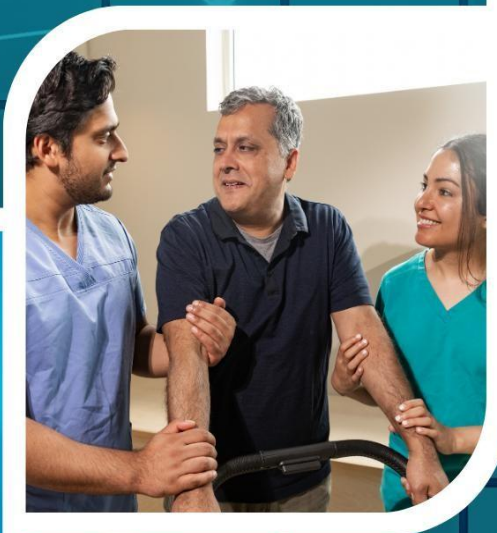


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# Pharmaceutical Inkjet Printing: An Overview of Research and Production

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### Abstract:

Current pharmaceutical industry business models need to evolve due to global manufacturing, consumer, and regulatory changes. The old centralized batch manufacturing paradigm, high-risk capital-intensive scale-up, and intrinsically high research costs are the main areas of concern. Inkjet printing is one of the new technologies being investigated to drastically change the end-to-end supply chain and pharmaceutical production processing. Before looking at the business environment influencing the investigation of inkjet printing in the pharmaceutical industry, this article gives a quick overview of inkjet printing technologies and their existing uses in production. After that, we look at the trends in pharmaceutical printing that have been documented in the literature. Next, we discuss the scientific issues and difficulties associated with this technology's introduction. We show that a wide variety of pharmaceutical types and printing systems are the focus of research activity. In order to reduce this complexity, we demonstrate that by classifying research findings according to targeted business models and Active Pharmaceutical Ingredient (API) chemistry, we can effectively translate a selected medicine to inkjet manufacturing and have a more coherent approach to comparing research findings.

## Section 1. Introduction to inkjet printing technologies

Recent years have seen significant investments in research and development for the inkjet printing of functional materials. This is a result of both greater production confidence and the adaptability of digital, non-contact patterning processes. The performance of industrial inkjet printing has now attained high levels of adaptability, durability, and dependability. Along the way, a greater amount of knowledge became available in the public domain and a variety of research tools were developed. This part reviews the evolution of the industry after discussing the variety of inkjet printing technologies and their crucial parameters.

The term "inkjet printing" refers to a broad range of techniques for creating and positioning tiny liquid droplets under digital control. Inkjet technology is typically divided into two categories: Drop on Demand (DoD) printing and Continuous Inkjet printing (CIJ). The physical method used

to create the drops separates the two. These are the most common commercial processes at the moment, but there are other ways to deliver small amounts of liquid, such as electrospray printing and different dispensing techniques that use a fluid switch or valve to stop a continuous flow (also known as "valve-jet" methods) (Martin and Hutchings, 2013).

A continuous stream of liquid is ejected via an orifice (nozzle) during CIJ printing. The liquid subsequently splits into a stream of drops due to surface tension forces. In the nineteenth century, Lord Rayleigh demonstrated that a liquid stream would naturally break up with a characteristic wavelength of surface distortion and, consequently, an eventual drop spacing of roughly 4.5 times the stream's initial diameter. In practical CIJ devices, this natural breakup under surface tension forces is enhanced by modulating the flow through the nozzle at an appropriate frequency, frequently by a piezoelectric transducer behind the nozzle. Individual ink droplets must be "steered" to a certain landing point in order to create a printed pattern when a continuous stream of droplets is employed for printing. This is often accomplished by giving some of the drops an electrical charge, which causes them to be deflected from the stream's main axis as they travel through an electrostatic field. The liquid is recirculated through the system after unwanted droplets are

captured in a "gutter." CIJ printers are currently frequently used for high-speed marking on production lines and are comparatively sturdy industrial instruments. However, the idea of creating a sequence of monodisperse droplets from a continuous liquid stream can also be used as a manufacturing technique in the creation of powders, as covered in section 3.3 below.

