D) Printing**

3D printing is a process for making a three-dimensional solid object of virtually any shape from a digital model. 3D printing is achieved using an additive process (Figure 3), where successive layers of material are laid down in different shapes. 3D printing is also considered distinct from traditional machining techniques, which mostly rely on the removal of material by methods such as cutting or drilling (*subtractive* processes). While 3D printing technology was introduced in the 1980s, only recently have printers become widely available commercially.

So called “solution phase” 3D printing has been used to form macro- and micro- sized structures for drug delivery. The final product often contains a number of structural and bioactive (drug) components [37]. A significant challenge is the development of suitable host/structural materials that can be processed using this technique.

Printing allows the deposition of precise quantities of structural/scaffolding materials and therapeutic substances, [38,39] and is versatile enough to incorporate concentration gradients and other spatial patterns of drug deposition within the polymer matrix. The versatility of 3D printing in the biomedical area is demonstrated by Ferris *et al* [40] and Chung *et al* [41] who published work on the development of extrusion printing of hydrogel structures loaded with living cells. Many research teams have utilized this versatility of 3D printing to construct



tissue engineering structures that contain biofactors, such as growth factors, for use in bone regeneration [42] and nerve repair. In these and many other publications detailing 3D printed structures that contain biofactors, these structures were fabricated to support the growth of desired cells with the incorporated factor present in order to facilitate growth. Rattanakit *et al* [18] reported the use of a novel extrusion printing system to create drug delivery structures wherein the drug dexamethasone-21-phosphate disodium salt (Dex21P) was encapsulated within a biodegradable polymer (PLGA<sup>75:25</sup>) and water soluble poly(vinyl alcohol) (PVA) configurations. The authors demonstrated the ability to control the drug release profile through the spatial distribution of drug within the printed 3-dimensional structures (Figure 3). The extrusion printing process was used to fabricate two different structural configurations (Figure 3c and h) that demonstrated very different release profiles. This approach clearly demonstrated that, through simply modifying the printing patterns and structure (whilst not altering the polymer-drug “ink” properties), it is possible to modify the drug release properties.

**Figure 3** Schematic representation of the printed PVA–Dex21P on the PLGA drop cast film: (a) top view, (b) side view and (c) scroll configuration. The drug release profiles (e), loaded with different PVA molecular weight. The schematic representation (side view) of PVA-Dex21P sandwiched between PLGA layers; (e) 1 layer system, (f) 2 layers system, and (g) 3 layers system. The digital image of a 1 layer structure (h) shows the printed PVA:Dex21P line (containing a small amount of violet dye for visualization) between PLGA layers and (i) the drug release profiles from the different layer systems. (Reproduced from reference [18] with permission)

### Hot-melt extrusion Printing

There are diverse methods used to prepare drug-loaded solid dispersions using polymers and other excipients meeting the requirements of the pharmaceutical industry. [43-47]. Another of these methods is melt extrusion, a solvent-free continuous tool for dispersing active pharmaceutical ingredients (APIs) in a polymeric matrix [47-50]. Extrusion is the process of

forcing a raw material through a die, resulting in a product that is uniform in cross-sectional shape (Figure 4) [51]. The shape of the hole in the die of the extrusion device dictates the cross-sectional shape of the final product, and in fact almost any shape can be produced. The raw material must have appropriate rheological properties to allow extrusion through the die. This can be achieved by multiple methods, the most common being by melting, often referred to as hot-melt extrusion (HME). This approach has been employed to produce polymer-based rods [52], pellets [53] and fibres [54] loaded with therapeutic substances. Hot -melt extrusion over recent years has found widespread application as a viable drug delivery option in the drug development process and has been successfully applied to enable integration/distribution of poorly soluble drugs [55-59].

**Figure 4** Hot-melt extrusion (HME) equipment (a) used in the formation of drug loaded rods, pellets and fibres. Hot-melt extrusion print head (b) and schematic (c) of the internal polymer/drug loaded syringe encased in the heating block.

Drugs are incorporated into the polymer by mixing the raw polymer and drug materials in the extrusion device before melting the polymer in a heated barrel. This results in one of several potential molten phases: the drug may melt along with the polymer; the drug may dissolve in the melted polymer; or the drug may be dispersed throughout the melted polymer. Drugs that melt or dissolve in the molten polymer usually result in extruded products that demonstrate molecular dispersions of the drug in the polymer matrix (termed glass dispersions) [60], while drugs that are dispersed in molten phase usually remain dispersed as aggregates throughout the polymer matrix after extrusion. The efficiency of melt extrusion to uniformly distribute the drug evenly throughout the dosage form was investigated by Park *et al* [61]. Using a fluorescent dye as a model drug and employing confocal laser scanning microscope (CLSM) imaging, they showed that model drugs were well distributed throughout the hot-

melt extrudate, giving better content uniformity with low batch-to-batch variations compared with simple physical mixtures.

A thorough understanding of the structure of a solid dispersion, particularly the existing physical form of a drug in the carrier matrix is required to predict the stability, solubility and hence bioavailability of melt extrudates [62]. Through the use of HME, Deng *et al* [63] were able to improve the dissolution rate and enhance the stability of a poorly water-soluble and low glass-transition temperature ( $T_g$ ) model drug, fenofibrate, in low molecular weight grades of hydroxypropylcellulose matrices. They showed that the dissolution rate of fenofibrate from melt extruded pellets was faster than that of the pure drug ( $p < 0.05$ ) and that the incorporation of sugars within the formulation further increased the fenofibrate release rates.

It is critical to effectively disperse the drug in a polymer matrix at the molecular level in order to enhance its bioavailability as well as control its release. Nagy *et al* [50] utilized melt extrusion and supercritical CO<sub>2</sub>-aided melt extrusion of solid pharmaceutical formulations to enhance the dissolution rate of the poorly water soluble drug carvedilol, a nonselective beta blocker/alpha-1 blocker indicated in the treatment of mild to severe congestive heart failure (CHF) and high blood pressure. They found the presence of the drug had a plasticizer effect of the polymer matrix (Eudragit E) and that the supercritical extrusion process did not decompose the drug. When comparing melt extrusion, supercritical extrusion and physical mixing methods it was shown that the extruded samples showed significantly improved dissolution rates (Figure 5a) with the supercritical samples showing slightly more rapid dissolution in the initial few minutes. This initial increase is attributed to an inner porosity of

the supercritical sample due to its foaming (high porosity) nature (Figure 5c compared to Figure 5b).

**Figure 5** Dissolution profiles (a) of (i) supercritical melt extruded, (ii) melt extruded, (iii) physical mix. Optical images of the melt extruded sample (b) and supercritical extruded sample (c). (Reproduced from reference [50] with permission).

The main disadvantage of the melt extrusion technique is the high temperatures needed to melt the polymer which prohibits the use of this method for therapeutic substances that are especially heat labile. However, Stankovic *et al* [64] synthesised a low melting biodegradable hydrophilic multiblock copolymer composed of poly (ethylene glycol) and poly ( $\epsilon$ -caprolactone) to allow extrusion at relatively low temperatures. They investigated the extrusion characteristics of this polymer and explored a strategy for controlling the release of the model protein lysozyme from small diameter extruded implants (Figure 6). It was found that the polymer could be extruded at temperatures as low as 55 °C. Moreover, lysozyme remained active both during extrusion as well as during release. This low temperature processing is highly attractive for further developing delivery systems whereby the payload of the printed structures is a biological molecule with poor thermal stability such as growth factors.

