Inkjet Printing for Pharmaceutics - A Review of Research and Manufacturing

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Abstract:
Global regulatory, manufacturing and consumer trends are driving a need for change in current pharmaceutical sector business models, with a specific focus on the inherently expensive research costs, high-risk capital-intensive scale-up and the traditional centralised batch manufacturing paradigm. New technologies, such as inkjet printing, are being explored to radically transform pharmaceutical production processing and the end-to-end supply chain. This review provides a brief summary of inkjet printing technologies and their current applications in manufacturing before examining the business context driving the exploration of inkjet printing in the pharmaceutical sector. We then examine the trends reported in the literature for pharmaceutical printing, followed by the scientific considerations and challenges facing the adoption of this technology. We demonstrate that research activities are highly diverse, targeting a broad range of pharmaceutical types and printing systems. To mitigate this complexity we show that by categorising findings in terms of targeted business models and Active Pharmaceutical Ingredient (API) chemistry we have a more coherent approach to comparing research findings and can drive efficient translation of a chosen drug to inkjet manufacturing.

Contents

Section 1. Introduction to inkjet printing technologies

There have been substantial investments in research and development for inkjet printing of functional materials in recent years. This is due in part to the versatility of digital, non-contact patterning techniques but also to increased manufacturing confidence. Industrial inkjet printing has now reached high standards of flexible, robust and reliable performance. That journey enabled the development of a wide range of research equipment and also the availability of a greater depth of knowledge in the public domain. The range of inkjet printing technologies and their critical parameters are discussed in this section, followed by a review of the development of the industry.

Inkjet printing is an umbrella term that encompasses a wide range of approaches to the digitally-controlled formation and placement of small liquid drops. Inkjet technology is usually classified as either Continuous Inkjet printing (CIJ) or Drop on Demand (DoD) printing: the two are distinguished by the physical process by which the drops are generated. These represent the currently dominant commercial processes, although other methods of delivering small volumes of liquid also exist, notably electrospray printing and various dispensing methods which involve interrupting a continuous flow by means of a fluid switch or valve (so-called 'valve-jet' methods) (Martin and Hutchings, 2013).

CIJ printing involves the ejection of a continuous stream of liquid through an orifice (nozzle), which then breaks up under surface tension forces into a stream of drops. Lord Rayleigh showed in the nineteenth century that a stream of liquid will tend to break up naturally with a characteristic wavelength of surface distortion, and hence eventual drop spacing, of about 4.5 times the initial diameter of the stream; in practical CIJ devices this natural breakup under surface tension forces is enhanced by modulating the flow through the nozzle at an appropriate frequency, often by a piezoelectric transducer behind the nozzle. For a continuous stream of ink drops to be used for printing, individual drops must be 'steered' to a particular landing site in order to produce a printed pattern. That is usually achieved by inducing an electrical charge on some of the drops, which are then deflected from the main axis of the stream as they pass through an electrostatic field. Unwanted drops are caught in a 'gutter' and the liquid recirculated through the system. CIJ printers are now relatively robust industrial tools and are widely used for high-speed marking on production lines. But the principle of breaking up a continuous liquid stream into a series of monodisperse droplets can also be applied as a manufacturing process in the production of powders, as discussed below in section 3.3.

In drop-on-demand printing the liquid is ejected from the printhead only when a drop is required: the production of each drop occurs rapidly in response to a trigger signal. A DoD printhead usually contains multiple nozzles (typically 100 to 1000, although specialist printheads may contain only a single nozzle), and instead of drop ejection resulting from external fluid pressure as in CIJ printing, the drop's kinetic energy derives from sources located within the printhead, very close to each nozzle. Many designs of printhead use the deformation of a piezoelectric ceramic element for this purpose, while in other types (thermal inkjet heads) the pressure pulse which ejects the drop is generated from the expansion of a small bubble of vapour produced by the action of a small electrical heating element on the liquid itself. There are advantages and disadvantages of both types of actuation. Piezoelectric printheads can handle a wider range of liquids than thermal printheads (which are restricted to fluids which will satisfactorily vaporise), while the latter can be simpler and cheaper to fabricate. DoD printing can employ small volumes of liquid, unlike CIJ printing in which a substantial recirculating volume is required, and thus has been used in most research applications of inkjet printing in the pharmaceutical field. Typical drop diameters in DoD printing range from 10 to 50 μm, corresponding to drop volumes between 1 and 70 pL; the drop diameter is similar to that of the nozzle from which it is ejected.

In DoD printing, the liquid first emerges from the printhead in the form of a jet, as shown in Figure 1a, which then detaches from the nozzle and collapses under surface tension forces to form one or more droplets. In many cases the main drop, which contains most of the liquid, is accompanied by one or more smaller 'satellite' drops. By controlling the ejection conditions, and sometimes also by modifying the rheology of the liquid, it can be possible to avoid the formation of satellite drops and ensure that only a single drop is produced. In many practical printing applications, however, the

presence of satellite drops is tolerated, especially if the satellite recombines on the surface with the original drop, as shown in Figure 1(b).

Surface tension, inertia and viscosity play key roles in the formation and behaviour of liquid jets and drops. The behaviour of a jet emerging from a nozzle turns out to be closely related to the value of the Ohnesorge number Oh, which depends on the physical properties of the liquid and the size scale of the jet or drop, but is independent of the driving conditions (which control the velocity). This dimensionless group is defined by Equation 1:

$$\mathrm{Oh} = \frac{\eta}{\sqrt{\gamma \rho d}} \tag{1}$$

where ρ is the density of the fluid, η is its viscosity, γ is its surface tension and d is a characteristic length, typically the diameter of the nozzle or drop.

If the Ohnesorge number is too high (Oh > ~1) then viscous forces will prevent the separation of a drop, while if it is too low (Oh < ~0.1) the jet will form a large number of satellite droplets. Satisfactory performance of a fluid in drop-on-demand inkjet printing thus requires an appropriate combination of physical properties, which will also depend on the droplet size and velocity (through the value of the Reynolds number Re, defined by $\mathrm{Re} = \rho dV/\eta$ where V is the drop velocity) as shown in Figure 1c (McKinley and Renardy 2011, Derby 2010).

The ranges of Ohnesorge number noted above provide some bounds to the 'printability' of the liquid, but other factors must also be considered: the jet must possess enough kinetic energy to be ejected from the nozzle (leading to the solid diagonal line in Figure 1c corresponding to Re = 2/Oh), and it is also desirable to avoid splashing of the drop on impact with the substrate (which leads to the broken diagonal line for which $\mathrm{OhRe}^{5/4} = 50$) (Derby 2010).

All these considerations apply to Newtonian liquids (i.e. those with a viscosity independent of shear-rate), but many liquids of practical importance are non-Newtonian, for example showing shear-thinning or viscoelastic behaviour. For these liquids, the behaviour may be more complex (see, for example, Hoath *et al.* 2012a and Hoath *et al.* 2012b). The challenges lie in the very high shear rate imparted to the liquid as it passes through the nozzle, which can lead to unexpected behaviour. The rheology of inkjet fluids has been explored extensively (e.g. Clasen *et al.* 2012, Hoath *et al.* 2013, Hoath *et al.* 2014). Inks containing particles, while having been printed at an industrial scale for some time (e.g. pigmented inks), also generate another set of constraints (particle size, morphology and concentration) which are normally empirically evaluated for a given ink and print head combination. While a large number of different materials have been successfully printed by inkjet, including cells, colloids and nanomaterials (Ferris *et al.* 2013, Perelaer *et al.* 2006, van Deen *et al.* 2013), ensuring that a material will print reliably and consistently in an industrial context is much more challenging and requires careful and long-term testing of the proposed system in conjunction with continued quality control.

Inkjet has advanced significantly since its concepts were developed in the 1970's and early 1980's (Endo *et al.* 1988, Kyser *et al.* 1976, Sweet 1971, Vaught *et al.* 1984, Zoltan 1972). DoD technology dominates the home printer market (pioneered for example by Canon, Hewlett Packard and Epson) and continuous inkjet (CIJ), as noted above, is widely used in manufacturing to date-mark and code a wide variety of product packages (pioneered by Videojet in the USA (Videojet) and Domino, a spin-out from Cambridge Consultants Ltd, in the UK (Domino Printing 2014a). Both DoD and CIJ have challenged conventional printing technologies by providing an alternative and cost-effective means for printing short runs and providing late-stage customisation (e.g. direct printing to packaging (Domino Printing 2014a). This aspect of inkjet use has been led by companies such as Kodak and Fujifilm Dimatix in the USA and Xaar (another Cambridge Consultants Ltd spin-out) in the UK. The advantages of inkjet have proved to be so beneficial for some applications that it has replaced conventional printing as the favoured approach (e.g. short run posters (Inca Digital 2014), and ceramic tiles (Hutchings 2010, Xennia 2014)).

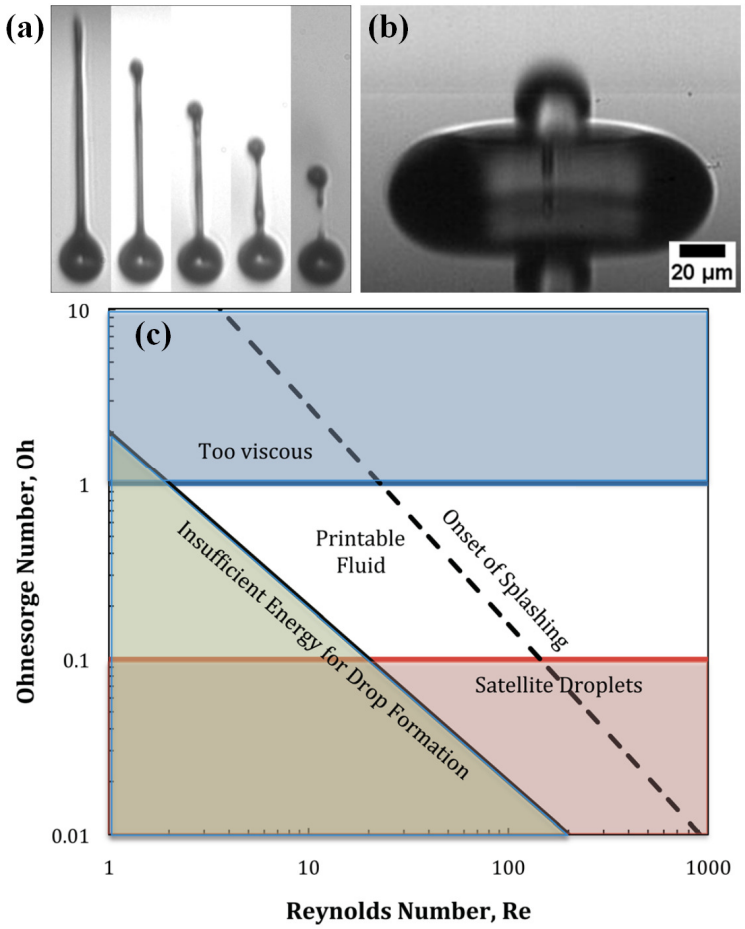

Figure 1: (a) A sequence of images of a jet of liquid being ejected downwards from a DoD printhead, forming a long jet attached to an approximately spherical head. The images towards the right correspond to later times. The tail condenses progressively into the main drop and also collapses radially under surface tension forces; in this case, it detaches from the main drop to form a satellite drop. (Reprinted with permission from Hoath et al. 2013. Copyright 2013, AIP Publishing LLC.). (b) A drop deposited by inkjet on a glass surface, followed by a satellite. The image of the drops is reflected in the glass surface. (c) Schematic diagram showing the operating regime for stable operation of DoD inkjet printing, in terms of the Ohnesorge and Reynolds numbers for Newtonian liquids (Reprinted with permission from McKinley and Renardy 2011. Copyright 2011, AIP Publishing LLC.).

Like many breakthrough technologies, it has taken inkjet a long time to develop and mature to its current state. Other parallel technology developments were needed to provide both the incentives and the means to advance inkjet printing. For example the development of the "personal" home and office computer led to a demand to produce "hard copy" not limited to black and white text. Advances in data processing power have also provided the means to manipulate and provide data to the increasing number of nozzles in each inkjet print head; the right data must be delivered at the right time to each of thousands, or in large industrial systems, hundreds of thousands of nozzles, at frequencies of tens of kilohertz per nozzle. The manufacturing technology required to form the critical parts of an inkjet print head has also continued to improve (Epson 2014). Individual parts of print heads such as nozzles and actuator arrays have always necessitated the use of Micro-Electro-Mechanical Systems (MEMS) processing. Such techniques often require very significant investment in appropriate tools and hence print heads destined for large volume home and office printers have been constructed in this way, while lower volume industrial inkjet systems have tended to be assembled more traditionally (with only some critical parts made using MEMS techniques). With the rapid proliferation of inkjet printing, MEMS fabrication techniques are now more widely implemented to construct print heads for commercial printing (e.g. Epson PrecisionCore, Fujifilm Dimatix SAMBA).