Only when a drop is needed is the liquid expelled from the printhead in drop-on-demand printing; each drop is produced quickly in response to a trigger signal. In contrast to CIJ printing, where drop ejection is caused by external fluid pressure, a DoD printhead typically has several nozzles (usually 100 to 1000, though specialized printheads may only have one nozzle). The kinetic energy of the drop comes from sources inside the printhead, very close to each nozzle. The deformation of a piezoelectric ceramic element is used in many printhead designs for this purpose, but in other types (thermal inkjet heads), the expansion of a tiny vapor bubble created by the action of a tiny electrical heating element on the liquid itself generates the pressure pulse that ejects the drop. Both forms of actuation have benefits and drawbacks. While thermal printheads can be easier and less expensive to make, piezoelectric printheads can handle a greater variety of liquids than thermal printheads, which are limited to fluids that would vaporize adequately. DoD printing has been utilized in the majority of inkjet printing research applications in the pharmaceutical industry because it can use tiny amounts of liquid, unlike CIJ printing, which requires a large recirculating volume. In DoD printing, typical drop diameters range from 10 to 50  $\mu\text{m}$ , which corresponds to drop volumes between 1 and 70 pL. The drop diameter is comparable to the nozzle from which it is ejected.

As seen in Figure 1a, the liquid in DoD printing initially comes from the printhead as a jet. It subsequently separates from the nozzle and collapses under surface tension forces to create one or more droplets. One or more smaller "satellite" drops frequently accompany the primary drop, which holds the majority of the liquid. It may be feasible to prevent the creation of satellite drops and guarantee that only one drop is created by adjusting the ejection parameters and, occasionally, the liquid's rheology. However, satellite drops are acceptable in many real-world printing applications, particularly if they recombine with the initial drop on the surface, as Figure 1(b) illustrates.

The production and behavior of liquid jets and droplets are significantly influenced by surface tension, inertia, and viscosity. The behavior of a jet that emerges from a nozzle is found to be strongly correlated with the value of the Ohnesorge number  $Oh$ , which is independent of the

driving circumstances (which regulate the velocity) but depends on the physical characteristics of the liquid and the size scale of the jet or drop. Equation 1 defines this dimensionless group:

$$\text{Oh} = \frac{\eta}{\sqrt{\gamma\rho d}}$$

(1)

where  $\rho$  is the density of the fluid,  $\eta$  is its viscosity,  $\gamma$  is its surface tension and  $d$  is a characteristic length, typically the diameter of the nozzle or drop.

Viscous forces will prevent a drop from separating if the Ohnesorge number is too high ( $\text{Oh} > \sim 1$ ), but the jet will generate many satellite droplets if it is too low ( $\text{Oh} < \sim 0.1$ ). As demonstrated in Figure 1c (McKinley and Renardy 2011, Derby 2010), a fluid's ability to perform satisfactorily in drop-on-demand inkjet printing thus requires a suitable combination of physical properties, which will also depend on the droplet size and velocity (through the value of the Reynolds number  $\text{Re}$ , defined by  $\text{Re} = \rho d V / \eta$  where  $V$  is the drop velocity).

The "printability" of the liquid is limited by the ranges of Ohnesorge number mentioned above, but other factors must also be taken into account: the jet must have sufficient kinetic energy to be ejected from the

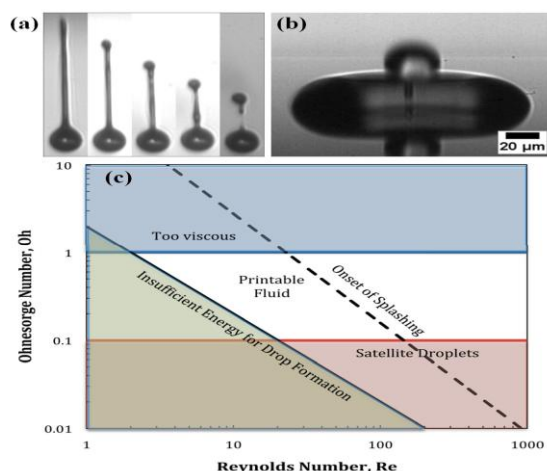
nozzle (resulting in the solid diagonal line in Figure 1c corresponding to  $\text{Re} = 2/\text{Oh}$ ), and it is also desirable to avoid splashing of the drop on impact with the substrate (which leads to the broken diagonal line for which  $\text{OhRe}^{5/4} = 50$ ) (Derby 2010).