**Figure 6** The *in vitro* release of lysozyme in 100 mM phosphate buffer, pH 7.4 at 37 °C for 260 days, (n = 3). The initial 24 h release (upper figure) is shown in hours. (Reproduced from reference [64] with permission).

Dierickx *et al* [65] produced co-extrudates consisting of two concentric polymer matrices: a core having a lipophilic character (ethylcellulose or poly ( $\epsilon$ -caprolactone)) and a coat with a hydrophilic character (Soluplus® or polyethylene oxide). Diclofenac sodium (DS) was incorporated as the model drug in both layers. The maximum drug load in the core and coat

depended on the extrusion temperature and the die dimensions, while adhesion between core and coat was mainly determined by the drug load and by the extrusion temperature (Figure 7).

**Figure 7** Mean dissolution profile ( $\pm$ SD) ( $n = 3$ ) of experimental formulations (●) F1, (X) F2, (▲) F3, (■) F4 and (- - -) Motifene. The insert table shows the formulation conditions. (Reproduced from reference [65] with permission).

The versatility of the HME process also provides a means to produce DDSs that possess variable release kinetics. The release of melanotan-I (MT-I) from biodegradable implants of poly(D,L lactide-co-glycolide) (PLGA; 50:50 molar ratio of lactic/glycolic acid) copolymer produced by HME have been reported by Bharadwaj and Blanchard [66,67]. The *in vitro* release of MT-I exhibited a triphasic profile with an initial rapid release (less than 5% of the drug load) followed by a secondary phase of slow release. It was also observed that a tertiary phase of rapid release commenced after about 3 weeks, due to erosion of the polymer. The polymer erosion and degradation were considered as the factors influencing the drug release and were controlled by the physical properties of the polymer, such as molecular weight and viscosity.

The HME process described above has also been adapted to function as a 3D printer (Figure 8) whereby the polymer melt is extruded from a movable tip and a structure can be printed on a moving x-y-z stage following a pre-designed structure shape; a process also referred to as fused deposition modelling (FDM). The work undertaken by Masood [68] clearly demonstrates the feasibility of using FDM to fabricate DDSs with varying drug release characteristics. Masood demonstrated the ability of HME printed structures to modulate the diffusion of drug (represented by model dyes) through the HME printed structures.

## **Electrospinning**

Among several methods for preparing bioactive loaded polymer structures for drug delivery, the electrospinning technique presents a number of advantages; in particular, the possibility of fabricating nanodimensional high specific surface area structures [69]. Electrospun fibres have been successfully developed for the encapsulation and the delivery of bioactive compounds for therapeutic treatments [70-74].

Typically drug enrichment at the surface of electrospun fibres occurs when the drug is blended into a polymer solution prior to electrospinning, and results in severe burst release phenomenon [75]. This burst release reduces the effective lifetime of the delivery device.

The development of coaxial electrospinning has gone some way towards improving drug encapsulation efficiency and thus release profiles, and is a relatively new technique. Coaxial electrospinning of core-shell fibres has added to the versatility of DDSs by affording a near zero-order drug release kinetics, dampening of burst release, and applicability to a wider range of bioactive agents. Controllable electrospinning of fibres and subsequent drug release from these chiefly polymeric vehicles depend on well-defined solution and process parameters. Viry *et al* [76] developed a novel technique combining coaxial and emulsion electrospinning to produce microstructured core-shell fibres from the degradable polymer PLGA. The structures were composed of a 75:25 PLGA core and an 85:15 PLGA shell, with the drug (the antiepilepsy drug Leviteracetam - Lev) contained within the core PLGA polymer. They demonstrated that when the core was formed from an emulsion of PLGA and drug, the core morphology varied considerably compared to when the core was formed from a solution of PLGA and drug. The coaxial-emulsion approach facilitated the design of drug microreservoirs of variable size within the bulk of the fibre and, combined with a tailored

diffusive barrier, allowed modulation of the release kinetics of these novel carriers. A nearly constant and linear release of Levetiracetam from PLGA emulsion-coaxial electrospun fibres was observed over 20 days (Figure 8).

**Figure 8** Coaxial electrospun fibres consisting of PLGA 75:25 core and 85:15 sheath observed by SEM (a and b). Coaxial fibre cores (a) were formed from a PLGA solution in which Lev was blended and emulsion/coaxial fibre (b) cores were formed from a reverse emulsion in which Lev was dispersed in the aqueous phase. Coaxial/emulsion (c) configuration showing schematics of the corresponding fibre structures produced from each method. Cumulative release (d) of Lev in artificial cerebrospinal fluid (aCSF) (37 °C, pH 6.8) from coaxial ( $\square$ ) and emulsion/coaxial ( $\diamond$ ) electrospun fibres represented as drug amount ( $M_t$ ) released relative to drug loading ( $M_{tot}$ ) of the carrier. Error bars represent standard errors from the average calculated on three specimens. (Reproduced from Ref. [76] with permission from The Royal Society of Chemistry)

The non-degradable polymer polyurethane (PU) has been used to form electrospun drug delivery structures [77-79]. Han *et al* [80] fabricated electrospun PU fibres containing the drug Rapamycin (RM). The RM-contained PU fibres, generated by three distinct blending methods, exhibited significantly different fibre diameters (200–500 nm) and distinct RM release kinetics. They found that as the concentration of RM increased, the electrospun fibre diameter also increased and that the amount of RM released at each sample time point was generally dependent on the amount of RM loading; but the release kinetics was not affected by the amount of RM. They concluded that this suggests that RM localized on/near the fibre surfaces accounted for the main sources of drug release within their 49 day release period.

### **Melt Electrospinning**

Melt electrospinning (MES) is a promising technique to prepare fibrous drug-loaded polymer-based solid dispersions for drug delivery systems with controlled release properties without the use of solvents. The absence of solvent in MES has a number of potential advantages. In particular, the risk of toxic solvent residue in the fibres can be eliminated;

making MES a preferred technique for tissue engineering [81-83] and oral drug delivery purposes.

Melt electrospinning (MES) was used to prepare fast dissolving fibrous drug delivery systems in the presence of plasticizers. Lowering of the process temperature was achieved by using plasticizers in order to avoid undesired thermal degradation. Carvedilol (CAR), a poorly water-soluble and thermal-sensitive model drug, was introduced into an amorphous methacrylate terpolymer matrix, Eudragit® E, suitable for fibre formation. [84]

The solvent-free melt electrospinning (MES) method was developed to prepare a drug delivery system with fast release of carvedilol (CAR), a drug with poor water solubility [85]. Cationic methacrylate copolymer of Eudragit® E type was used as a fibre forming polymer matrix. For comparison, ethanol-based electrospinning and melt extrusion (EX) methods were used to produce samples that had the same composition as the melt electrospun system (Figure 9). The drug release rate of the melt electrospun fibres was significantly higher than that of the ground extrudate with the same composition due to the increased specific surface area. The MES method also appears to produce structures with increased porosity (i.e., less dense fibres within the structures). The authors suggested that this variation in morphology results in the increased drug dissolution rate observed for the MES material due to increased release media solvent accessibility to the drug loaded fibres.