Today the focus for print head development and the major source of income for print head manufacturers is still their application to printing images. The use of inkjet as a manufacturing tool (of which pharmaceutical manufacturing is a sub-set) has been much discussed and analysed (e.g. Hutchings and Martin 2013) and a great deal of research effort has been expended in exploring its potential. The key constraint is the limited palette of materials that can be deposited by the inkjet process. Printheads and inks have been developed in tandem over many years for current printing applications. The application of inkjet to other uses has greatly multiplied the types of materials which need to be dispensed, leading to significant research into ink formulation but with very little focus on printhead redesign. In a shift to inkjet printing for pharmaceutical applications it is clear that we must consider the business case for such a significant investment, but also of great importance is research into the interactions between the printhead and the fluids being printed, to define technology and formulation requirements and ensure deliver of a functional dose. This review now considers in turn both the business and technology drivers and the key barriers to implementing pharmaceutical inkjet printing.

Section 2. The incentive to print pharmaceuticals

While service levels to the distributor exceed 98% on-time and in-full (OTIF) and gross margins remain healthy in the range of 70-80% (Harrington and Najim 2014), clear drivers for change in the pharmaceutical sector have been identified. The industry exhibits long, slow, expensive supply chains with a significant challenge specifically in optimising inventory levels (Kim and Lee, 1993; Calabrese and Pissavini 2011). The value of stock levels is estimated to be in the range of $100-150 billion for the top 25 Pharma companies (Harrington and Srai 2014). Replenishment lead times are often in excess of 200 days, inventories are more than 50% of Cost of Goods Sold (COGS) and annual manufacturing losses are estimated to be $20-25 billion for this same cluster of companies (Harrington and Srai 2014; Srai *et al*. 2014; Srai *et al*. 2015).

The emergence of both new technologies and therapy areas has the potential for dramatically changing this manufacturing and supply chain landscape. Based on future trends, the overall aim should be to ensure a sufficiently flexible sector in order to sustain a broader range of more specialised products at lower volumes (i.e. more stratified and personalised medicines), for specific patient populations (Voura *et al.* 2011), as well as satisfying current market and volume demands. For new technologies, such as inkjet printing, to become more generally accepted and exploited commercially, the business case for change will need to be both better understood and economically viable. Hence, a move away from the predominant 'blockbuster' model will need to consider the impact on and benefits for (a) product variety/customisation, (b) energy and resource efficiency, (c) inventory optimisation and (d) overall industry structure (Harrington *et al*. 2014).

It is in this context that inkjet printing is becoming attractive to manufacturers. Figure 2 shows a simplified view of a product transition through the innovation pipeline and indicates the broad set of potential applications where inkjet printing can potentially enable continuous and semi-continuous manufacturing, as well as a more rapid feeding of the innovation pipeline, namely:

1) High throughput API "system discovery" techniques
2) Deliver inherently scalable technologies to enable rapid transition to clinical trials
3) Manufacturing as (a) a primary process (i.e. API manufacture) or (b) a secondary process (i.e. delivery format fabrication)
4) Packaging and Distribution (e.g. security tags printed directly to product)
5) Final drug delivery method (e.g. aerosol technology, needle-free injection).

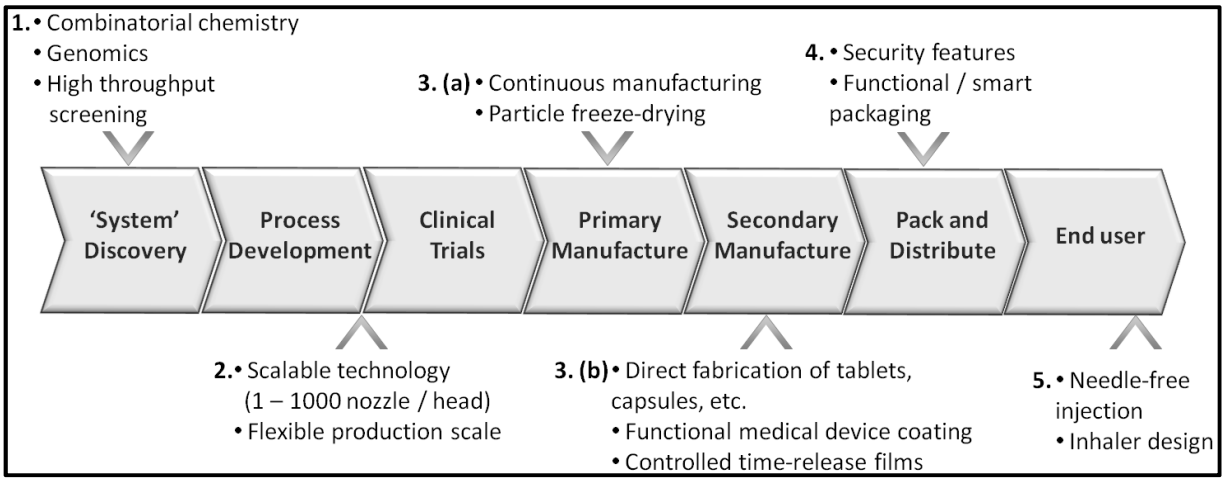

Figure 2: Applications of inkjet printing in a simplified manufacturing innovation pipeline (adapted from Srai, Christodoulou and Harrington, 2014). There are six entry points identified

An ideal new model to replace the blockbuster approach should incorporate technologies compatible with rapid scale-up of both new drugs and delivery formats, agile facilities, late-stage customisation and multiple co-existing agile supply chains to cope with the potential of significantly increased stock keeping unit (SKU) counts. The drive to explore inkjet printing in this context is partly due to success in implementing similar late-stage customisation tactics at scale in other sectors. For example, the European ceramics industry has benefitted significantly from implementation of digital inkjet decoration. A dramatic rebound in fortunes occurred due to the sudden decrease in inventory levels, the responsive, flexible nature of inkjet printing and the ease of implementation into a manufacturing environment (I.T. Strategies 2013). There may be similar, easily achievable benefits for drug products if they are pre-disposed to inkjet printing. For example, the steroid prednisolone is used for a range of different inflammatory diseases but requires carefully controlled and varying doses throughout the course of treatment. Currently, it is only available in doses of 1 mg, 2.5 mg, 5 mg and 25 mg. The ability to increase the SKU count to include a much greater range of concentrations and an advanced level of personalisation would immediately increase patient compliance by tackling end-user product complexity. While this is one simple example of one product, there is a rapidly increasing number of pharmaceutical products manufactured at scale and so a coherent structured approach is needed to understand if firstly, inkjet printing is a scientifically feasible approach to deliver the required product and if, secondly, a conversion to a continuous/semi-continuous manufacturing process is a suitable business model.

The former point is the focus of this review, exploring the technologies and challenges reported to-date, examined in detail in sections 3 and 4. While this review does not provide an in-depth study into business models, this section briefly reviews an approach for considering where continuous processing technologies, such as inkjet printing, may provide attractive opportunities for model transformation. This has been considered previously by identifying where products are positioned in terms of production volume and product variety (SKU count), as illustrated in Figure 3 (Srai *et al*. 2014). Future scenarios, based on an emerging process technology such as inkjet printing, can then be developed to examine opportunities in terms of volume and SKU profile. In a preliminary study of the oncology market, these factors were considered in identifying a series of candidate drug products with an attractive business case for transformation - made possible in the context of adopting new continuous processing technologies. In this specific case, the potential candidates were shown to cluster within a volume-variety matrix into three distinct groupings (Harrington and Najim 2014), namely:

- "New niche" products (Low volume, high cost, high inventory),
- "Old niche" products (Medium volume, medium cost, medium inventory)
- "Established generic" products (High volume, low cost, low inventory)

Designated as "product-process archetypes" (Harrington *et al*. 2013), each cluster exhibits very similar areas of benefit and at similar scale for patients and government health service providers (Harrington and Najim 2015). This simple classification system may enable ease of comparability to identify other drugs that will benefit from similar approaches. Equally, such a matrix will allow comparison of pathways across the matrix as business decisions lead to e.g. reformulation, increased personalisation or combinations and increased volumes. By way of illustration, and based on secondary data, a series of scenarios has been developed as part of a current-future state product volume-SKU variety analysis for an anti-malarial drug product (ACT) with current manufacturing volumes in the range of 200-300 tonnes per annum. In Figure 3, four pathways are currently being explored, i.e. (A) reduced volumes with opportunities in reformulation, (B) additional combinations and reformulation, (C) increase in combinations and SKU count only or (D) total volume increase, with future opportunities in clinical trials and viability in other therapy areas (Harrington and Srai 2014). Using supply network configuration mapping methodologies previously reported (Srai and Gregory, 2008), target applications and drug products may then be assessed in terms of these different transformation scenarios - bringing together inputs on market analysis, technology readiness and business viability to build the business case (Harrington *et al*. 2014). Examining clusters of pharmaceuticals in this way will help with the efficient identification of where a broad portfolio of products can avail of inkjet printing processes. The inkjet technologies that enable development of new processes and applications shown in Figure 2 will now be reviewed, followed by the shared scientific challenges of pharmaceutical inkjet research.

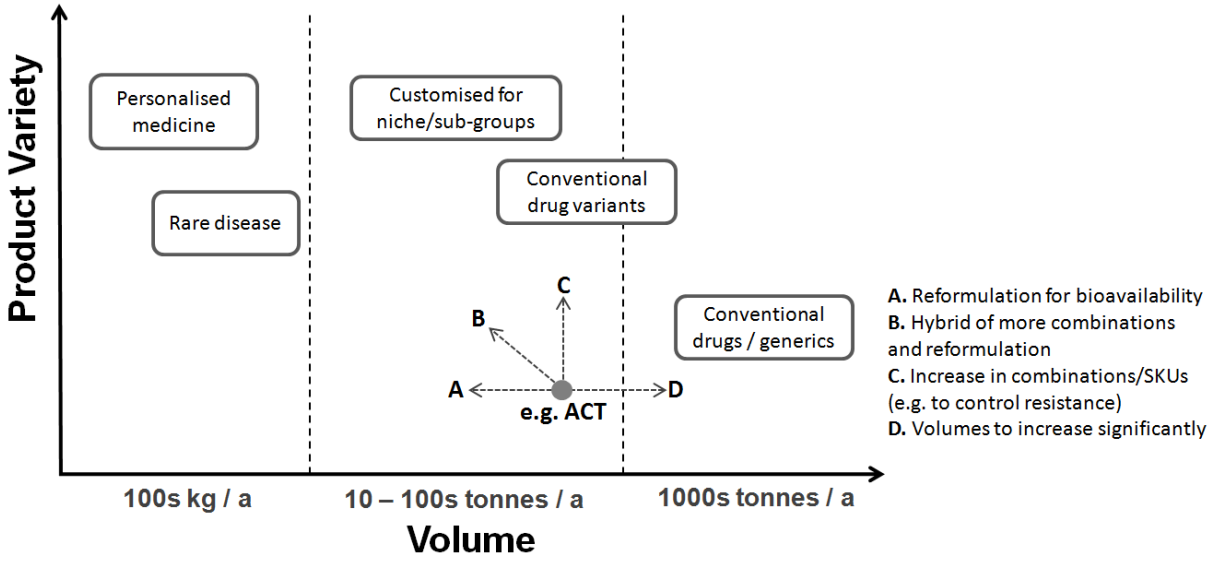

Figure 3: Product variety/volume matrix of pharmaceuticals showing some of the key product types (adapted from Srai *et al*. 2014). One example (a combination therapy drug product, ACT) is included with potential paths for future product development included (A-D), (adapted from Harrington and Srai 2014).

Section 3. Applications of inkjet printing to pharmaceutical technologies

As noted in Figure 2, initial examination of the literature shows that inkjet printing is being considered across the supply chain for pharmaceutical manufacturing. This review now examines each application in turn, with a particular focus on high throughput research applications and secondary manufacturing.

3.1 High throughput 'system discovery' techniques

Work in the early 1990s at Protogene Laboratories, Inc. led to a patent (Brennan 1995) focusing on fabrication of highly localised binding sites as part of a high throughput genomic technique. This highlighted the recognition of a need within industry for assay miniaturisation and also marked the beginning of a focused period of work examining the applications of inkjet printing to drug discovery techniques.