All of these factors apply to Newtonian liquids, or those whose viscosity is independent of shear rate. However, many practically significant liquids exhibit non-Newtonian properties, such as shear thinning or viscoelastic behavior. The behavior may be more complicated for certain liquids (see, for instance, Hoath et al. 2012a and Hoath et al. 2012b). The difficulties stem from the extremely high shear rate that the liquid experiences as it travels down the nozzle, which may cause unanticipated behavior. Many studies have been conducted on the rheology of inkjet fluids (e.g. Clasen et al. 2012, Hoath et al. 2013, Hoath et al. 2014). Particle-containing inks, such as colored inks, have been printed on an industrial scale for a while, but they also produce additional limitations (particle size, morphology, and concentration), which are typically assessed empirically for a particular ink and print head combination. Although inkjet printing has been successful for a wide range of materials, including cells,

colloids and nanomaterials (Ferris et al. 2013, Perelaer et al. 2006, van Deen et al. 2013), it is far more difficult to guarantee that a material will print consistently and reliably in an industrial setting. This calls for thorough testing of the suggested system over an extended period of time in addition to ongoing quality control.

Since its concepts were created in the 1970s and early 1980s, inkjet has come a long way (Endo et al. 1988, Kyser et al. 1976, Sweet 1971, Vaught et al. 1984, Zoltan 1972). Continuous inkjet (CIJ), as mentioned 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)). DoD technology dominates the home printer market (pioneered for example by Canon, Hewlett Packard, and Epson). By offering a different and more affordable way to print short runs and provide late-stage customization (such as direct printing to packaging), DoD and CIJ have both challenged traditional printing technologies (Domino Printing 2014a). Companies like Kodak and Fujifilm Dimatix in the USA and Xaar (another spin-out of Cambridge Consultants Ltd.) in the UK have led this element of

inkjet use. For some applications, like as short run posters (Inca Digital 2014) and ceramicia 2014, the benefits of inkjet printing have been so great that they have supplanted traditional printing as the preferred method.



**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).

The use of print heads for image printing continues to be the primary focus of print head development and a significant source of revenue for print head manufacturers. There has been a lot of discussion and analysis on the use of inkjet as a manufacturing technique, of which pharmaceutical manufacturing is a subset (e.g. Hutchings and Martin 2013), and a lot of research has been done to explore its possibilities. The primary limitation is the small range of materials that the inkjet method can deposit. For modern printing applications, printheads and inks have been developed simultaneously over many years. The variety of materials that must be delivered has significantly increased due to the usage of inkjet for various purposes, which has led to extensive study into ink formulation but little attention to printhead redesign. It is obvious that the business case for such a large investment must be taken into account when switching to inkjet printing for pharmaceutical applications. However, research into the interactions between the printhead and the fluids being printed is also crucial in order to define technology and formulation requirements and guarantee the delivery of a functional dose. This evaluation now takes into account the main obstacles to the adoption of pharmaceutical inkjet printing as well as the business and technological drivers.

#### **Section 2. The incentive to print pharmaceuticals**

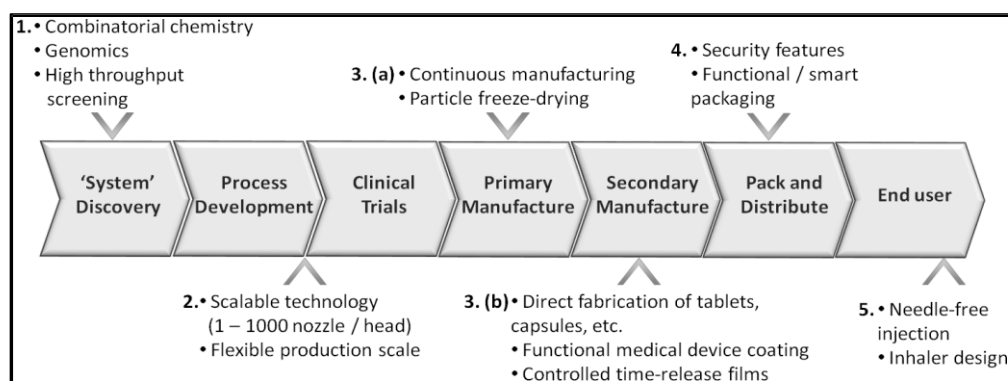
Clear motivations for change in the pharmaceutical industry have been recognized, even though service levels to the distributor surpass 98% on-time and in-full (OTIF) and gross margins remain robust in the range of 70–80% (Harrington and Najim 2014). The sector has lengthy, costly, and slow supply chains, and optimizing inventory levels is particularly difficult (Kim and Lee, 1993; Calabrese and Pissavini 2011). For the top 25 pharmaceutical businesses, stock levels are expected to be worth between \$100 and \$150 billion