**Figure 9** Scanning electron microscopic image of (a) solvent based electrospun fibres (10,000x magnifications) and (b) melt electrospun fibres (330x magnification) each containing Eudragit® E and 20% carvedilol. *In vitro* dissolution (c) of carvedilol (CAR). MES: melt electrospun Eudragit® E based fibres with 20% carvedilol content; SES: solvent-based electrospun Eudragit® E based fibres with 20% carvedilol content; EX, Eudragit® E based extrudates with 20% carvedilol; CAR, unprocessed crystalline carvedilol. (Reproduced from reference [85] with permission).



## Conclusions

The versatility of the techniques outlined in this review clearly indicates the advantages associated with improving controlled release, delivery of poorly water soluble drugs, drug stability and facilitating reduced drug dosage without compromising efficacy. It is obvious from the above that innovative 3D fabrication approaches can be used to engineer delivery systems that provide the desired performance through manipulating the assembly process for a given material composition.

Combined with the ever increasing improvements being made in advanced fabrication methods, it is inevitable that these approaches will become routine in the area of drug delivery and may be the approach of choice to provide personalised drug delivery systems, on demand.

## Acknowledgements

The authors thank the Australian Research Council (ARC) for continuing financial support. GGW thank the ARC for his Laureate Fellowships. The authors also thank Dr Chee O Too for his help in proof reading this review.

## References

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- 1 J.W. Cui, Y. Yan, Y.J. Wang, F. Carus, Templated Assembly of pH-Labile polymer-drug particles for intracellular drug delivery, *Adv. Funct. Mater.* 22 (2012) 4718-4723.
- 2 J.W. Cui, Y. Yan, G.K. Such, K. Liang, C.J. Ochs, A. Postma, F. Caruso, Immobilization and intracellular delivery of an anticancer drug using mussel-inspired polydopamine capsule, *Biomacromol.* 13 (2012) 2225-2230.
- 3 C. Ward, S.P. Langdon, P. Mullen, A.L. Harris, D.J. Harrison, C.T. Supuran, I.H. Kunkler, New strategies for targeting the hypoxic tumour microenvironment in breast cancer, *Cancer Treatment Rev.* 39 (2013) 171-179.

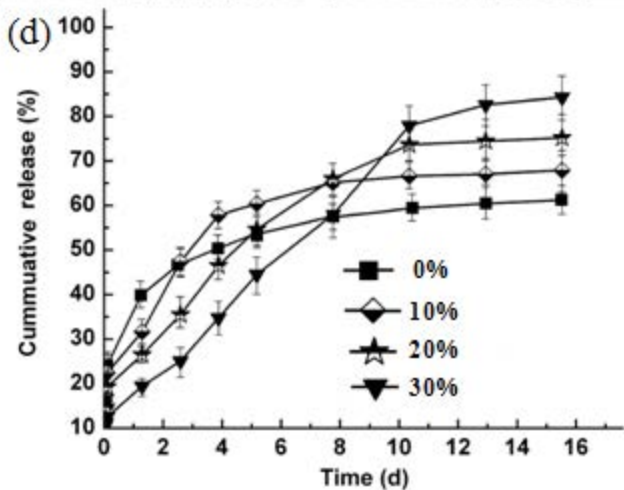
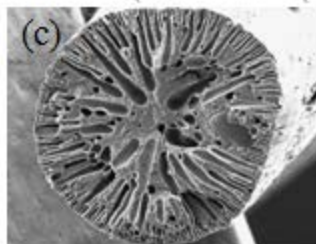
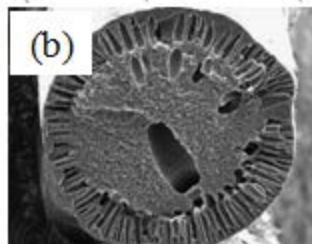
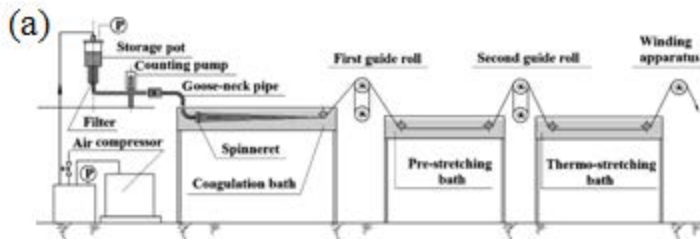
- 
- 4 O. Shimoni, A. Postma, Y. Yan, A.M. Scott, J.K. Heath, E.C. Nice, A.N. Zelikin, F. Caruso, Macromolecule Functionalization of Disulfide-Bonded Polymer Hydrogel Capsules and Cancer Cell Targeting, *ACS Nano*, 6 (2012) 6 1463-1472.
  - 5 C.F. Weiniger, L. Golovanevski, A.J. Domb, D. Ickowicz, Extended release formulations for local anaesthetic agents, *Anaesthesia*, 67 (2012) 906-916.
  - 6 C. Deng, Y.J. Jiang, R. Cheng, F.H. Meng, Z.Y. Zhong, Biodegradable polymeric micelles for targeted and controlled anticancer drug delivery: Promises, progress and prospects, *Nano Today*, 7 (2012) 467-480.
  - 7 H.A. Santos, J. Salonen, L.M. Bimbo, V.P. Lehto, L. Peltonen, J. Hirvonen, Mesoporous materials as controlled drug delivery formulations, *J. Drug Delivery Sci. and Technol.*, 21 (2011) 139-155.
  - 8 L.L. Lebel, B. Aissa, M.A. El Khakani, D. Therriault, Ultraviolet-assisted direct-write fabrication of carbon nanotube/ polymer nanocomposite microcoils. *Adv. Mater.* 22 (2010) 592–596.
  - 9 T.D. Brown, P.D Dalton, D.W. Hutmacher, Direct writing by way of melt electrospinning. *Adv. Mater.* 23 (2011) 5651–5657.
  - 10 R.A. Barry, R.F. Shepherd, J.N. Hanson, R.G. Nuzzo, P. Wiltzius, J.A. Lewis, Direct-write assembly of 3D hydrogel scaffolds for guided cell growth. *Adv. Mater.* 21 (2009) 2407–2410.
  - 11 J. Zheng, H. Xie, W. Yu, M. Tan, F. Gong, X. Liu, F. Wang, G. Lv, W. Liu, G. Zheng, Y. Yang, W. Xie, X. Ma, Enhancement of Surface graft density of MPEG on alginate/chitosan hydrogel microcapsules for protein repellency. *Langmuir* 28 (2012) 13261–13273.
  - 12 U. Gbureck, E. Vorndran, F.A. Müller, J.E. Barralet, Low temperature direct 3D printed bioceramics and biocomposites as drug release matrices, *J. Control. Release* 122 (2007) 173–180.
  - 13 G.M. Gratson, F. García-Santamaría, V. Lousse, M. Xu, S. Fan, J.A. Lewis, P.V. Braun, Direct-write assembly of three-dimensional photonic crystals: Conversion of polymer scaffolds to silicon hollow-woodpile structures. *Adv. Mater.* 18 (2006) 461–465.
  - 14 W. Wu, A. DeConinck, J.A. Lewis, Omnidirectional printing of 3D microvascular networks. *Adv. Mater.* 23 (2011) H178–H183.
  - 15 D. Therriault, R.F. Shepherd, S.R. White, J.A. Lewis, Fugitive inks for direct-write assembly of three-dimensional microvascular networks. *Adv. Mater.* 17 (2005) 395–399.
  - 16 J.N. Hanson Shepherd, S.T. Parker, R.F. Shepherd, M.U. Gillette, J.A. Lewis, R.G. Nuzzo, 3D microperiodic hydrogel scaffolds for robust neuronal cultures. *Adv. Funct. Mater.* 21 (2011) 47–54.
  - 17 V. Karageorgiou, D. Kaplan, Porosity of 3D biomaterial scaffolds and osteogenesis. *Biomaterials* 26 (2005) 5474–5491.
  - 18 P. Rattanakit, S.E. Moulton, K.S. Santiago, S. Liawruangrath, G.G. Wallace, Modification of drug release profiles using extrusion printed polymer structures. *Int. J. Pharm.* 422 (2012) 254-263.
  - 19 V. Chan, P. Zorlutuna, J.H. Jeong, H. Kong, R. Bashir, Three-dimensional photopatterning of hydrogels using stereolithography for long-term cell encapsulation. *Lab Chip* 10 (2010) 2062–2070.
  - 20 A. van Blaaderen, R. Ruel, P. Wiltzius, P. Template-directed colloidal crystallization. *Nature* 385 (1997) 321–324.
  - 21 G.M. Gratson, M. Xu, J.A. Lewis, Microperiodic structures: direct writing of three-dimensional webs. *Nature* 428 (2004) 386–386.