This exploration of alternative routes to drug discovery was also reflected in the literature (Bellavance *et al.* 2000, Lemmo *et al.* 1998, Blanchard *et al.* 1996). At this time, the route to delivering new small

molecule biopharmaceuticals to market had a duration of 10-15 years and cost of USD300 - USD800 million (Bellavance *et al.* 2000). An increasing library of potential molecules and a growing range of targets were leading to a rapidly growing series of assays. The pharmaceutical industry as a whole recognised the benefits of highly multiplexed and parallel analysis through large matrices of reacting units, driving a trend in moving from millilitre-scale work in test tubes to tens of microlitres in high density well-plates and ultra-high throughput techniques (Dunn and Feygin 2000) of sub-microlitre volumes. An early example of an industry-led cost-benefit analysis (Rose 1999) estimated the benefits of moving to higher density assays at USD156,000 per year for one assay equivalent to savings of USD5 million for 32 assays/year. Rather than driving savings, it enabled companies to maintain a sensible cost while increasing the number of feasible assays to unprecedented levels (e.g. 100,000 assays/year). Interestingly, there are multiple contributions to these savings. The reagents involved are expensive and the dramatic decrease in volumes has a significant impact on costings. Considerable savings in space requirements are also anticipated, while moving from centralised to de-centralised testing approaches is expected to drive more flexible and rapid innovation.

However, miniaturisation of assays leads to a series of key challenges, reviewed by a range of authors late in the 20th century (Hertzberg and Pope 2000, Sittampalam *et al.* 1997, Silverman *et al.* 1998, Lemmo *et al.* 1998) such as (i) assay methods and detection, (ii) liquid handling and robotics and (iii) process flow and information management. It is the second challenge for which inkjet printing was identified as a potentially important tool (Blanchard *et al.* 1996, Lemmo *et al.* 1997, Sittampalam et al 1997, Burbaum et al 1997, Lemmo et al 1998, Oldenburg et al 1998, Tisone 1998, Schena *et al.* 1998, Rose 1999, Dunn and Feygin 2000, Bellavance *et al.* 2000, Taylor *et al.* 2002). The key features of inkjet that lend themselves to the liquid handling challenges of micro-array technologies are (i) non-contact deposition with a significant stand-off distance, ensuring that the size of the well is no longer limited by the size of the dosing nozzle, (ii) repeatability and accuracy of inkjet-deposited drops once their formation is optimised, (iii) accurate control of both individual drop volumes and total volumes by waveform and print signal controls, (iv) low reservoir volume requirements and (v) minimal space requirements for the system.

This application of inkjet printing will need to encompass three main categories of drug discovery where assays are an essential component, namely combinatorial chemistry, genomics and high throughput screening. (Bellavance *et al.* 2000, Lemmo et al 1998).

Combinatorial chemistry involves the small scale parallel synthesis of large numbers of molecules. These are compounds that are formulated in a systematic manner, often from the same set of starting materials (Tiebes 1999). The goal is to build up a large library of similar molecules for testing as potential active pharmaceuticals. Lemmo (Lemmo et al 1997) showed some of the initial work, where solenoid valve-jet printing was used.

Similarly, inkjet printing has been applied to genomics (Allain *et al.* 2004, Shena *et al.* 1998, Okamoto *et al.* 2000, Blanchard *et al.* 1996, Goldmann *et al.* 2000). The study of structure, variation, and function of a genome inherently requires high throughput, multiplexed approaches to quantify nucleic acids. This is achieved through monitoring their interaction with a library of well-defined molecular probes. A good history of the development of tools in this field is provided by McWilliam *et al.* 2011. This details the history of progression from test tube scale to inkjet printing microarrays for a range of applications, such as the addition of nucleotides for in situ synthesis of nucleic acids (Schena *et al.* 1998, Hughes *et al.* 2001, Blanchard *et al.* 1996, Goldmann *et al.* 2000, Saaem et al 2010), with an example of an array created by inkjet printing shown in Figure 4a (Schena *et al.* 1998).

The need to develop the third category, high-throughput screening (HTS), is directly driven by the advances in the previous two categories. Combinatorial chemistry in particular delivers ever more molecules that must then be screened for their effectiveness. HTS is the miniaturisation of analytical assays, used to determine the effectiveness of a pharmaceutical. This scaled-up approach to 'trial and error' is used to identify the lead options for specific drug targets. Microarrays for HTS are a necessary development in the next stage after combinatorial chemistry, to show the potential effectiveness of the library that has been built up. As laid out clearly by Burbaum *et al.* 1997, the predicted throughput required to test 10^6 compounds against 200 targets would require a prohibitively

expensive investment in compound and reagent manufacture without miniaturisation to ultra-high throughput techniques using sub micro-litre volumes (Dunn and Feygin 2000, Rodriguez-Devora 2012, Tisone 1998). These small volume regions can be within wells, or increasingly of interest, on flat surfaces with the drop localised to the printed region by barriers of poor wettability (Kudo *et al.* 2007). Potyrailo *et al.* 2007 discussed the existence of applications outside pharmaceuticals for this technology, in a similar way to combinatorial chemistry. Earlier work by GlaxoSmithKline Pharmaceuticals (Taylor *et al.* 2002) showed that piezo-actuated inkjet and capillary deposition were the only non-contact techniques that could be tailored to the correct throughput and reliability for this approach.

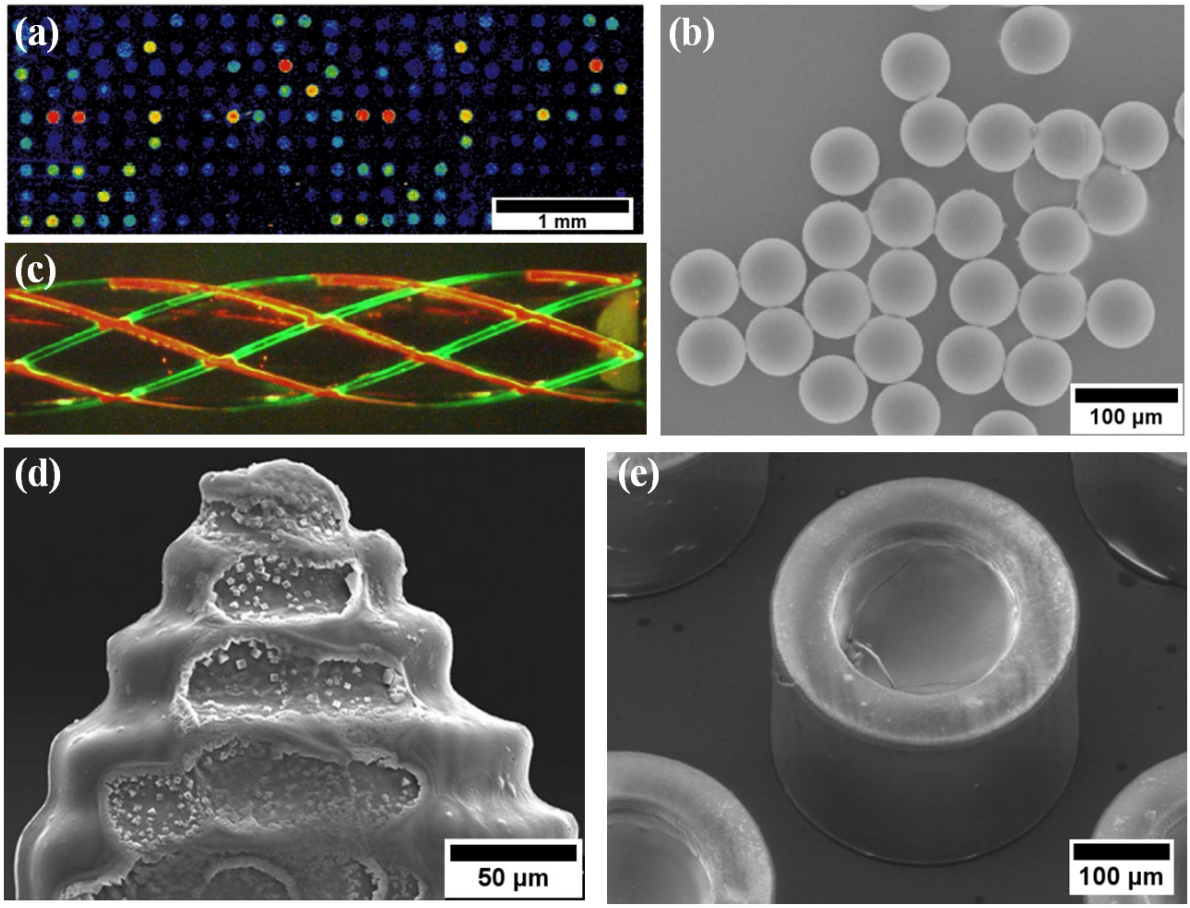

Figure 4: Gene-expression monitoring with an ink-jetted microarray, 2500 cDNA groups cm^{-2} (Reprinted with permission from (Schena et al.) Copyright 1998, AIP Publishing LLC.), (b) Inkjet printed paclitaxel-PLGA microspheres (Radulescu *et al.* 2003, copyright Microfab Technologies, Inc.), (c) Mock-up stent coated at Microfab Technologies, Inc. with two paclitaxel solutions containing two fluorescent dyes. (Reprinted with permission from (Antohe and Wallace). Copyright 2003, ASME Publications), (d) Gantrez® AN-139 polymer microneedles coated with quantum dot "model drug" by inkjet printing (Reprinted with permission from (Boehm *et al.* 2011). Copyright 2011, AIP Publishing LLC), (e) Inkjet polymer-filled microcontainers, impregnated with ketoprofen with supercritical CO_2 (Reprinted from (Marizza et al. 2014). Copyright 2014, with permission from Elsevier).

3.2 Design for manufacture with inherently scalable technologies

One of the main benefits of inkjet printing is its scalability (Hutchings and Martin 2013). While ink/printhead co-development are critical for long-term printing stability, the physical properties of inks developed for single nozzle research tools are still very close to those used with higher throughput development tools, commercial desktop printers and industrial inkjet printheads with hundreds or thousands of nozzles. From the review of literature, discussed later in Section 4.3, it is important to note that most reports are focused on research scale printheads such as Microfab and

MicroDrop single nozzle, piezo-actuated glass capillary devices. Development tools, such as the Dimatix Materials Printer and modified consumer desktop printers are the next most prevalent. These have been examined due to their applicability to the predicted scale for personalised medicine where it is envisioned that a printer would be used in a pharmacy or hospital for late-stage customisation. This approach is expected to revolutionise drug formulation. For example, 1,2,3-trinitroxypropane (nitroglycerin), a drug used to treat angina pectoris, is known to degrade during storage but this challenge is avoided if the drug can be produced for immediate use (Kommanaboyina and Rhodes 1999). Despite the importance placed on personalised medicine, continuous manufacturing of pharmaceuticals and the multiple roles of inkjet printing, this review finds that no standard industrial printheads have been used. It is essential to understand the targeted scale and to research the appropriate printing technique as early as possible, as each printhead type will have individual formulation and printing challenges when moving to scaled-up production.

3.3 Primary and secondary process manufacturing

Primary processes in the manufacturing of pharmaceuticals refer to the extraction and production of the active ingredient from its sources. As noted in Section 2, there is a shift in the pharmaceutical sector from large-scale batch production to de-centralised, smaller, continuous manufacturing facilities. Significantly smaller quantities of material are added at any given step and the level of control or material handling capability needs to be able to maintain the same or improved overall batch variability. Currently, inkjet printing is not used as a major tool in primary manufacturing but the recent focus on continuous manufacturing of pharmaceuticals suggests that it will be examined closely over the coming years. The ongoing exploration of reactive inkjet printing (Smith and Morrin 2012, Wang *et al.*, 2008) and its already prevalent use in combinatorial chemistry, which can be applied to the synthesis of small quantities of pharmaceuticals, show the promise for this area.

When examining inkjet printing of pharmaceuticals in the case of secondary manufacturing, there are four technologies immediately identifiable, namely (i) particulate printing for injectable, inhalable or liquid-based dosing, (ii) direct printing for rapid, dissolvable oral dose development, (iii) 3D printing technologies, focusing on powder-bed technologies to make tablets with controllable geometry and release profiles and (iv) thin film coatings for drug delivery applications.