(Harrington and Srai 2014). Lead times for replenishments are frequently encountered beyond 200 days, stocks exceed 50% of COGS, and manufacturing losses for the same group of businesses are projected to be between \$20 and \$25 billion per year (Harrington and Srai 2014; Srai et al. 2014; Srai et al. 2015).

This industrial and supply chain environment could be drastically altered by the development of both new technologies and therapeutic fields. According to future trends, the overall goal should be to guarantee a sector that is sufficiently adaptable to support a wider range of more specialized products at lower volumes (i.e., more stratified and personalized medicines), for particular patient populations, and to meet current market and volume demands (Voura et al. 2011). The business case for change must be more clearly understood and financially feasible in order for new technologies, like inkjet printing, to gain widespread acceptance and commercial exploitation. Therefore, a shift away from the popular "blockbuster" model will need to take into account the advantages for (a) product customization and diversity, (b) energy and resource efficiency, (c) inventory optimization, 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 Srail, 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.

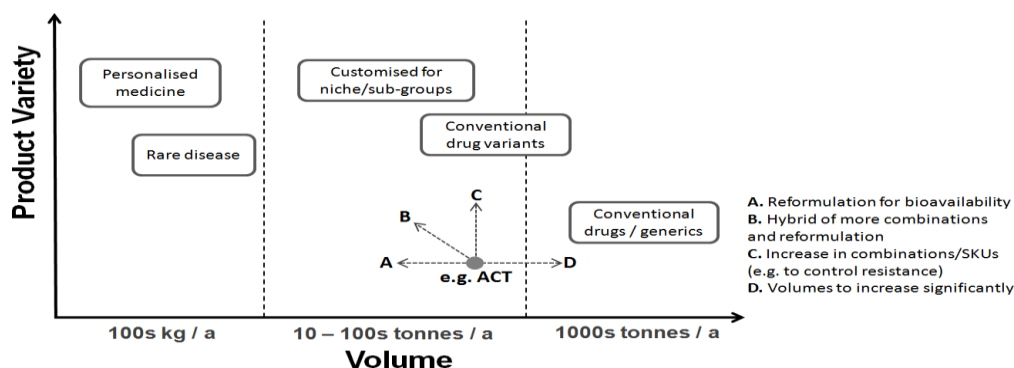
The former point is the focus of this review, exploring the technologies and challenges reported to-date, examined in detail in sections 3 and 4. While this review does not provide an in-depth study into business models, this section briefly reviews an approach for considering where continuous processing 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 (Srail *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 Srαι 2014). Using supply network configuration mapping methodologies previously reported (Srαι 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 Srαι *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 Srαι 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.

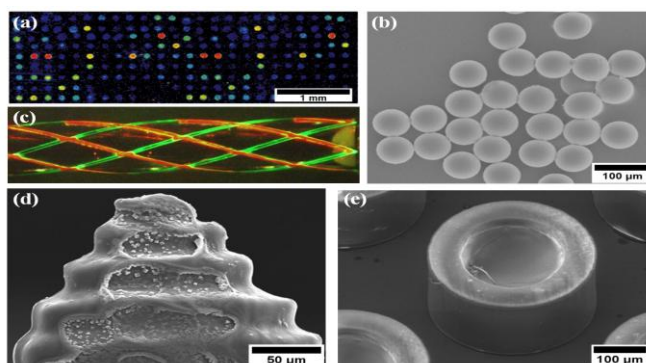
However, miniaturisation of assays leads to a series of key challenges, reviewed by a range of authors late in the 20th century (Hertzberg and Pope 2000, Sittampalam *et al.* 1997, Silverman *et al.* 1998, Lemmo *et al.* 1998) such as (i) assay methods and detection, (ii) liquid handling and robotics 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 (Skena *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 (Skena *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  $\text{cm}^{-2}$  (with supercritical  $\text{CO}_2$  (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 preserve or increase overall batch variability. Although inkjet printing is not now a significant technique in primary manufacturing, the recent emphasis on pharmaceutical continuous manufacturing indicates that it will be thoroughly investigated in the years to come. The potential for this field is demonstrated by the current investigation of reactive inkjet printing (Smith and Morrin 2012, Wang et al., 2008) and its already widespread application in combinatorial chemistry, which can be used to synthesize small amounts of drugs.