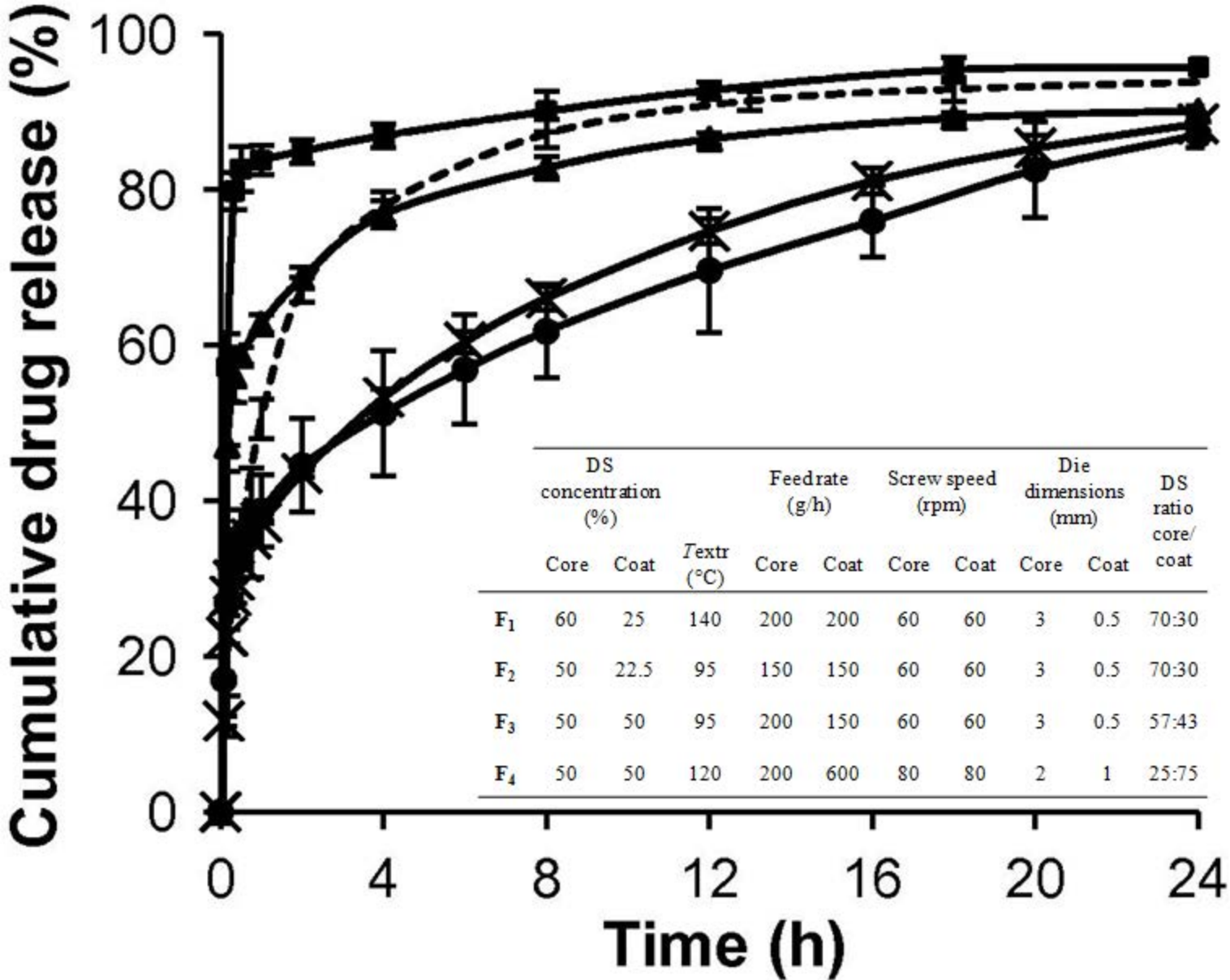
- 
- 22 D. Therriault, S.R. White, J.A. Lewis, Chaotic mixing in three-dimensional microvascular networks fabricated by direct-write assembly. *Nat. Mater.* 2 (2003) 265–271.
  - 23 J.A. Lewis, Direct ink writing of 3D functional materials. *Adv. Funct. Mater.* 16 (2006) 2193–2204.
  - 24 J.A. Lewis, G.M. Gratson, Direct writing in three dimensions. *Mater. Today* 7 (2004) 32–39.
  - 25 J.E. Smay, G.M. Gratson, R.F. Shepherd, J. Cesarano, J.A. Lewis, Directed colloidal assembly of 3D periodic structures. *Adv. Mater.* 14 (2002) 1279–1283.
  - 26 J.E. Smay, J. Cesarano, J.A. Lewis, Colloidal inks for directed assembly of 3-D periodic structures. *Langmuir* 18 (2002) 5429– 5437.
  - 27 G.M. Gratson, J.A. Lewis, Phase behavior and rheological properties of polyelectrolyte inks for direct-write assembly. *Langmuir* 21 (2005) 457–464.
  - 28 J. Malda, J. Visser, F.P. Melchels, T. Jüngst, W.E. Hennink, W.J.A. Dhert, J. Groll, D.W. Hutmacher, 25th anniversary article: engineering hydrogels for biofabrication. *Adv. Mater.* 25 (2013) 5011–5028.
  - 29 W. Schuurman, P.A. Levett, M.W. Pot, P.R. van Weeren, W.J.A. Dhert, D.W. Hutmacher, F.P.W. Melchels, T.J. Klein, J. Malda, Gelatin-methacrylamide hydrogels as potential biomaterials for fabrication of tissue-engineered cartilage constructs. *Macromol. Biosci.* 13 (2013) 551–561.
  - 30 S.Z. Guo, M.C. Heuzey, D. Therriault, Properties of Polylactide Inks for Solvent-Cast Printing of Three-Dimensional Freeform Microstructures, *Langmuir* 30 (2014) 1142–1150.
  - 31 R. Kolakovic, T. Viitala, P. Ihalainen, N. Genina, J. Peltonen, N. Sandler, *Expert Opinion Drug Delivery*, 10 (2013) 1711-1723.
  - 32 Wang, Q., Zhang, N., Hu, X., Yang, J., Du, Y., Chitosan/starch fibers and their properties for drug controlled release. *Eur. J. Pharm. Biopharm.* 66 (2007) 398– 404.
  - 33 X. Shen, D. Yu, X. Zhang, C. Branford-White, L. Zhu, Preparation and Characterization of TAM-Loaded HPMC/PAN Composite Fibers for Improving Drug-Release Profiles, *J. Biomater. Sci.* 22 (2011) 2227–2240
  - 34 H.L. Nie, Z.H. Ma, Z.X. Fan, C.J. Branford-White, X. Ning, L.M. Zhu, J. Han, Polyacrylonitrile fibers efficiently loaded with tamoxifen citrate using wet-spinning from co-dissolving solution, *International Journal of Pharmaceutics* 373 (2009) 4–9.
  - 35 B.B. Crow, A.F. Borneman, D.L. Hawkins, G.M. Smith, K.D. Nelson, evaluation of *in vitro* drug release, pH change, and molecular weight degradation of poly(L-lactic acid) and poly(D,L-lactide-co-glycolide) fibers, *Tissue Eng.* 11 (2005) 7-8.
  - 36 B.C. Mack, K.W. Wright, M. Davis, A biodegradable filament for controlled drug delivery, *Journal of Controlled Release* 139 (2009) 205–211.
  - 37 J. Giannatsis, V. Dedoussis, Additive fabrication technologies applied to medicine and health care: a review, *Int. J. Adv. Man. Tech.*, 40 (2009) 116-127.
  - 38 T. Boland, T. Xu, B. Damon, X. Cui, Application of inkjet printing to tissue engineering. *Biotech. J.* 1 (2006) 910-917.
  - 39 C. Zhang, K. Zhao, T. Hu, X. Cui, N. Brown, T. Boland, Loading dependent swelling and release properties of novel biodegradable, elastic and environmental stimuli-sensitive polyurethanes. *J. Control. Release* 131 (2008) 128-136.
  - 40 C.J. Ferris, K.J. Gilmore, G.G. Wallace, M. in het Panhuis, Modified gellan gum hydrogels for tissue engineering applications, *Soft Matter*, 9 (2013) 3705-3711.