3.3.1 Particle printing: Microparticle pharmaceutical-polymer composites form an important mode of drug delivery. Through inhalable, liquid and injectable dosing forms, the bioresorbable properties and the small particle size ensure that the drug reaches its targeted destination. For example, particles smaller than 5 μm can target the deep lung and ensure rapid delivery to the cardiovascular system (Wong *et al.* 2011). Spray drying and freeze drying are standard techniques for particle synthesis, with commercial examples including paclitaxel (PXL), an important drug for chemotherapy treatment. Standard spray drying relies on atomising the material from a nozzle. As the drops descend a tower, countercurrent hot air drives evaporation to leave dried particles that can then be separated, e.g. in a cyclone separator (Sinnott 2005).Spray freeze drying is also widely applied in the pharmaceutical industry. It is performed below the triple point of water to ensure sublimation and is often used to ensure drug stability. Inkjet printing has been explored in both contexts as a means of creating the liquid droplets. For example, PXL is normally dosed to a patient by injection in the form of a stable two phase colloidal suspension, due to solubility challenges. To avoid complications due to aggregation or blockages, there are tight controls over the particle sizes allowed. A PGLA/PXL microparticle composite was formed by jetting and showed a very narrow size distribution (Yeo *et al.* 2003). Rudalesco *et al.* (Radulescu *et al.* 2003) pioneered research in this area, examining a range of inkjet printing strategies from commercially available Microfab printheads delivering PGLA/PXL in 1,2-dichloroethane. A similar but more complex approach was taken by Yeo *et al.* to deliver a wide range of microstructures. Carefully chosen polymer solutions enabled controlled precipitation at solvent/water interfaces. Double emulsions, bilayer structures and shells were fabricated with this technique. More recently, in work to produce particles for pulmonary formulations, salbutamol sulphate was successfully freeze dried into porous particles using thermal inkjet printing into liquid nitrogen (Mueannoom et al. 2012, Sharma et al. 2013). This work is key because it simplified the processing and formulation by removing the excipient component completely. Excipients are added to a formulation for a range of reasons, such as providing a carrier material or enhancing stability and are discussed in detail in Section 4.1.3. Removal of an excipient while ensuring suitable stability and

robustness is suggested in this work to improve bioavailability. This is mainly due to simplification of particle surface properties and interactions.

DoD is not the only feasible approach for particle fabrication, and indeed CIJ provides a higher throughput of drug-loaded particles per nozzle. Bohmer *et al.* 2006 made further progress by examining in detail a method to collect significant volumes of particles in liquid, printing at 20 kHz with a submerged single nozzle. Two approaches were noted in this work. First, groups examine directly the fabrication of particles and determine the final active content (or release rate). Ehtezazi *et al.* 2014, for example, demonstrated the rapid production of small monodisperse droplets from piezoelectrically vibrated glass capillaries, which were dried to produce particles of salbutamol sulphate with a narrow size distribution. Second, researchers choose a model system (such as sodium alginate solutions) and examine the role of size distribution on release rate. For example, Desai *et al.* 2010 showed that an elevated rate of drug release occurs with smaller particle size, while Iwanaga *et al.* 2013 showed that the particle size and release profile were best tuned through altering the concentration of alginate, while maintaining the same liquid drop size. Also, tuning the surface area to volume ratio can control the overall release profile (Lee *et al.* 2012).

It is clear, however, that no study examines a full systems approach. The fundamental effect of inkjet on the pharmaceutical chemical structure and crystallisation is rarely linked to studies understanding the release profile when using different formulation/fabrication techniques. Finally, there has been no evident translation of fundamental single nozzle research studies to the use of manufacturing-scale printheads, which may expose the materials to different forces and flow conditions.

3.3.2 Oral dose development: The most intuitive entry point for pharmaceutical secondary manufacturing by inkjet printing is the delivery of active materials to a film of rapidly dissolving polymer for oral dosing, with examples of products listed in an early review paper by Sastra *et al.* 2000. Early work by Melendez *et al.* 2008, shows that small molecule drugs can be delivered in a format useful for industry to solve the challenge of water solubility. A similar approach is used for dosing to tablets, with GSK developing a technique for late stage customisation and functionalisation of an inactive tablet structure (GSK 2014). The key physical and chemical changes in the API molecule caused by inkjet delivery are discussed in Section 4, where we examine the underlying science of inkjet printing of pharmaceuticals, such as the potential for polymorph control. The formulation and printability has been explored with this oral dose technology (Raijada 2013) and it is clear that it is difficult to ensure printability while constrained to work with a palette of ink modifiers available from a list of carrier fluids with regulatory clearance. As with bio-printing, there is an additional constraint that ink modifiers are rarely volatile and so lead to locally high concentrations of additional components in the final product (Di Risio and Yan 2007). However, even with these constraints, manufacturing benefits are noted, such as a minimisation of waste because of the small stand-off distance and also a reduction in operator exposure. Very low errors are also recorded, for example salbutamol sulphate was printed (Buanz *et al.* 2011) with only a 5% error, which may be sufficiently accurate for many doses. However, the full system of errors has not been explored. Initial process changes have shown effects on polymorphism and crystallinity and so it is clear that pharmaceutical inkjet printing must co-develop precise in-line controls to ensure regulatory compliance.

3.3.3 3D printing (3DP): Additive manufacturing (commonly referred to as 3D printing) of pharmaceuticals with inkjet printing is focused entirely on powder-bed technologies (Wu *et al.* 1996, Ursan *et al.* 2013, Khaled *et al.* 2014). A combination of a powder and a binder 'ink' is used to construct solid macroscopic structures in a layer-by-layer process. This generic principle is manifested in a range of similar techniques, illustrated in detail elsewhere (Katstra *et al.* 2000) but the permanence of the final structure is often achieved through thermal sintering, an unsuitable approach for delicate functional molecules. An ink that solubilises the powder is therefore chosen to ensure a good structure, with the API used either as (1) the powder or (2) as a component in the binder ink. A typical powder-bed system builds up a structure in a layer-by-layer approach. Early work (Wu *et al.* 1996) showed that standard 3D printing of PCL and PEO, bioresorbable polymers, is feasible to a high resolution by inkjet printing of a binder. However, chloroform and DCM solvents were used in that work and are not appropriate for medical use due to their toxicity and the difficulty of ensuring removal of trace

quantities. At this early experimental stage, a dye was added by micropipette to represent addition of the model 'drug' for timed release. As noted in an early review (Sastry *et al.* 2000), the binder can be an active or passive medium, with the inclusion of a polymer or drug also influencing decisions as to the phase change behaviour: rapid to avoid particle rearrangement, or slow to enable better matrix binding by solubility. Katstra *et al.* 2000 examined in more detail the translation of the 3DP process to oral dose (tablet) fabrication. Using cellulose powder, they noted the importance of the powder packing function and the properties of the binding solution to control the layer thickness. These tablets had an API simulated by fluorescein to examine dosage control. Following on from this work, it is clear that both erosion- and diffusion-based tablet technologies enable far more complex release profiles and personalised doses. A clear example of this is shown by Rowe *et al.* 2000 who fabricated a single tablet to release in two bursts at two different parts of the digestion system with the lag controlled by geometry. While complex release profiles have also been designed and examined by others (Huang *et al.* 2007, Yu *et al.*, 2007, Yu *et al.*, 2009), it is recognised that there are still significant challenges in ink formulation for each printhead, powder deposition in the layer-by-layer process and also in the post-treatment methods (Yu *et al.* 2008).

3.3.4 Thin film coatings: More advanced applications that exploit the particular advantages of inkjet printing include tuneable coatings of polymers with active, slow release APIs, especially applied to surfaces where digital manufacturing is required. For example, coronary stents require coatings to ensure immunosuppression and to prevent coagulation and clogging. Highly tuned image analysis and digital printing enable accurate inkjet printing on to the stents, with the feasible approach of depositing multiple layers and changing the functionality or gradient of concentrations along the device. A clear example is shown in Figure 4c (Antohe and Wallace 2008). Transdermal pharmaceutical delivery by microneedles is an approach of growing importance (Boehm *et al.* 2011). While the fabrication of the microneedles still uses MEMS technologies, inkjet printing the API on to the needle surface, as shown in Figure 4d, enables accurate, digital control of API dose with a late-stage manufacturing approach.

3.4 Packaging and Distribution

The pharmaceutical industry has already embraced inkjet printing as part of its packaging and distribution activities. A range of companies specialise in pharmaceutical packaging printing and target traceability, security and anti-counterfeit protection (Domino Printing 2014). The industry has significant challenges in the face of growing levels of forgery. Complex, secure but inexpensive and flexible coding systems are critical to keep track of elements of the final product and packaging at every stage of the supply chain. Printing is carried out at all levels, directly to tablets, internal packaging, customer-facing packaging and also secondary packaging for transport and stock management purposes. As pharmaceutical materials are not being printed in this context, this is not the focus of the review but the application is important to highlight as it demonstrates that pharmaceutical companies will most likely already have familiarity and in-house expertise in inkjet printing, which may enable its rapid uptake in a manufacturing context.

3.5 Final drug delivery method

Inhalation of active materials requires aerosolisation into droplets of a very specific size range. The narrower the size distribution and the more targeted the peak size can be, the more effective the inhaler technology. Recent developments in inkjet (Memjet 2014) have provided very large numbers of nozzles on a single print head. This method of generating large numbers of small droplets is being explored as an alternative to traditional methods of generating sprays from nozzles and ultrasonically-driven nebulizers. The move to inkjet printing promises to improve monodispersity and provide bettter control of dosage volume. An additional method for drug delivery is being explored, where special jet-forming techniques are used to produce supersonic jets of the API to penetrate the dermis layer and create needle-free injection techniques (Stachowiak *et al.* 2009, Hemond *et al.* 2011). Very high jet velocities have been achieved but such techniques are still under development. However, the potential for a significant reduction in clinical waste, injury and cross-contamination mean this area will continue to be examined.

The technologies discussed in this section show that there are a range of opportunities for inkjet printing to influence the manufacturing system. However, there are a significant number of shared

underlying challenges and barriers to implementation that must be examined through research, and the review now looks at these main challenges.

Section 4. Scientific challenges of inkjet printing pharmaceuticals

Sections 3.1-3.5 discuss the opportunities identified in the literature where inkjet printing can be employed in the manufacturing of pharmaceutical products. Across the range of applications reviewed, it is clear that there is a set of four shared underlying barriers to manufacturing that require research, as illustrated in Figure 5 (i-iv):

i. Fluid formulation and supply,
ii. Ancillary fluid-delivery equipment (e.g. reservoir, tubing, recirculation system),
iii. Drop formation (Internal printhead / fluid interactions, nozzle flow, jet break-up)
iv. Impact/collection, phase change/drying/fixing/absorption, stability and characterisation.

These categories include issues noted in the literature on pharmaceutical printing and more generally in inkjet research. Overall, it is clear that very few articles have examined in detail more than one category, despite the need for all to be addressed to enable effective manufacturing. This section details the key challenges faced and shows that the detailed chemical nature of the API needs to be considered in each case. A product-volume versus variety matrix, as used in Section 2 to classify a business model, is therefore inappropriate and instead clustering and classification must focus on the detailed chemistry of functional molecules to help comparison across the literature.

INSERT FIGURE 5

Figure 5: Lifecycle of ink en route to printing from (i) formulation and supply to (ii) flow through ancillary equipment, (iii) transfer from printhead via nozzle to surface, (iv) drop impact, drying and stable product formation.

4.1 Formulation

The following basic ingredients are required for any application of inkjet in pharmaceutical manufacturing, and will be considered in turn:

- API,
- Carrier fluid,
- Excipients,
- Surface tension and viscosity modifiers.

