Thermal Inkjet Printing: Prospects and Applications in the Development of Medicine

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

Department of Pharmacy
Brac University
August 2019

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Approval

The thesis titled "Thermal inkjet printing: prospects and applications in the development of medicine" submitted by Tasneem Souria Prapty (15146078) of Spring, 2015 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on August,2019.

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Ethics Statement

This study does not involve any human or animal trial.

Abstract

Most of the medicines are in oral dosage form, so formulation of personalized medicine is quite critical. During the manufacturing of drugs, to have a control over the process and the APIs is necessary, as it gives an opportunity to enhance the drug delivery process. Inkjet printing technology has been an overwhelming technology for the last few eras for not only pharmaceuticals but also for biologics along with a way to control product and material properties precisely. Here the potential applications and prospects of conventional inkjet printing technology has been described which is usually used for various printable pharmaceutical dosage form and also focusing some anticipation regarding the manufacturing and optimization of various other dosage form. Moreover, it is being anticipated that in the near future it will solve many other problems related to poorly water soluble and low dosages drug. Furthermore, there are many researches on-going for more individualized QR coded medicines which will give faster response.

Keyword: Inkjet Printing; Personalized medicine; Thermal inkjet printing; Printable pharmaceutical dosage form; Poorly water soluble; Low dosages drug

Dedication

Dedicated to my parents

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List of Acronyms

DOD	Drop on demand
EHD	Electro hydrodynamic printing
ODF	Oro dispersible film
LbL	Layer by layer
TIJ	Thermal inkjet printing
PIJ	Piezoelectric inkjet printing
PLA	Polyacetic acid
DAMPP	Drop wise additive manufacturing
FDA	The US Food & Drug Administration

Chapter 1

Introduction

Inkjet printing has recently become an interesting technology for the manufacture of drug delivery systems and this has coincided with a burgeoning interest in the personalization of medicine. Although inkjet printing is an established technology it has not historically been heavily researched in regards to applications within the pharmaceutical industry, in part due to a focus on mass production and markets. As niche markets and individual needs are given more attention and are more economically and therapeutically pertinent, the suitability of inkjet printing as a means of manufacture of several drug delivery systems has been considered and researched within the last decade (Raijada et al., 2013).

1.1 Inkjet printing of pharmaceuticals

Conventional tablet producing process has numerous powders treating and blending stages. It is tedious and limits individualized dosing. Besides, consistency of the portion is hard to accomplish. Present day inkjet printing innovation has been effectively connected to polymer electronics and biomaterial applications. It has numerous points of interest that could be used in medication fabricating process, for example, quicker production cycle with less steps, exact dosing, on-request individualized dosing and plausibility for on-line quality control (Takala et al., 2012). A nitro heart and artery medicine pill has a 0.5 mg dynamic portion of glyceryl trinitrate, though the pill itself loads around 110 mg. By presenting innovation utilized in printers it could be conceivable to make the procedure quicker, progressively precise, increasingly unique and less demanding to control. Printing innovation makes it conceivable to straightforwardly infuse dynamic fixings onto the outside of a palatable substrate hence making medications that respond quicker. Contrasted with a prescription bead, inkjet bead can be up to 20 times smaller (Raijada et al., 2013). new potential outcomes

emerge when different active ingredients could be infused onto the equivalent surface (Takala et al., 2012).