- 
- 41 J.H.Y. Chung, S. Naficy, Z. Yue, R.M.I. Kapsa, A. Quigley, S.E. Moulton, G.G. Wallace, Bio-ink properties and printability for extrusion printing living cells, *Biomater. Sci.*, 1 (2013) 763-773.
  - 42 S. Bose, S. Vahabzadeh, A. Bandyopadhyay, Bone tissue engineering using 3D Printing, *Materials Today*, 16 (2013) 496-504.
  - 43 Z. Fulop, T.T. Nielsen, K.L. Larsen, T. Loftsson, Dextran-based cyclodextrin polymers: Their solubilising effect and self-association. *Carbohydr. Polym.* 97 (2013) 635–642.
  - 44 A. Szuts, P. Lang, R. Ambrus, L. Kiss, M.A. Deli, P. Szabo-Revesz, Applicability of sucrose laurate as surfactant in solid dispersions prepared by melt technology. *Int. J. Pharm.* 410 (2011) 107–110.
  - 45 B. Vajna, I. Farkas, A. Farkas, H. Pataki, Z.K. Nagy, J. Madarasz, G. Marosi, Characterization of drug–cyclodextrin formulations using Raman mapping and multivariate curve resolution. *J. Pharm. Biomed.* 56 (2011) 38–44.
  - 46 M. Allesø, N. Chieng, S. Rehder, J. Rantanen, T. Rades, J. Aaltonen, Enhanced dissolution rate and synchronized release of drugs in binary systems through formulation: Amorphous naproxen–cimetidine mixtures prepared by mechanical activation. *J. Control. Release* 136 (2009) 45–53.
  - 47 G. Patyi, A. Bodis, I. Antal, B. Vajna, Z.K. Nagy, G. Marosi, Thermal and spectroscopic analysis of inclusion complex of spironolactone prepared by evaporation and hot melt methods. *J. Therm. Anal. Calorim.* 102 (2012) 349–355.
  - 48 M. Sauceau, J. Fages, A. Common, C. Nikitine, E. Rodier, New challenges in polymer foaming: A review of extrusion processes assisted by supercritical carbon dioxide. *Prog. Polym. Sci.* 36 (2010) 749–766.
  - 49 M. Thommes, P. Kleinebudde, Use of 6-carrageenan as alternative pelletisation aid to microcrystalline cellulose in extrusion/spheronisation. I. Influence of type and fraction of filler. *Eur. J. Pharm. Biopharm.* 63 (2006) 68–75.
  - 50 Z.K. Nagy, M. Sauceau, K. Nyul, E. Rodier, B. Vajna, G. Marosi, J. Fages, Use of supercritical CO<sub>2</sub>-aided and conventional melt extrusion for enhancing the dissolution rate of an active pharmaceutical ingredient. *Polym. Adv. Technol.* 23 (2012) 909–918.
  - 51 J. Breitenbach, Melt extrusion: from process to drug delivery technology. *European Journal of Pharmaceutics and Biopharmaceutics* 54 (2002)107-117.
  - 52 P. Viitanen, E. Suokas, P. Tormala, N. Ashammakhi, Release of diclofenac sodium from polylactide-co-glycolide 80/20 rods, *J. Mater. Sci. Mater. Med.* 17 (2006) 1267-1274.
  - 53 L. Wang, J. Wang, X. Lin, X. Tang, Preparation and in vitro evaluation of gliclazide sustained-release matrix pellets: formulation and storage stability *Drug Dev. Ind. Pharm.* 36 (2010) 814-822.
  - 54 B. Younes, A. Fotheringham, Factorial optimization of the effects of melt-spinning conditions on biodegradable as-spun aliphatic-aromatic copolyester fibers. III. diameter, tensile properties, and thermal shrinkage, *J. App. Poly. Sci.* 122 (201) 1434-1449.
  - 55 J. Feng, L. Xu, R. Gao, Y. Luo, X. Tang, Evaluation of polymer carriers with regard to the bioavailability enhancement of bifendate solid dispersions prepared by hot-melt extrusion. *Drug Dev. Ind. Pharm.* 38 (2011) 735–743.
  - 56 J.P. Lakshman, Y. Cao, J. Kowalski, A.T. Serajuddin, Application of melt extrusion in the development of a physically and chemically stable high-energy amorphous solid dispersion of a poorly water-soluble drug. *Mol. Pharm.* 5 (2008) 994–1002.
  - 57 X. Liu, M. Lu, Z. Guo, L. Huang, X. Feng, C. Wu, Improving the chemical stability of amorphous solid dispersion with cocrystal technique by hot melt extrusion. *Pharm. Res.* 29 (2012) 806–817.