4.1.1 API: The available literature on inkjet printing of pharmaceuticals shows no significant focus on any one API. This is in contrast to biological printing and standard inkjet printing research, which has focused on model systems such as glucose oxidase (Cook *et al.* 2010) and idealised Newtonian liquids such as water/glycerol mixtures (Castrejón-Pita *et al.* 2013) prior to experimenting with more complex, fully formulated inks. There is, however, an emphasis in general on small molecule drugs, for example paclitaxel, rifampicin, an antibiotic and naproxen, an anti-inflammatory. Biopharmaceuticals such as nucleic acids (i.e. for gene therapy) are also explored, mainly in the context of high throughput screening (Goldmann *et al.*2000, Sakuri *et al.* 2011). The required concentration of API varies with each application. For example, in high throughput screening there is a move to higher density arrays, reducing the required volume while keeping the molar concentration high to ensure adequate reaction kinetics (Schena *et al.* 1998). Conversely, the printing of particles or films for drug delivery, as discussed in Sections 3.3.1 and 3.3.4, targets an API concentration based on the required therapeutic release profile. In either case, however, it is usually a challenge to deliver the high concentrations needed without compromising stability and printability. This leads to manufacturing limitations, as observed by Boehm *et al.* when using 26 mg/mL concentration of Amphotericin B in their DMSO-based formulation. This relatively low concentration leads to a manufacturing process in which approximately 40,000 ejected drops coat each needle to deliver 10.4 μg of API . With an average dose of 20 mg/day when using standard intravenous delivery, this requires an estimated 50 × 50 array of needles each day assuming 80% delivery efficiency. When delivering felodipine (Scoutaris *et al.* 2012) 9,000 drops are needed per dose and for salbutamol

sulphate, a very large surface area (13-26 cm^2) is required (Buanz *et al.* 2011) to reach the required dosage at the highest feasible API loading. These three cases show that a higher ink concentration would be beneficial to minimise fabrication time and also to improve the ease of dosing. Nanoemulsions and nanosuspensions of API can be used to increase the loading in a carrier fluid with poor solvency (Tarcha *et al.* 2007, Dohnal and Stepanek 2011, Grau *et al.* 2000, Gu *et al.*, 2012, Mueller *et al.* 2001). This leads instead to challenges in stabilising against flocculation, aggregation, settling and nozzle blocking at later stages. The detailed chemistry of the API therefore determines the feasibility of stabilising and printing a formulation.

4.1.2 Carrier Fluid: As noted in Section 1, the physical properties of the ink based on density, viscosity and surface tension, must lie within a narrow window for satisfactory inkjet printing. These properties are driven mainly by the bulk component in the formulation, i.e. the choice of carrier fluid. The main carrier fluids used in pharmaceutical inkjet printing are water (Sharma *et al.*, Pardeike *et al.*, Rattanakit *et al.*, Mueannoom *et al.*, Sharma *et al.*, Marizza *et al.*), DMSO (Boehm *et al.* 2011, 2013, 2014, Gu *et al.* 2012), ethanol (Scoutaris *et al.* 2011, Genina *et al.* 2013, Raijada *et al.* 2013, Melendez *et al.* 2008) and acetone (Scoutaris *et al.* 2012, Wu *et al.* 2009). The role of the carrier fluid can be either to (i) dissolve the API, (ii) act as an immiscible carrier phase in a colloidal dispersion, and/or (iii) evaporate at a controlled rate after printing to deliver the pharmaceutical component in the appropriate solid form. The pharmaceutical inkjet research literature mostly reports water as a carrier fluid. Improving API solubility, in aqueous and organic media, is clearly a key objective (Mueller *et al.* 2001) as this will ensure good biological uptake and minimal regulatory concerns. It is estimated that up to 40% of drug candidates have been abandoned because of poor aqueous solubility (Kennedy 1997, Gaisford and Saunders 2013) and between 35 and 40% of compounds currently in development have aqueous solubilities below 5 mg mL^{-1} at pH 7 (Stegemann *et al.*, 2007, Gaisford and Saunders 2013). The choice of carrier fluid is also largely responsible for chemical stability. For example, some APIs undergo hydrolysis in water (Rose 1999), photolysis or oxidation (Gaisford and Saunders 2013b), especially at high dilutions, which will reduce the shelf-life of inks considerably. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has guidelines for stability testing of formulations, Q1A(R2) (2003), including long-term storage, intermediate-term storage, accelerated stability and stress testing. For each application noted in Figure 2, an appropriate test needs to be defined to ensure that inkjet formulations conform to these requirements.

4.1.3 Excipients: The next component is an excipient. While a low concentration of API is standard, the excipients (along with carrier fluids) form the bulk of the formulation. Pharmaceutical excipients or additives are compounds added to the finished drug products to serve a specific function (Sougata *et al.* 2013). They are defined by The International Pharmaceutical Excipients Council as "substances, other than the active drug substance of finished dosage form, which have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing of the drug delivery system during its manufacture; protect; support; enhance stability, bioavailability, or patient acceptability; assist in product identification; or enhance any other attributes of the overall safety and effectiveness of the drug delivery system during storage or use" (Apte and Ugwu 2003). Lists of pharmaceuticals with their associated excipients and inclusion levels are detailed by Apte and Ugwu 2003, Sougata *et al.* 2004 and Strickley 2004. Excipients may be present at low levels, e.g. 0.005% in the case of tocopherol alpha, used as an excipient for Torisel, a temsirolimus-containing treatment for renal cell carcinoma producted by Wyeth. In contrast, propylene glycol is included at 80% in Ativan (Wyeth-Ayerst). This is a trademarked product containing lorazepam for anxiety-related disorders (Sougata *et al.* 2004). While included to ensure good formulation stability, these excipients will modify viscosity, surface tension and final bioavailability and so must be considered at every stage of the printing process.

4.1.4 Surface tension and viscosity modifiers: The final class of component included in pharmaceutical printing inks is that of viscosity and surface tension modifiers. The viscosity of an ink needs to be of the order of 2-20 mPa s and is typically around 10 mPa s for most inkjet printers (Hutchings and Martin 2013). Pure water at room temperature has a viscosity of 1 mPa s and thus aqueous inks are usually of too low a viscosity and require additional modifying ingredients. Typical modifiers in standard inkjet printing and bioprinting techniques include polyhydric alcohols such as

glycols, glycerol and diols (Di Risio and Yan 2007). The surface tension needs to be relatively low and so aqueous inks often require surfactants to reach a level of the order of 30 mN m^{-1}(Hutchings and Martin 2013), pure water having a surface tension of 72 mN m^{-1}, but these must be carefully monitored due to potential effect on the API and especially denaturing of some molecules in biopharmaceuticals.

While the present section describes the key challenges to consider when formulating a stable pharmaceutical ink, it is also important to consider how the ink will subsequently be supplied to the manufacturing process, as discussed in the next section.

4.2 Ancillary equipment

A recognised element of ensuring successful development of 'system discovery' techniques using inkjet printing (Figure 2(1)) is that of highly precise fluid handling (Dunn and Feygin 2000, Lemmo *et al.* 1998, Rose 1999, Taylor *et al.* 2002, Chai *et al.* 2013). In inkjet printing the effect on a pharmaceutical agent must be considered during:

- Transfer and storage in a reservoir,
- Pump- or pressure-driven flow through a system of tubes to a small buffer reservoir,
- Flow within the printhead,
- Nozzle flow during printing.

However, while this is a recognised consideration in standard inkjet research, and in designing 'system discovery' techniques, it is clear from the literature that it is often neglected when researching pharmaceutical printing. Approximately 10-500 pL drop volumes are ejected per nozzle, depending on the nozzle diameter and printing conditions, but the internal volume of the reservoir, tubing and printhead will be many orders of magnitude larger. This means that the ink is usually flowing very slowly in these locations, possibly allowing adsorption of the active molecules to internal surfaces and also leaching of bioactive components from ancillary equipment into the pharmaceutical ink (Chai *et al.* 2013, McDonald 2008).The formulation must be carefully considered when selecting a printing system, as common carrier fluids such as water, DMSO, dichloromethane or ethanol each have their own compatibility challenges and so can swell or degrade components in the fluid path to varying degrees. Initial validation of the ancillary equipment is especially important in the context of pharmaceutical manufacturing because there is also the added complexity that each new component introduced may interact with the API activity or trigger immune responses in patients. For example, a serious case of patients generating an immune response to an essential natural human protein, recombinant human erythropoietin (EPO), has led to studies that focus on the potential leaching of chemicals from rubber stoppers of pre-filled syringes (Casadevall *et al.* 2005). There is also the expectation that an interaction may occur with the final drug delivery format itself, for example any change in plasticizing effects due to competing actions of formulation components will lead to unpredictability in a controlled dosing technique (Chamarthy *et al.* 2008). It is also critical to ensure a stable formulation when including a high loading of nanoparticulates, as is often the case in pharmaceutical printing. This is a common challenge in inkjet printing (Derby and Reis 2003) and may lead to blockages at the nozzle or within the printing system due to phenomena such as Ostwald ripening (Grau *et al.* 2000). A build up or separation of ingredients within the printing system can then lead to unpredictable concentrations of the delivered API. Again, it is clear from this section of the review that the detailed chemistry of the API and the associated ink formulation are the key factors that determine the suitability of ancillary components in a printing system.

4.3. Drop formation

Once the ink has reached the internal channels and reservoirs within the printhead that feed the nozzles, we need to consider all of the printing challenges noted in Section 1 and specifically jet break-up, drop formation and characterisation, printability and the effect of nozzle flow on the API. A detailed optimisation of print settings and ink formulation is needed to ensure repeatable droplet formation, as noted previously. This is especially complex with pharmaceutical printing as every small change in excipient or API concentration must be validated for final use. Guidance on long term stability of the printing process through control of the frequency of droplet ejection, the fluidic pressure within the dispensing device and the number of droplets dispensed in a burst is reported by Verkouteren *et al.* 2011, with details about feature resolution examined by Derby (2010) where the ink

rheology, droplet spacing and surface patterning are shown to be essential considerations to ensure stable, accurate features. Additional challenges that have been noted with industrial scale printing systems include droplet in-flight deviation leading to poor placement due to aerodynamic effects (Hsiao *et al.* 2012) and the difference in morphology, trajectory, velocity, and volume of the first drop dispensed from subsequent drops (Famili *et al.* 2011). Due to the stringent regulatory environment for pharmaceutical manufacturing, it is likely that precise volume/dosage data must be recorded. This may, in future, be carried out using in-line holographic techniques (Martin *et al.* 2011), simple optical imaging (with the compromise of a larger stand-off distance) or ultra-precise gravimetric analysis (Verkouteren *et al.* 2009). These positive confirmation approaches are very difficult to achieve even in an industrial environment and there are no simple solutions yet applicable to a future pharmacy-, hospital- or home-based printer. Alternatively, regular cleaning and gravimetric testing steps could be included. This regular testing approach is more straightforward but at the expense of increased waste of API and an acceptance of a level of risk.

Droplet breakup phenomena can be analysed best with research-level inkjet equipment, such as systems by MicroFab and MicroDrop as they allow precise control of the piezo-actuation and ease of examination. However, it is clear from the list of devices reported in the literature, shown in Table 4.1, that the range of printing systems includes both these highly controlled drop-manipulation tools and also modified desktop printing units. These have minimal control but are used to show more direct relevance to point-of-use printing. The Dimatix Materials Printer 2800 series from FujiFilm is also used to enable both some waveform control and drop-watching capability while remaining closer to the industrial printhead format.

Print System	Printed Pharmaceutical Example
Fujifilm Dimatix Materials Printer DMP-2800 series.	Rifampicin (Gu *et al.* 2012), piroxicam (Raijada *et al.* 2013)
Hewlett-Packard Deskjet TIJ (e.g. 340)	Terbutaline sulphate (Sharma *et al.* 2013), salbutamol sulphate (Mueannoom *et al.* 2012).
Sciflexarrayer S5	Felodipine, hydrochlorothiazide (Scoutaris *et al.* 2012)
Gesim A010-201	Felodipine (Scoutaris *et al.* 2012)
MicroFab	Paclitaxel (Radulescu *et al.* 2003), fenofibrate, rapamycin (Tarcha *et al.* 2007).
Nanoplotter	Ketoprofen (Marizza *et al.* 2014).
Canon TIJ (e.g. Pixma MP495)	Loperamide hydrochloride, caffeine (Genina *et al.* 2013)
Microdrop	Folic acid (Pardeike *et al.* 2011).
Positive displacement DoD	Naproxen (Hirshfield *et al.* 2014).

Table 4.1: List of inkjet dispensing systems reported in the literature for the study of pharmaceutical printing.

All these approaches are applicable only to very low throughput manufacturing. The literature demonstrates a gap in research into the suitability of industrial-scale inkjet printheads. These are accepted tools for robust and reliable large-scale graphical printing and so are important to providing confidence that pharmaceutical printing is a feasible path. Also, with 100-1000 nozzles firing at up to several tens of kHz, they are capable of significantly greater throughput while also reducing the potential hazard associated with nozzle blockage, due to the lower individual contribution of each nozzle to the total printed volume. Recent developments have shown that inkjet printhead developments are moving towards more flexible, multiple-material printers that can cope with aqueous-based bio-inks (Cambridge Network 2013, Hewlett Packard, 2014), recognising the need to extend products to include biological printing. This approach will need to be extended to pharmaceutical printing also. Once research includes the final inkjet devices, the effect of nozzle flow on pharmaceutically active molecules can also be examined quantitatively to ensure that their functionality is unimpaired. For example, Melendez *et al.* 2008 showed that there was no effect on the small molecule drug prednisolone when printed with the Hewlett-Packard 970 Cxi DeskJet thermal DoD personal printer. The manufacturing and underlying scientific research need to be closely aligned

here because formulations tested and qualified on one printhead still may need considerable modification to work optimally on a different device.