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  $\mu\text{m}$  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.

**3.3.2** 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.

**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. 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).

**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 better 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.

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 (Schna *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<sup>2</sup>) 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.

**4.1.1 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.*, Mueannoorn *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, Rajjada *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<sup>-1</sup> 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.

**4.1.2 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 produced 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.

**4.1.3 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  $30 \text{ mN m}^{-1}$  (Hutchings and Martin 2013), pure water having a surface tension of  $72 \text{ mN m}^{-1}$ , 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 nano particulates, 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.

<b>Print System</b>	<b>Printed Pharmaceutical Example</b>
Fujifilm Dimatix Materials Printer DMP-2800 series.	Rifampicin (Gu <i>et al.</i> 2012), piroxicam (Raijada <i>et al.</i> 2013)
Hewlett-Packard Deskjet TII (e.g. 340)	Terbutaline sulphate (Sharma <i>et al.</i> 2013), salbutamol sulphate (Mueannoom <i>et al.</i> 2012).
Sciflexarrayer S5	Felodipine, hydrochlorothiazide (Scoutaris <i>et al.</i> 2012)
Gesim A010-201	Felodipine (Scoutaris <i>et al.</i> 2012)
MicroFab	Paclitaxel (Radulescu <i>et al.</i> 2003), fenofibrate, rapamycin (Tarcha <i>et al.</i> 2007).
Nanoplotter	Ketoprofen (Marizza <i>et al.</i> 2014).

Canon TIJ (e.g. Pixma MP495)	Loperamide hydrochloride, caffeine (Genina <i>et al.</i> 2013)
Microdrop	Folic acid (Pardeike <i>et al.</i> 2011).
Positive displacement DoD	Naproxen (Hirshfield <i>et al.</i> 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), 34eterogenei 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 34eteroge 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 34eteroge.

#### 4.4. Deposition, fixing and functionality

The final category where underlying scientific challenges arise is in the deposition of the drug and 34eterogeneitie 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 34eterogeneities34 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 heterogeneities tool.

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

The financial incentives, existing technologies, and upcoming difficulties associated with pharmaceutical inkjet printing have all been covered in this research. Although it is evident that this sector has been developing for a long time, recent years have seen substantial advancements in our understanding of the underlying technology and ink compositions, much like the growth of commercial inkjet printing. This article has reviewed a number of technologies that allow inkjet printing to play a variety of roles in the pharmaceutical manufacturing supply chain, including accelerating drug discovery, creating materials for drug delivery, producing customized medications, and enhancing product security through innovative packaging. The pharmaceutical industry's motivations have been briefly discussed, with an emphasis on the recent shift away from the blockbuster strategy and toward the development of new business models. This analysis highlights a classification strategy that will allow a reasonable comparison of items in terms of their eligibility for inkjet printing from a business viewpoint, given the complexity of this area and the wide range of pharmaceutical products to take into account.

Although there is presently a wide range of literature on the subject, two crucial elements should be taken into account as the community advances. Specific technologies and inkjet difficulties have been addressed. First, in order to facilitate a more cohesive comparison of research findings and efficient translation to manufacturing, a classification approach based on the underlying API chemistry should be investigated, given the limited combinations of excipients, carrier fluids, and APIs. Second, and much more important for the future of the pharmaceutical inkjet printing vision, research needs to start thinking about the exact industrial scale that is being sought early. This will result in the selection of suitable commercially available printheads (both in terms of material compatibility and volume throughput). Because each device has different formulation and jetting parameter needs, it is crucial to analyze formulations in conjunction with a suitable printhead. The manufacturing and business factors have been integrated with the underlying scientific problems in this assessment. The community should be able to push for a quick, targeted, and cohesive transfer of pharmaceutical inkjet printing to the production scale thanks to the trends found here.

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