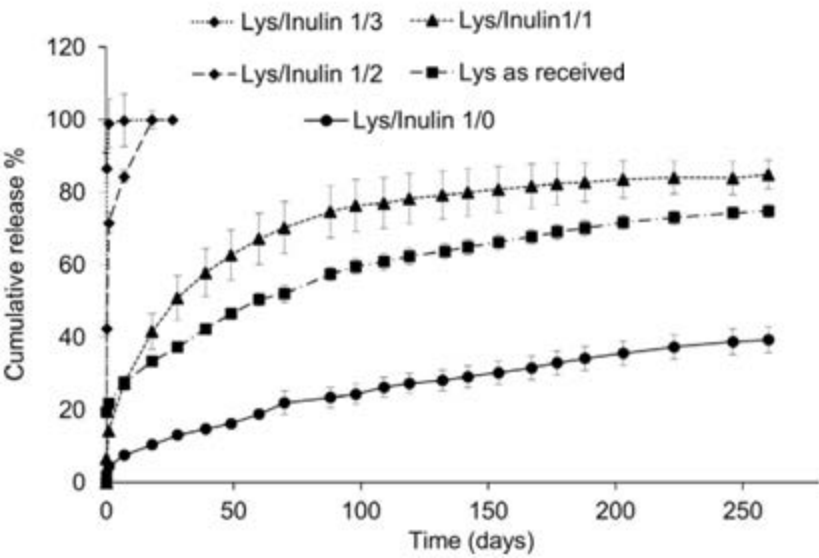
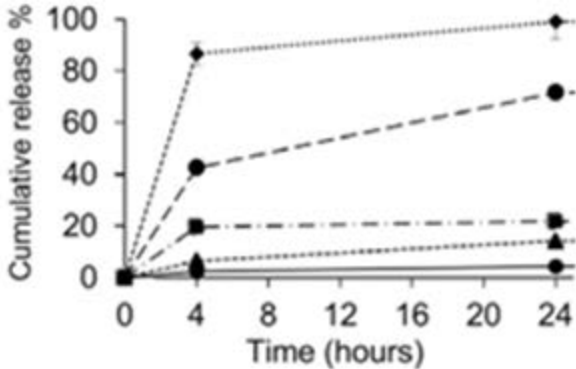
- 
- 58 A. Sakurai, T. Sakai, K. Sako, Y. Maitani, Polymer combination increased both physical stability and oral absorption of solid dispersions containing a low glass transition temperature drug: physicochemical characterization and in vivo study. *Chem. Pharm. Bull. (Tokyo)* 60 (2012) 459–464.
- 59 I. Tho, B. Liepold J. Rosenberg, M. Maegerlein, M. Brandl, G. Fricker, Formation of nano/micro-dispersions with improved dissolution properties upon dispersion of ritonavir melt extrudate in aqueous media. *Eur. J. Pharm. Sci.* 40 (2010) 25–32.
- 60 O.A. Abu-Diak, D.S Jones, G.P. Andrews, An Investigation into the dissolution properties of celecoxib melt extrudates: understanding the role of polymer type and concentration in stabilizing supersaturated drug concentrations, *Molecular Pharm.* 8 (2011) 1362-1371.
- 61 B.J. Park, C.Y. Kang, W.S. Kang, H.G. Choi, H.K. Han, B.J. Lee, New investigation of distribution imaging and content uniformity of very low dose drugs using hot-melt extrusion method, *International Journal of Pharmaceutics*, 458 (2013) 245-253.
- 62 S. Shah, S. Maddineni, J. Lu, M.A. Repka, Melt extrusion with poorly soluble drugs, *Int. J. Pharm.* 453 (2013) 233– 252.
- 63 W. Deng, S. Majumdar, A. Singh, S. Shah, N.N. Mohammed, Stabilization of fenofibrate in low molecular weight hydroxypropylcellulose matrices produced by hot-melt extrusion, *Drug Dev. Indust. Pharm.* 39 (2013) 290–298.
- 64 M. Stankovic, H. de Waard, R. Steendam, C. Hiemstra, J. Zuidema, H.W. Frijlink, W.L.J. Hinrichs, Low temperature extruded implants based on novel hydrophilic multiblock copolymer for long-term protein delivery, *European J. Pharm. Sci.* 49 (2013) 578-587.
- 65 L. Dierickx, J.P. Remon, C. Vervaet, Co-extrusion as manufacturing technique for multilayer mini-matrices with dual drug release, *European J. Pharm. Biopharm.* 85 (2013) 1157-1163.
- 66 R. Bhardwaj, J. Blanchard, In vitro evaluation of Poly (D,L-lactide-co-glycolide) polymer-based implants containing the alpha-melanocyte stimulating hormone analog, *Melanotan-I. J. Control. Release* 45 (1997,) 49-55.
- 67 R. Bhardwaj, J. Blanchard, In vitro characterization and in vivo release profile of a poly (D,L-lactide-co-glycolide)-based implant delivery system for the [alpha]-MSH analog, *melanotan-I. Int. J. Pharm.* 170 (1998) 109 -117.
- 68 S.H. Masood, Application of fused deposition modelling in controlled drug delivery devices, *Assembly Automation*, 2007, 27(3), 215 – 221.
- 69 N. Bhardwaj, S. C. Kundu, Electrospinning: A fascinating fiber fabrication technique , *Biotech. Adv.*, 28 (2010) 325-347.
- 70 Z.M. Huang, C.L. He, A.Z. Yang, Y.Z. Zhang, X.J. Hang, J.L. Yin, Q.S. Wu, Encapsulating drugs in biodegradable ultrafine fibers through co-axial electrospinning, *J. Biomed. Mater. Res. A.* 77 (2006) 169-179.
- 71 H. Zhang, C.G. Zhao, Y.H. Zhao, G.W. Tang, X.Y. Yuan, Electrospinning of ultrafine core/shell fibers for biomedical applications, *Science China-Chemistry*, 53 (2010) 1246-1254.
- 72 A. Szentivanyi, T. Chakradeo, H. Zernetsch, and B. Glasmacher, Electrospun cellular microenvironments: Understanding controlled release and scaffold structure, *Adv. Drug Del. Rev.* 63 (2010) 209-220.
- 73 H.L. Jiang, Y.Q. Hu, Y. Li, P.C. Zhao, K.J. Zhu, W.L. Chen, A facile technique to prepare biodegradable coaxial electrospun nanofibers for controlled release of bioactive agents, *J. Control. Release*, 108 (2005) 237-243.