As APIs of the same family will employ very similar carrier fluids and excipients (Strickley 2004), the behaviour of the drop formation event will therefore be correlated to the API chemistry and structure. It is anticipated from this review that proof of concept systems for pharmaceutical printability should focus on developing a series of model systems to enable easy transfer to other similar products. This classification would most likely include functional groups and molecular weight to ensure similar surface tension, viscosity and elasticity behaviour.

4.4. Deposition, fixing and functionality

The final category where underlying scientific challenges arise is in the deposition of the drug and characterising its functionality. For most applications, this stage involves impact of the drop on a surface, droplet drying, fixing or imbibition into a porous medium leading to a bioactive material ready for controlled release when exposed to the relevant environment. An additional application noted earlier involves a phase change prior to droplet impact on a surface, leading to particle formation with active material trapped within a polymeric matrix, again achieving slow release in the right biological environment.

This category of challenge has received the most attention to date, with the literature focusing on capture of active materials and subsequent release profiles on oral dose strips such as potato starch (Buanz *et al.* 2011), porous papers (Sandler *et al.* 2007), coatings on microneedles (Boehm *et al.* 2011), polymeric particles (Radulescu *et al.* 2003), coated tablets (GSK 2014) and coronary stents (Antohe and Wallace 2008). Activity upon printing is carefully monitored in these reports and also for all assay-based inkjet developments, such as combinatorial chemistry and high throughput screening. A vast range of characterisation techniques is employed in the pharmaceutical inkjet literature, with those most commonly described shown in Table 4.2. It will be critical to understand the relevant techniques for use as an industrial in-line characterisation tool.

Characterisation Technique	Objective and Reference
Differential scanning calorimetry (DSC)	Verify crystallinity (Genina *et al.* 2013)
Thermogravimetric analysis (TGA)	Water content analysis (Sharma *et al.* 2013)
Dynamic vapour sorption (DVS)	Crystallisation behaviour under humidity (Sharma *et al.* 2013)
High-performance liquid chromatography (HPLC)	Drug release rate from stent (Tarcha *et al.* 2007)
Content analysis	Quantity of pharmaceutical in printed area. (Genina *et al.* 2013)
Second harmonic generation (SHG)	Analyze the surface of crystal forms (Hirshfield *et al.* 2014)
Energy-dispersive X-ray spectroscopy (EDX)	Distribution of API in sample (Raijada *et al.* 2013)
Fourier transform infrared spectroscopy (FTIR)	Confirming co-crystal formation (Buanz *et al.* 2013)
Ultraviolet–visible spectroscopy (UV-Vis)	Verify dose in real time (Voura *et al.* 2011)
Raman spectroscopy	Polymorph identification (Melendez *et al.* 2008)
X-Ray Diffraction (XRD)	Polymorph identification (Melendez *et al.* 2008)
Near-infrared spectroscopy (NIR)	Verify dose in real time (Voura *et al.* 2011)
Mass spectroscopy	Analysis of degradation products (Sandler et al 2011)
Time-of-Flight secondary ion mass spectrometry (TOF SIMS)	Analysis of chemical heterogenities (Scoutaris *et al.* 2012)

Table 4.2: Characterisation techniques and specific examples of use in inkjet printing of pharmaceuticals.

Some of the main challenges noted to date in this challenge category are listed below.

4.4.1 Nozzle flow influences

As noted in section 1, high shear and extensional flows are experienced in the liquid passing through an inkjet nozzle. It is highly likely that biopharmaceuticals will be significantly affected, based on similar bioprinting experiments (Cook *et al.* 2010). While control of formulation (specifically excipient or polymeric components) is shown to influence pharmaceutical crystallisation (Trasi *et al.* 2012), Melendez *et al.* (2008) hypothesise that the control of the inkjet printing parameters may lead to selectivity of polymorphs. This is reinforced by the work of Zhang *et al.* (2004) who examined the interconversion among polymorphs due to processing techniques.

4.4.2 Mixing and reaction

Reactive inkjet printing is a separate field of study with particular relevance to drug discovery. Droplet coalescence, propagation of the boundary line and reaction kinetics are critical parameters to ensuring useful HTS (high-throughput screening) results. As ultra-miniature HTS assays are developed, the complexities of laminar flow 'mixing' and localised chemical kinetics need also to be tackled in tandem (Castrejón-Pita *et al.* 2013, Smith and Morrin 2012)

4.4.3 Deposition influences

The crystal form of a pharmaceutical is extremely important, with examples seen on the market such as an antiretroviral drug ritonavir, which was temporarily withdrawn from the market due to the emergence of a polymorph with a lower bioavailability. In this case, the targeted polymorph was stabilised through refrigeration. It was found by Genina *et al.* (2013b), and also Hirshfield *et al.* (2014), that the recrystallisation behaviour of the API differed with the choice of printed surface and surface wettability, while Hsu *et al.* (2013) reported the influence of surface microstructure. Crystallisation is also shown to be driven by the rate of evaporation after printing and the volatility of the carrier fluid (Hirshfield *et al.* 2014). It is critical to consider the influence of the excipients, viscosity modifiers and surfactants upon evaporation of the carrier fluid. These, predominantly non-volatile, components will remain but in a higher relative concentration. This is noted elsewhere in biosensor fabrication (Akram *et al.* 2014) and also in the preparation of microneedle coatings using a salt buffer carrier fluid (Boehm *et al.* 2011). Because the detailed processing is important as well as the API ink formulation, these aspects need to be examined in future studies with the specific, targeted industrial-scale printheads. The influence of printing on functionality is again clearly linked to the underlying chemistry of the API molecule, as this determines both the ease of printing, likelihood of polymorphism and also the sensitivity to the imparted forces.

5. Conclusions

This review has examined the business incentives, current technologies and future challenges involved in inkjet printing of pharmaceuticals. It is clear that this field has been under development for a significant time but, as with the development of commercial inkjet printing, there have been great strides in understanding the underlying technology and ink formulations over recent years. A range of technologies has been reviewed here that enables inkjet printing to take on several different roles within the pharmaceutical manufacturing supply chain, from driving rapid drug discovery to fabrication of materials for drug delivery, manufacturing of personalised medicines and improving product security through packaging innovations. The drivers for the pharmaceutical industry have been briefly described, focusing on the recent move to develop new business models as an alternative to the blockbuster approach. As this is a highly complex field with a diverse map of pharmaceutical products to consider, an approach to classification is highlighted in this review that will enable a logical comparison of products in terms of their suitability to inkjet printing from a business perspective.

Specific technologies and inkjet challenges have been presented; while there is currently a diverse literature on the topic, there are two key factors that should be considered as the community moves

forward. Firstly, as there are limited combinations of excipients, carrier fluids and APIs, a classification approach should be explored based on the underlying API chemistry to enable a more coherent comparison of research findings and effective translation to manufacturing. Secondly, and even more critical to the future of the pharmaceutical inkjet printing vision, research must begin to consider at an earlier stage the precise industrial scale that is targeted. This will lead to selection of appropriate commercially available printheads (in terms of both volume throughput and material compatibility). The analysis of formulations in conjunction with an appropriate printhead is essential because of the different formulation and jetting parameter requirements associated with each device. This review has combined the underlying research challenges with the manufacturing and business considerations. The trends identified here will hopefully enable the community to drive a rapid, focused and coherent translation of pharmaceutical inkjet printing to the manufacturing scale.

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References:

Akram, M.S., Daly, R., Vasconcellos, F., Yetisen, A., Hutchings, I., Hall, E., 2014, Applications of Paper-based diagnostics in "Lab-on-a-Chip and Micro Total Analysis Systems - A Practical Guide, Springer Publishing.

Allain, L.R., Stratis-Cullum, D.N., Vo-Dinh, T., 2004, Investigation of microfabrication of biological sample arrays using piezoelectric and bubble-jet printing technologies, Analytica Chimica Acta, 518, 77–85.

Antohe, B. V., Wallace, D. B., 2008, Ink-jet As A Manufacturing Method For Drug Delivery Applications, Proceedings of the Asme International Manufacturing Science and Engineering Conference 2008, 2, MSEC/ICMP2008-72248.

Apte, S.P., Ugwu, S.O., 2003, A Review and Classification of Emerging Excipients in Parenteral Medications, Pharmaceutical Technology, March, 46-60.

Bellavance, L., Burbaum, J., Dunn, D., 2000, Miniaturisation of HTS assays, Innovations in Pharmaceutical Technology, 5 , 12-17.

Blanchard, A. P.; Kaiser, R. J., Hood, L. E., 1996. High-density oligonucleotide arrays, in Biosensors & Bioelectronics , Vol. 11, European Science Foundation, European Scientific Research Council.

Boehm, R. D., Miller, P.R., Philip R., Daniels, J., Stafslien, S., Narayan, R.J., 2014, Inkjet printing for pharmaceutical applications, Materials Today, 2014, 17, 247-252.

Boehm, R. D., Miller, P.R., Philip R., Schell, W.A., Perfect, J.R., Narayan, R.J., 2013, Inkjet Printing of Amphotericin B onto Biodegradable Microneedles Using Piezoelectric Inkjet Printing, Journal of Metals, 65, 525-533.

Boehm, R. D., Miller, P.R.,Hayes, S.L., Monteiro-Riviere, N.A., Narayan, R.J., 2011, Modification of microneedles using inkjet printing, AIP Advances, 1, 022139.

Bohmer, M. R., Schroeders, R., Steenbakkers, J.A.M., de Winter, S.H.P.M., Duineveld, P.A., Lub, J., Nijssen, W.P.M., Pikkemaat, J.A., Stapert, H.R., 2006, Preparation of monodisperse polymer particles and capsules by ink-jet printing, Colloids and Surfaces A, 289, 96-104.

Brennan, T.M., 1995. US Patent 5,474,796

Buanz, A.B.M., Saunders, M.H., Basit, A.W., Gaisford, S., 2011, Preparation of Personalized-dose Salbutamol Sulphate Oral Films with Thermal Ink-Jet Printing, Pharmaceutical Research, 28, 2386-2392.

Buanz, A.B.M., Telford, R., Scowen, I.J., Gaisford, S., 2013, Rapid preparation of pharmaceutical co-crystals with thermal ink-jet printing, CrystEngComm, 15, 1031–1035.

Burbaum, J.J., Sigal, N.H., 1997, New technologies for high-throughput screening, Current Opinion in Chemical Biology, 1, 72-78.

Cambridge Network, https://www.cambridgenetwork.co.uk/news/ttp-unveils-new-multi-material-breakthrough-in-3d-printing/

Calabrese, G.S., Pissavini, S., 2011. From batch to continuous flow processing in chemical manufacturing, AIChE Journal, 57(4), 828-834.

Castrejón-Pita, J. R., Baxter, W., Morgan, J., Temple, S., Martin, G. D., & Hutchings, I. M., 2013. Future, Opportunities and Challenges of Inkjet Technologies. Atomization and Sprays, 23, 571–595.

Castrejón-Pita, J.R., Kubiak, K.J., Castrejón-Pita, A.A., Wilson, M.C.T., Hutchings, I.M., 2013, Mixing and internal dynamics of droplets impacting and coalescing on a solid surface, Physical Review E, 88, 02302.

Chai, S.C., Goktug, A.N., Cui, J., Low, J., Chen, T., 2013, Practical Considerations of Liquid Handling Devices, Chp. 6 in 'Drug Discovery', ed. El-Shemy, H.A., Intech.

Chamarthy, S.P., Pinal, R., 2008, Plasticizer concentration and the performance of a diffusion-controlled polymeric drug delivery system, Colloids and Surfaces A, 331, 25-30.

Clasen, C., Phillips, P., Palangetic, L., & Vermant, J., 2012. Dispensing of rheologically complex fluids: The map of misery. AIChE Journal, 58, 3242–3255.

Cook, C. C., Wang, T., Derby, B., 2010, Inkjet delivery of glucose oxidase, Chemical Communications, 46, 5452-5454.

Derby, B., 2010, Inkjet Printing of Functional and Structural Materials: Fluid Property Requirements, Feature Stability, and Resolution, Annual Review of Materials Research, 40, 395–414.

Derby, B., Reis, N., 2003, Inkjet Printing of Highly Loaded Particulate Suspensions, MRS Bulletin, November, 815-818.

Desai, S., Perkins, J., Harrison, B.S., Sankar, J., 2010, Understanding release kinetics of biopolymer drug delivery microcapsules for biomedical applications, Materials Science and Engineering B, 168, 127-131.

Di Risio, S., Yan, N., 2007, Piezoelectric ink-jet printing of horseradish peroxidase: Effect of ink viscosity modifiers on activity, Macromolecular Rapid Communications, 28, 1934-1940.

Domino Printing accessed 2014 (a) http://www.domino-printing.com/Global/en/Your-Market/Packaging-Coding/PharmaNew/Coding-Marking-Pharmaceutical-Sector.aspx, (b) Resource Print, http://www.resourceprint.co.uk/pharmaceutical/, (c) Label One, http://www.labelone.co.uk/sectors/pharma-veterinary.html, (d) Linx Global, http://www.linxglobal.com/en-gb/coding-solutions/industry-solutions/pharmaceuticals, (e) EyeC, http://www.eyec-ukandireland.co.uk/print-inspection-solutions-for-printers-of-pharma-packaging/.

Dunn, D. A., Feygin, I., 2000. Challenges and solutions to ultra-high-throughput screening assay miniaturization: submicroliter fluid handling, Drug Discovery Today, 5, S84-S91.

Ehtezazi, T., Dempster, N.M., Martin, G.D., Hoath, S.D., Hutchings, I.M., 2014, Development of High-Throughput Glass Inkjet Devices for Pharmaceutical Applications, Journal of Pharmaceutical Sciences, 103, 3733-3742.

Endo, I., Sato, Y., Saito, S., Nakagiri, T., & Ohno, S., 1988. Bubble jet recording method and apparatus in which a heating element generates bubbles in a liquid flow path to project droplets, U.S. Patent 4723129.

Famili, A., Palkar, S.A., Baldy Jr., W.A., 2011, First drop dissimilarity in drop-on-demand inkjet devices, Physics of Fluids, 23, 012109.

Ferris, C. J., Gilmore, K. J., Beirne, S., McCallum, D., Wallace, G. G., & in het Panhuis, M., 2013. Bio-ink for on-demand printing of living cells. Biomaterials Science, 1, 224.

Gaisford, S., Saunders, M., 2013, Essentials of Pharmaceutical Preformulation, Chp. 4, John Wiley & Sons, Ltd.

Gaisford, S., Saunders, M., 2013b, Essentials of Pharmaceutical Preformulation, Chp. 1, John Wiley & Sons, Ltd.

Genina, N., Fors, D., Palo, M., Peltonen, J., Sandler, N., 2013, Behavior of printable formulations of loperamide and caffeine on different substrates-Effect of print density in inkjet printing, International Journal of Pharmaceutics, 453, 488-497.

Goldmann, T., Gonzalez, J.S., 2000, DNA-printing: utilization of a standard inkjet printer for the transfer of nucleic acids to solid supports, Journal of Biochemical and Biophysical Methods, 42, 105-110.

GSK, http://www.gsk.com/media/279688/liquid-dispensing-technology-leaflet.pdf, accessed 2014.

Gu, Y., Chen, X., Lee, J.H., Monteiro, D.A., Wang, H., Lee, W.Y., 2012, Inkjet printed antibiotic- and calcium-eluting bioresorbable nanocomposite micropatterns for orthopedic implants, Acta Biomaterialia, 8, 424-431.

Harrington, T.S., Alinaghian, L., Srai, J.S., 2013. Continuous Manufacturing and Product-Process Archetypes: Implications for Supply Network Design in Pharma. Proceedings of the 24th Annual Production and Operations Management Society (POMS) Conference, Denver CO, May 3-6th. http://www.pomsmeetings.org/ConfProceedings/043/FullPapers/FullPaper_files/043-0248.pdf (accessed 07.10.2014)

Harrington, T.S., Alinaghian, L., Srai, J.S., 2014. Making the business case for continuous manufacturing in the Pharmaceutical Industry. Proceedings of the 25th Annual Production and Operations Management Society (POMS) Conference, Atlanta GA, May 9-12th. http://www.pomsmeetings.org/ConfProceedings/051/FullPapers/Final%20Full%20length%20Papers/051-0603.pdf (accessed 07.10.2014)

Harrington, T.S., Najim, I., 2014. An exploratory study assessing value chain reconfiguration opportunities in oncology. Proceedings of the 18th Cambridge International Manufacturing Symposium, Cambridge, 11-12th September, 707-714.. ISBN 978-1-902546-45-2. http://www.ifm.eng.cam.ac.uk/uploads/Resources/Reports/CIM_Proceedings_for_web3.pdf (accessed 02.02.2015)

Harrington, T.S., Srai, J.S. 2014. Manufacturing Operations and Supply Chain Management Challenges in Continuous Manufacturing. Continuous Manufacturing and Crystallisation (CMAC) annual report, 12-13. http://www.cmac.ac.uk/files/media/cmac_brochure_2014.pdf (accessed 07.10.14).

Harrington, T.S., Najim, I. 2015. Emerging product-process archetypes in oncology: Implications for supply network design, Proceedings of the 26th Annual Production and Operations Management Society (POMS) Conference, Washington DC, May 8-11th (in press)

Hemond, B. D. Taberner, A., Hogan, C., Crane, B., and Hunter, I. W., 2011, Development and performance of a controllable autoloading needle-free jet injector, Journal of Medical Devices, 5, 015001-015001.

Hertzberg, R. P., Pope, A.J., 2000. High-throughput screening: new technology for the 21st century, Current Opinion in Chemical Biology, 4, 445-451.

Hewlett Packard, http://www8.hp.com/uk/en/commercial-printers/thermal-inkjet/d300.html, accessed November 2014

Hoath, S. D., Castrejón-Pita, J. R., Hsiao, W., Jung, S., Martin, G. D., Hutchings, I. M., Yow, H. N., 2013. Jetting of Complex Fluids. Journal of Imaging Science and Technology, 57, 040403–1–10.

Hoath, S. D., Harlen, O. G., Hutchings, I. M., 2012. Jetting behaviour of polymer solutions in drop-on-demand inkjet printing. Journal of Rheology, 56, 1109-1127.

Hoath, S. D., Hutchings, I. M., 2013. A simple criterion for filament break-up in drop-on-demand inkjet printing. Physics of Fluids, 25, 021701.

Hoath, S. D., Jung, S., Hsiao, W. -K.,Hutchings, I. M., 2012. How PEDOT:PSS solutions produce satellite-free inkjets. Organic Electronics, 13, 3259–3262.

Hoath, S. D., Vadillo, D. C., Harlen, O. G., MacIlroy, C., Morrison, N. F., Hsiao, W., Hutchings, I. M., 2014. Inkjet printing of weakly elastic polymer solutions. Journal of Non-Newtonian Fluid Mechanics, 205, 1–10.

Hsiao, W.-K., Hoath, S.D., Martin, G.D., Hutchings, I.M., 2012, Aerodynamic Effects in Ink-Jet Printing on a Moving Web,Proceedings IS&T's NIP28: International Conference on Digital Printing Technologies and Digital Fabrication, 412-415.

Hsu, H.-Y., Toth, S., Simpson, G. J., Taylor, L. S., Harris, M. T., 2013, Effect of substrates on naproxen-polyvinylpyrrolidone solid dispersions formed via the drop printing technique, Journal of Pharmaceutical Sciences, 102, 638-648.

http://www.domino-printing.com

http://www.domino-printing.com/Global/en/Your-Market/Your-Market.aspx

http://www.epson.com/_alfresco/LandingPages/landing/PrecisionCore/PrecisionCore_White_Paper.pdf

http://www.incadigital.com

http://www.videojet.com

http://www.xennia.com/applications/digital-ceramic-printing

Huang, W., Zheng, Q., Sun, W., Xu, H., Yang, X.L., 2007, Levofloxacin implants with predefined microstructure fabricated by three-dimensional printing technique, International Journal of Pharmaceutics, 339, 33-38.

Hughes, T. R., Mao, M., Jones, A.R., Burchard, J., Marton, M.J., Shannon, K.W., Lefkowitz, S.M., Ziman, M., Schelter, J.M., Meyer, M.R., Kobayashi, S., Davis, C., Dai, H., He, Y.D., Stephaniants, S.B., Cavet, G., Walker, W.L., West, A., Coffey, E., Shoemaker, D.D., Stoughton, R., Blanchard, A.P., Friend, S.H., Linsley, P.S., 2001, Expression profiling using microarrays fabricated by an ink-jet oligonucleotide synthesizer, Nature Biotechnology, 19, 342-347.

Hutchings, I. M., 2010, Proc. Qualicer '10, XIth World Congress on Ceramic Tile Quality, Castellón, Spain, Invited paper, 'Ink-jet printing for the decoration of ceramic tiles: technology and opportunities'.

Hutchings, I.M., Martin, G. D., 2013. Fundamentals of inkjet technology. 21-44 in Hutchings, I.M., Martin, G. D. Inkjet Technology for Digital Fabrication, Wiley-Blackwell.

I.T. Strategies, 2013. Ink Jet Ceramic Tile Printing Analysis-2013 in Research on Emerging Print Markets

Iwanaga, S., Saito, N., Sanae, H., Nakamura, M., 2013, Facile fabrication of uniform size-controlled microparticles and potentiality for tandem drug delivery system of micro/nanoparticles, Colloids and Surfaces B-biointerfaces, 109, 301-306.

Jang, D., Kim, D., & Moon, J., 2009. Influence of fluid physical properties on ink-jet printability. Langmuir, 25, 2629–2635.

Katstra, W. E., Palazzolo, R. D., Rowe, C. W., Giritlioglu, B., Teung, P., Cima, M. J., 2000, Oral dosage forms fabricated by Three Dimensional Printing, Journal of Controlled Release, 66, 1-9.

Kennedy, T., 1997, Managing the drug discovery/development interface, Drug Discovery Today, 2, 436–444.

Khaled, S.A., Burley, J.C., Alexander, M.R., Roberts, C.J., 2014, Desktop 3D printing of controlled release pharmaceutical bilayer tablets, International Journal of Pharmaceutics, 461, 105-111.

Kim, Y., Lee, J., 1993. Manufacturing strategy and production systems: An integrated framework. Journal of Operations Management, 11, 3-15.

Kommanaboyina, B., Rhodes, C.T., 1999. Trends in stability testing, with emphasison stability during distribution and storage. Drug Development and Industrial Pharmacy, 25, 857–868.

Kudo, Y., Nakahara, T., Nakagama, T., Seino, N., Shinoda, M., Uchiyama, K., 2007, Development of a Surface-Reaction System in a Nanoliter Droplet Made by an Ink-jet Microchip, The Japan Society for Analytical Chemistry, 23, 91-95.

Kyser, E. L., & Sears, S. B., 1976. Method and apparatus for recording with writing fluids and drop projection means therefore, U.S. Patent 3946398.

Lee, B.K., Yun, Y.H., Choi, J.S., Choi, Y.C., Kim, J.D., Cho, Y.W., 2012, Fabrication of drug-loaded polymer microparticles with arbitrary geometries using a piezoelectric inkjet printing system, International Journal of Pharmaceutics, 427, 305-310.

Lemmo, A. V.; Rose, D. J., Tisone, T. C., 1998. Inkjet dispensing technology: applications in drug discovery, Current Opinion In Biotechnology, 9, 615-617.

Macromolecular Rapid Communications, 28, 1934–1940.

Manufacturing Operations and Supply Chain Management Challenges in Continuous Manufacturing, CMAC annual report, pp. 12-13. http://www.cmac.ac.uk/files/media/cmac_brochure_2014.pdf (accessed 07.10.14).

Marizza, P., Keller, S.S., Mullertz, A., Boisen, A., 2014, Polymer-filled microcontainers for oral delivery loaded using supercritical impregnation, Journal of Controlled Release, 173, 1-9.

Martin, G. D., Castrejon-Pita, J. R., and Hutchings, I. M., 2011, 'Holographic Measurement of Drop-on-Demand Drops in Flight', Proceedings IS&T's NIP27: International Conference on Digital Printing Technologies and Digital Fabrication 620-623.

McDonald, G.R., Hudson, A.L., Dunn, S.M.J., You,H., Baker,G.B., Whittal, R.M., Martin, J.W., Jha, A., Edmondson, D.E., Holt, A., 2008, Bioactive Contaminants Leach from Disposable Laboratory Plasticware, 322, 917.

McKinley, G.R. and Renardy, M., 2011. Wolfgang von Ohnesorge. Physics of Fluids, 23, 127101.