- 
- 74 T.J. Sill, H.A. von Recum, Electrospinning: Applications in drug delivery and tissue engineering, *Biomaterials*, 29 (2008) 1989-2006.
  - 75 Y. Yeo, K.N. Park, Control of encapsulation efficiency and initial burst in polymeric microparticle systems, *Archives of Pharm. Research*, 27 (2004) 1-12.
  - 76 L. Viry, S.E. Moulton, T. Romeo, C. Suhr, D. Mawad, M.J. Cook, G.G. Wallace, Emulsion-coaxial electrospinning: Designing novel architectures for sustained release of highly soluble low molecular weight drugs, *J. Mater. Chem.* 2 (2012) 11347-11353.
  - 77 Y. Choi, R. Nirmala, J.Y. Lee, M. Rahman, S.T. Hong, H.Y. Kim, Antibacterial ciprofloxacin HCl incorporated polyurethane composite nanofibers via electrospinning for biomedical-applications, *Ceramics Inter.*, 39 (2013) 4937-4944.
  - 78 X.L. Lin, D.Y. Tang, H.F. Du, Self-assembly and controlled release behaviour of the water-insoluble drug nifedipine from electrospun PCL-based polyurethane nanofibres, *J. Pharm. Pharmacol.* 65 (2013) 673-681.
  - 79 X.J. Han, Z.M. Huang, C.L. He, L. Liu, Preparation and characterization of core-shell structured nanofibers by coaxial electrospinning, *High Performance Polymers*, 19 (2007) 147-159.
  - 80 J. Han, S. Farah, A.J. Domb, P.I. Lelkes, Electrospun rapamycin-eluting polyurethane fibers for vascular grafts, *Pharm. Res.* 30 (2013) 1735-1748.
  - 81 P.D. Dalton, K. Klinkhammer, J. Salber, D. Klee, M. Moller, Direct in-vitro electrospinning with polymer melts. *Biomacromolecules* 7 (2006) 686-690.
  - 82 B.L. Farrugia T.D. Brown, Z. Upton, D.W. Hutmacher, P.D. Dalton, T.R. Dargaville, Dermal fibroblast infiltration of poly(g-caprolactone) scaffolds fabricated by melt electrospinning in a direct writing mode. *Biofabrication* 5 (2013) 025001.
  - 83 N. Bock, M.A. Woodruff, R. Steck, D.W. Hutmacher, B.L. Farrugia, T.R. Dargaville, Composites for delivery of therapeutics: Combining melt electrospun scaffolds with loaded electrosprayed microparticles. *Macromol Biosci.* 14 (2013) 202-214.
  - 84 A. Balogh, G. Dravavolgyi, K. Farago, A. Farkas, T. Vigh, P. Lajosoti, I. Wagner, J. Madarasz, H. Pataki, G. Marosi, Z.K. Nagy, Plasticized drug-loaded melt electrospun polymer mats: characterization, thermal degradation, and release kinetics *J. Pharm. Sci.* 103 (2014) 1278-1287.
  - 85 Z.K. Nagy, A. Balogh, G. Dravavolgyi, J. Ferguson, H. Pataki, B. Vajna, G. Marosi, Solvent-free melt electrospinning for preparation of fast dissolving drug delivery system and comparison with solvent-based electrospun and melt extruded systems, *J. Pharm. Sci.* 102 (2013) 508-517.

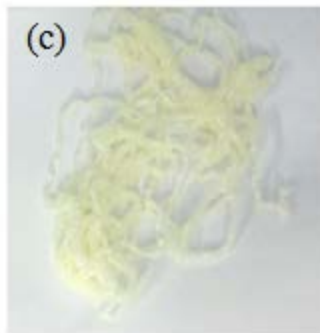
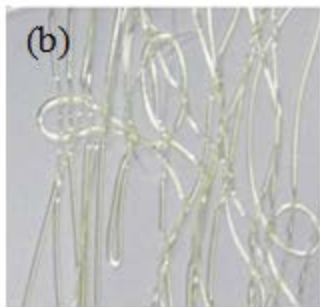
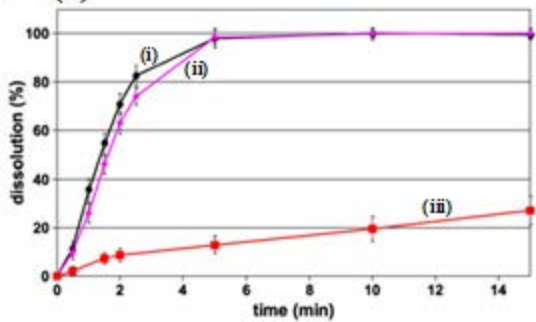


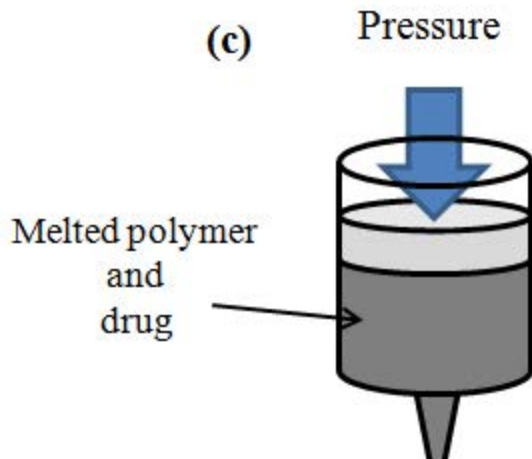
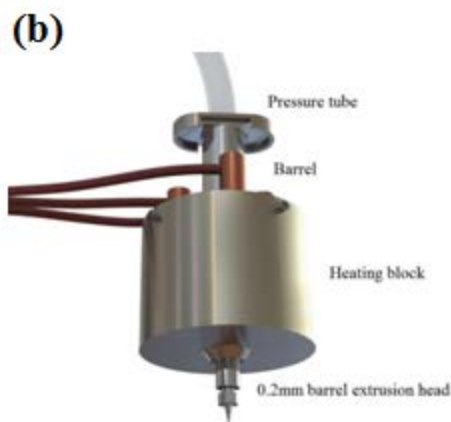
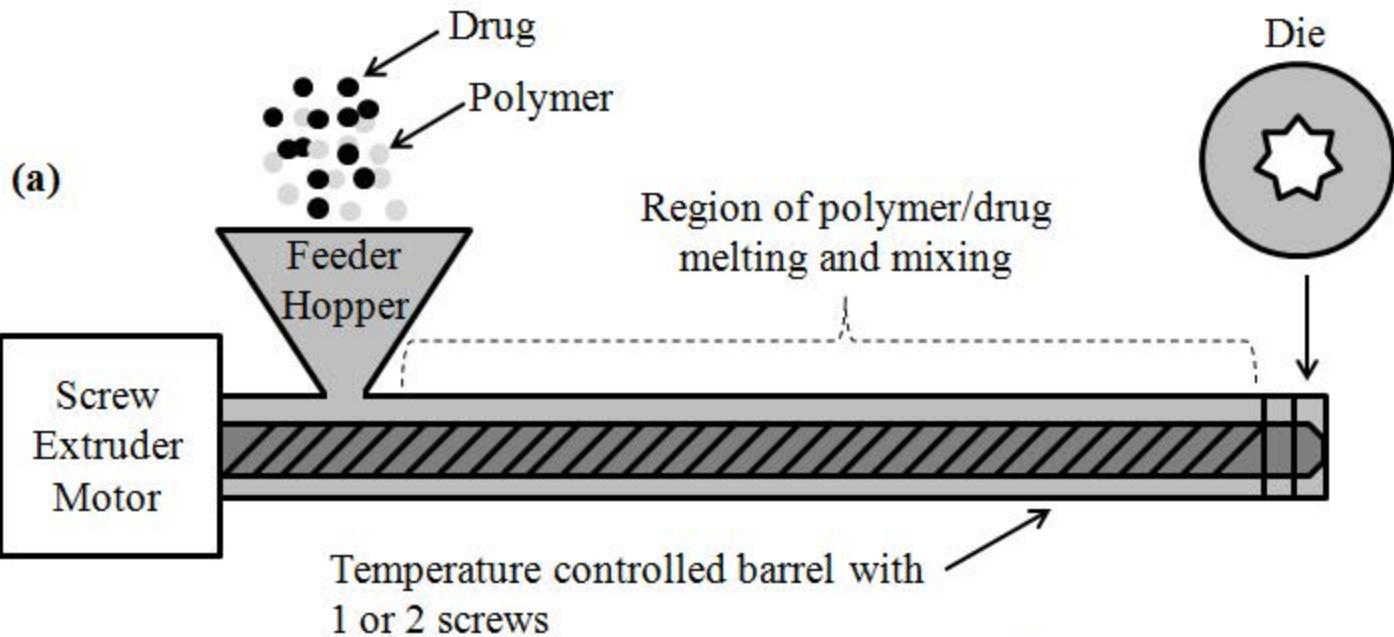