McWilliam, I., Kwan, M.C., Hall, D., 2011, Inkjet Printing for the Production of Protein Microarrays in Ulrike Korf (ed.), Protein Microarrays: Methods and Protocols, Methods in Molecular Biology, 785.

Melendez, P. A., Kane, K. M., Ashvar, C. S., Albrecht, M., Smith, P. A., 2008, Thermal inkjet application in the preparation of oral dosage forms: Dispensing of prednisolone solutions and polymorphic characterization by solid-state spectroscopic techniques, Journal of Pharmaceutical Sciences, 97, 2619-2636.

Memjet, accessed 2014, http://www.memjet.com/technology.

Mueannoom, W., Srisongphan, A., Taylor, K.M.G., Hauschild, S., Gaisford, S., 2012, Thermal ink-jet spray freeze-drying for preparation of excipient-free salbutamol sulphate for inhalation, European Journal of Pharmaceutics and Biopharmaceutics, 80, 149-155.

Mueller, R.H., Jacobs, C., Kayser, O., 2001, Nanosuspensions as particulate drug formulations in therapy: Rationale for development and what we can expect for the future, Advanced Drug Delivery Reviews, 47, 3-19.

Okamoto, T., Suzuki, T., Yamamoto, N., 2000, Microarray fabrication with covalent attachment of DNA using Bubble Jet technology, Nature Biotechnology, 18, 438-441.

Oldenburg, K.R., Zhang, J-H., Chen, T., Maffia III, A., Blom, K.F., Combs, A.P., Chung, T. D. Y., Tisone, T. C., 1998, Dispensing systems for miniaturized diagnostics, http://www.mddionline.com/ivdarticle/dispensing-systems-miniaturized.

Pardeike, J., Strohmeier, D.M., Schroedl, N., Voura, C., Gruber, M., Khinast, J.C., Zimmer, A., 2011, Nanosuspensions as advanced printing ink for accurate dosing of poorly soluble drugs in personalized medicines, International Journal of Pharmaceutics, 420, 93-100.

Perelaer, J., de Gans, B.-J., & Schubert, U. S., 2006. Ink-jet Printing and Microwave Sintering of Conductive Silver Tracks. Advanced Materials, 18, 2101–2104.

Potyrailo, R., Rajan, K., Stoewe, K., Takeuchi, I., Chisholm, B., Lam., H., 2011, Combinatorial and High-Throughput Screening of Materials Libraries: Review of State of the Art, ACS Combinatorial Science, 13, 579-633.

Radulescu, D., Schwade, N., Wawro D., Uniform Paclitaxel-Loaded Biodegradable Microspheres Manufactured by Ink-Jet Technology, Proceedings of the Recent Advances in Drug Delivery Systems, 1-5, 2003.

Raijada, D., Genina, N., Fors, D., Wisaeus, E., Peltonen, J., Rantanen, J., Sandler, N., 2013, A Step Toward Development of Printable Dosage Forms for Poorly Soluble Drugs, Journal of Pharmaceutical Sciences, 102, 3694-3704.

Rattanakit, P., Moulton, S.E., Santiago, K.S., Liawruangrath, S., Wallace, G.G., 2012, Extrusion printed polymer structures: A facile and versatile approach to tailored drug delivery platforms, International Journal of Pharmaceutics, 422, 254-263.

Reis, N., & Derby, B., 2000. Ink jet deposition of ceramic suspensions: modelling and experiments of droplet formation. MRS Symposium Proceedings, 624, 65–70.

Rodrıguez-Devora, J.I., Zhang, B., Reyna, D., Shi, Z., Xu, T., 2012, High Throughput miniature drug-screening platform using bioprinting technology, Biofabrication, 4, 035001.

Rose, D., 1999., Microdispensing technologies in drug discovery Drug Discovery Today, 4, 411-419.

Rowe, C. W., Katstra, W. E., Palazzolo, R. D., Giritlioglu, B., Teung, P., Cima, M. J., 2000, Multimechanism oral dosage forms fabricated by three dimensional printing, Journal of Controlled Release, 66, 11-17.

Saaem, I., Ma, K.S., Marchi, A.N., LaBean, T.H., Tian, J., 2010, In situ Synthesis of DNA Microarray on Functionalized Cyclic Olefin Copolymer Substrate, Applied Materials and Interfaces, 2, 491-497.

Sandler, N., Maattanen, A., Ihalainen, P., Kronberg, L., Meierjohann, A., Viitala, T., Peltonen, J., 2011, Inkjet Printing of Drug Substances and Use of Porous Substrates-Towards Individualized Dosing, Journal of Pharmaceutical Sciences, 100, 3386-3395.

Sastry, S.V., Nyshadham, J.R., Fix, J.A., 2000, Recent technological advances in oraldrug delivery – a review, Pharmaceutical Science & Technology Today, 3, 138-145.

Schena, M., Heller, R. A., Theriault, T. P., Konrad, K., Lachenmeier, E., Davis, R. W., 1998. Microarrays: biotechnology's discovery platform for functional genomics, Trends in Biotechnology, 16, 301-306.

Scoutaris, N., Alexander, M.R., Gellert, P.R., Roberts, C.J., 2011, Inkjet printing as a novel medicine formulation technique, Journal of Controlled Release, 156, 179-185.

Sharma, G., Mueannoom, W., Buanz, A.B.M., Taylor, K.M.G., Gaisford, S., 2013, In vitro characterisation of terbutaline sulphate particles prepared by thermal ink-jet spray freeze drying, International Journal of Pharmaceutics, 447, 165-170.

Silverman, L., Campbell, R., Broach, J.R., 1998. New assay technologies for high-throughput screening, Current Opinion in Chemical Biology, 2, 397-403.

Sinnott, R.K., 2005, Coulson and Richardson's Chemical Engineering Volume 6 - Chemical Engineering Design (4th Edition), Elsevier

Sittampalam, G.S., Kahl, S.D., Janzen, W.P., 1997. High-throughput screening: advances in assay technologies, Current Opinion in Chemical Biology, 1, 384-391.

Smith, P.J., Morrin, A., 2012, Reactive Inkjet Printing, Journal of Materials Chemistry, 22, 10965-10970.

Sougata P., Deepak S., Vikas C., 2013, Excipient Selection In Parenteral Formulation Development, Pharma Times, 45, 65-77.

Srai J.S, Gregory, M (2008) A supply network configuration perspective on international supply chain development. International Journal of Operations & Production Management 28(5), 386-411.

Srai, J.S., Christodoulou, P., Harrington, T.S., (2014) ‘Configuring global value networks within industrial ecosystems’, in ‘Capturing value from global networks: gaining global competitive advantage through configuring production, supply and service networks’, University of Cambridge, editors. J.S. Srai and P. Christodoulou, pp. 62-89. ISBN 978-1-902546-45-2

Srai, J.S., Harrington, T.S., Alinaghian, L., 2014. An approach to exploring integration benefits of continuous flow technologies within Pharmaceutical supply chains. Monographic supplement series: CROs/CMOs – Chimica Oggi - Chemistry Today, Vol. 32, No.4, July/August, 27-32

Srai, J.S., Badman, C., Krumme, M., Futran, M., Johnston, C., 2015. Future supply chains enabled by continuous processing – opportunities and challenges. May 20–21, 2014 Continuous Manufacturing Symposium. Journal of Pharmaceutical Sciences, Article first published online: 28th January 2015. DOI: 10.1002/jps.24343.

Stachowiak, J. C., Li, T. H., Arora, A., Mitragotri, S., and Fletcher, D. A., 2009, Dynamic Control of Needle-Free Jet Injection, Journal of Controlled Release, 135, 104–112.

Stegemann S., Leveiller F., Franchi D., de Jong H, L.H., 2007, When poor solubility becomes an issue: from early stage to proof of concept, European Journal of Pharmaceutical Sciences, 31, 249–261.

Strickley, R.G., 2004, Solubilizing Excipients in Oral and Injectable Formulations, Pharmaceutical Research, 21, 201-230.

Sweet, R. G. (1971). Signal apparatus with fluid drop recorder, U.S. Patent 3596275.

Taylor, P.B., Ashman, S., Baddeley, S.M., Bartram, S.L., Battle, C.D., Bond, B.C., Clements, Y.M., Gaul, N.J., McAllister, W.E., Mostacero, J.A., Ramon, F., Wilson, J.M., Hertzberg, R.P., Pope, A.J., Macarron, R., 2002, Journal of Biomolecular Screening, 7, 554-569.

Tiebes, D., 1999, Combinatorial Chemistry in Jung, J. (Ed.) 'Combinatorial Chemistry: Synthesis, Analysis, Screening', Wiley-VCH Verlag GmbH.

Trasi, N.S., Taylor, L.S., 2012, Effect of Additives on Crystal Growth and Nucleation of Amorphous Flutamide, Crystal Growth & Design, 12, 3221-3230.

Ursan, I., Chiu, L., Pierce, A., 2013, Three-dimensional drug printing: A structured review, Journal of the American Pharmacists Association, 53, 136-144.

Van Deen, M. S., Bertrand, T., Vu, N., Quéré, D., Clément, E., & Lindner, A., 2013. Particles accelerate the detachment of viscous liquids. Rheologica Acta, 52, 403–412.

Vaught, J. L., Cloutier, F. L., Donald, D. K., Meyer, J. D., Tacklind, C. A., & Taub, H. H., 1984. Thermal Ink-Jet Printer, U.S. Patent 4490728.

Verkouteren, R.M., Verkouteren, J.R., 2009, Inkjet Metrology: High-Accuracy Mass Measurements of Microdroplets Produced by a Drop-on-Demand Dispenser, Analytical Chemistry, 81, 8577-8584.

Verkouteren, R.M., Verkouteren, J.R., 2011, Inkjet Metrology II: Resolved Effects of Ejection Frequency, Fluidic Pressure, and Droplet Number on Reproducible Drop-on-Demand Dispensing, Langmuir, 27, 9644-9653.

Voura, C., Schroedl, N., Gruber, M.M., Strohmeier, D., Eitzinger, B., Bauer, W., Brenn,G., Khinast, J.G., Zimmer, A. 2011, Printable medicines: a microdosing device for producing personalised medicines, Pharmaceutical Technology Europe, 23, 32-36.

Wang, T., Patel, R., Derby, B., 2008, Manufacture of 3-dimensional objects by reactive inkjet printing, Soft Matter, 4, 2513-2518.

Wong, W., Fletcher, D. F., Traini, D., Chan, H.-K., Crapper, J., Young, P. M., 2011, Particle Aerosolisation and Break-Up in Dry Powder Inhalers: Evaluation and Modelling of Impaction Effects for Agglomerated Systems, Journal of Pharmaceutical Sciences, 100, 2744-2754.

Wu, B. M., Borland, S. W., Giordano, R. A., Cima, L. G., Sachs, E. M., Cima, M. J., 1996, Solid free-form fabrication of drug delivery devices, Journal of Controlled Release, 40, 77-87.

Wu, W., Zheng, Q., Guo, X., Sun, J., Liu, Y., 2009, A programmed release multi-drug implant fabricated by three-dimensional printing technology for bone tuberculosis therapy, Biomedical Materials, 4, 065005.

Yeo, Y., Basaran, O. A., Park, K, 2003, A new process for making reservoir-type microcapsules using ink-jet technology and interfacial phase separation, Journal of Controlled Release, 93, 161-173.

Yu, D.G., Branford-White, C., Ma, Z.H., Zhu, L.M., Li, X.Y., Yang, X.L., 2009, Novel drug delivery devices for providing linear release profiles fabricated by 3DP, International Journal of Pharmaceutics, 370, 160-166.

Yu, D.G., Yang, X.L., Huang, W.D., Liu, J., Wang, Y.G., Xu, H., 2007, Tablets with material gradients fabricated by three-dimensional printing, Journal of Pharmaceutical Sciences, 96, 2446-2456.

Yu, D.G., Zhu, L.M., Branford-White, C.J., Yang, X.L., 2008, Three-dimensional printing in pharmaceutics: Promises and problems, Journal of Pharmaceutical Sciences, 97, 3666-3690.

Zhang, G.G.Z., Law, D., Schmitt, E.A., Qiu, Y.H., Phase transformation considerations during process development and manufacture of solid oral dosage forms, Advanced Drug Delivery Reviews, 2004, 56, 371-390.

Zhu, Q., Harris, M.T., Taylor, L.S., 2012, Modification of Crystallization Behavior in Drug/Polyethylene Glycol Solid Dispersions, Molecular Pharmaceutics, 9, 546-553.

Zoltan, S. I., 1972. Pulse droplet ejection system, U.S. Patent 3683212.