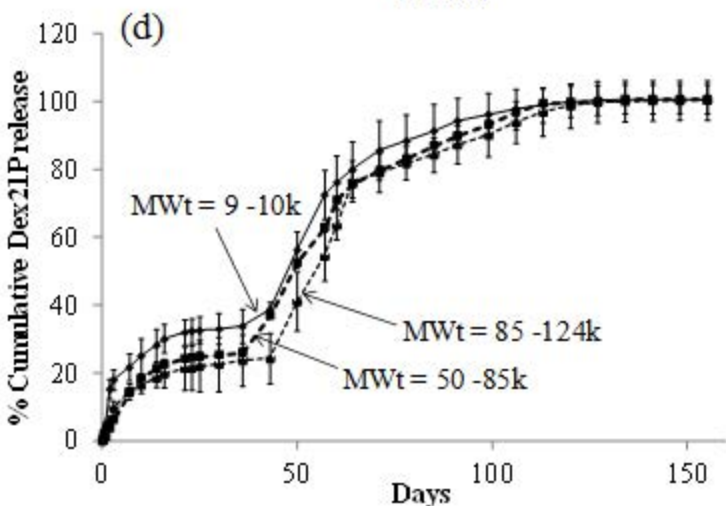
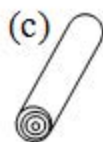
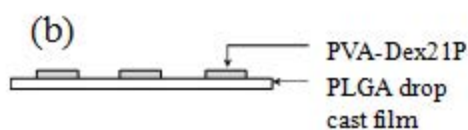
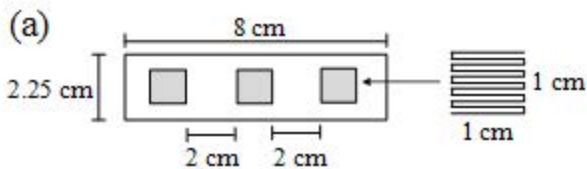




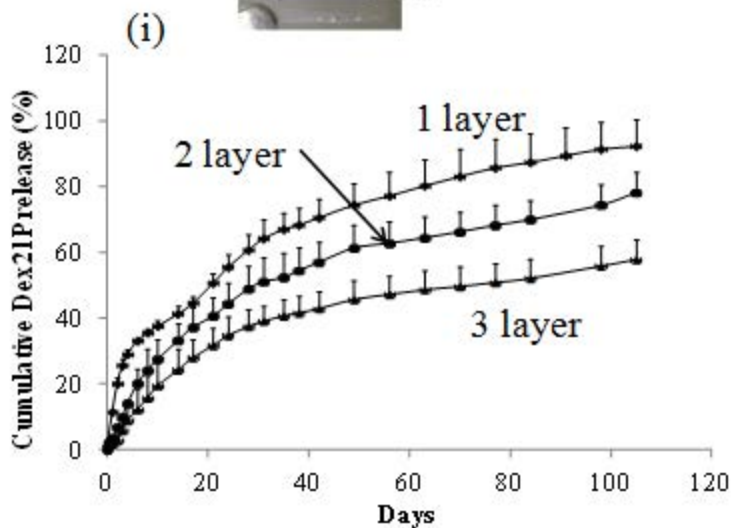
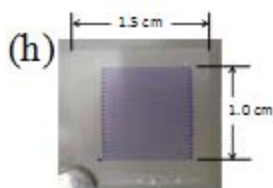
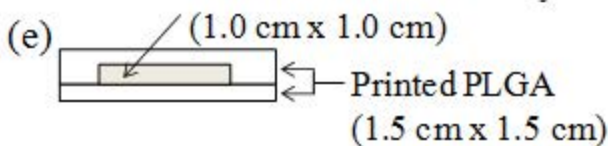
(a)



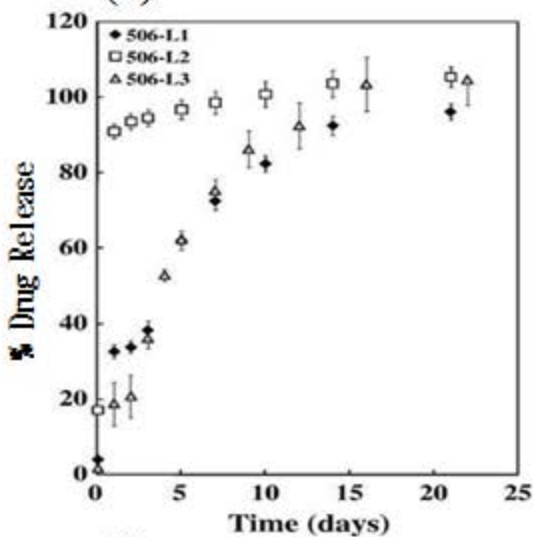




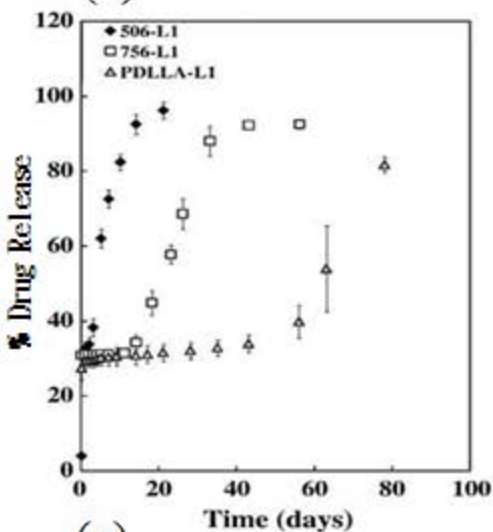
Printed PVA: Dex21P layer



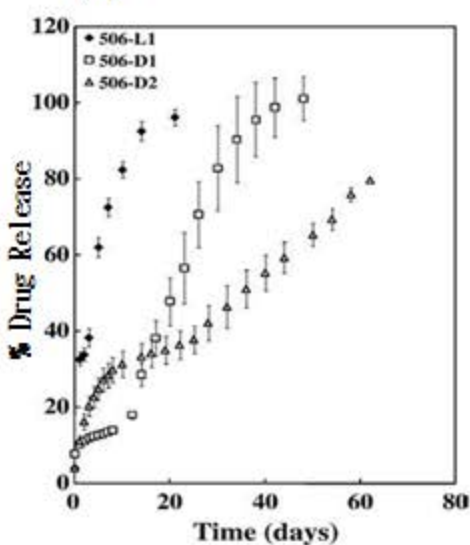
(a)



(b)



(c)



Sample	Polymer Type	Drug Type	Solution composition (%wt)
506-L1	PLGA 50:50	Levo	7.0
506-L2	PLGA 50:50	Levo	11.1
756-L1	PLGA 75:25	Levo	7.0
506-D1	PLGA 50:50	Dex	7.0
506-D2	PLGA 50:50	Dex	18.4
PDLLA-L1	PDLLA	Levo	7.0