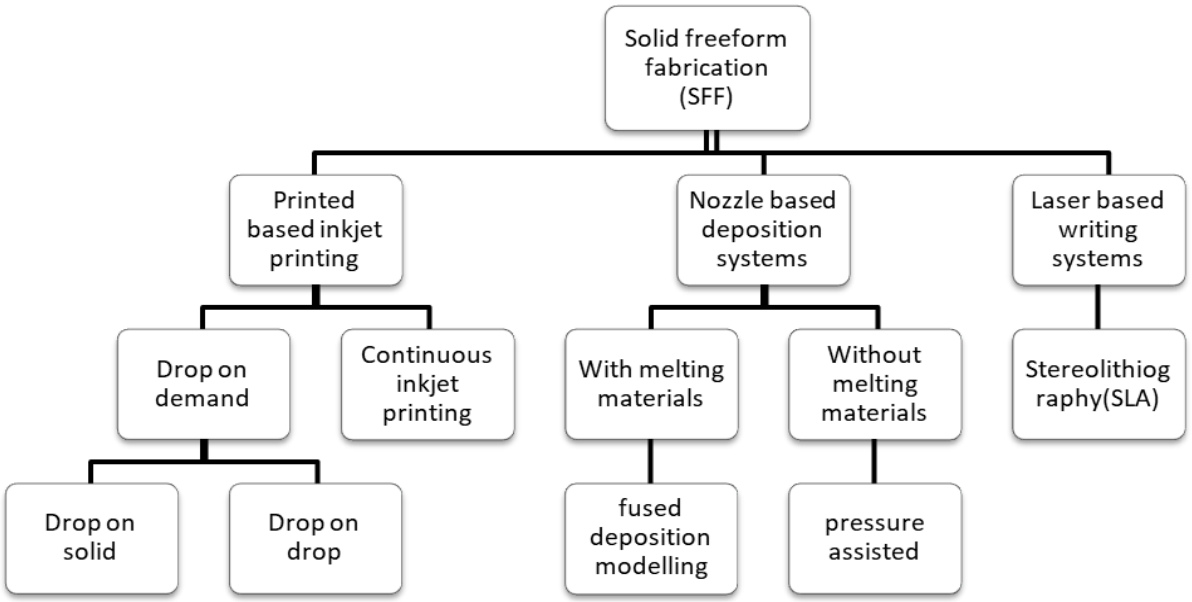

Figure 1printing technologies for medicine manufacture (Jonathan, G.; Karim, A., 2016)

1.2 Expert opinion regarding inkjet printing of pharmaceuticals

Dr Gaisford's group has just demonstrated that dosages can be imprinted onto film made of starch which disintegrates in the mouth (much like Listerine breath strips) and the following stage would be that he is hoping to get financed is the utilization of printer innovation to accomplish customized dosing, he disclosed to The Journal. "Regarding customized dosing and why [printer] innovation is helpful in respect to other different strategies, it comes down to the extremely fine control of the volume which is being streamed," Dr Gaisford said. He clarified that on the grounds that every project is regularly somewhere in the range of 7 and 24 Pico litres the inkjet is equipped for printing minute dosages — so printer innovation

could be utilized to make more secure the organization of very low portion, exceedingly intense, narrow therapeutic index drugs, particularly for children. “The innovation of an inkjet printer is so a long way in front of what we need in pharmaceutics, we're practically making a inefficient step," he said. Be that as it may, the little droplet measure additionally constrains the quantity of medications appropriate for printing on the grounds that the most extreme portion the group could able to print is 35µg per cm^2. Until this point, they have been working with tacrolimus. Squares of film (or "oral wafers") could be imprinted in week by week bundles for a specific patient. The thought is that you can fluctuate the portion patient to persistent by, for example, jetting an alternate concentration of solution, an alternate portion on the film, or you can put the film several number of times, developing the quantity of layers that you are printing. You could even print each film with multi day of the week, with the medication contained in the text, Dr Gaisford proposed (2013, T. P. 2013, July 03).

1.3 Drug formulation by inkjet printing

Inkjet printing is comparatively a novel drug invention notion including narrow study reports. In expansion of poor water soluble APIs os solid dosage form, the use of thermal inkjet printing as a substitute has been reported by Melindez et al. Thus, a low water soluble molecule prednisolone was being nominated for this and being allotted from organic polymer solution by using micropipette. The existence of two prednisolone polymorphs has been found in the printed films as consequences of the experiment due to the use of the particular solvent combination (Scoutaris, Ross, & Douroumis, 2016).Meanwhile, by using inkjet-printing technology many researchers have been trying to advance the dissolution properties of many poorly water soluble drugs. In a previous study by Scoutaris et al. A poorly soluble molecule felodipine was jetted with an excipient, PVP to enhance the dispersion property of controlled release solid dosage form (Genina, Janßen, Breitenbach, Breitkreutz, & Sandler, 2013) The consequences showed that then changes in drug-polymer ratio alter the discharge

of the drug consequently. Hence, a micro-spot preparation has been designed containing different drug polymer ratios, to accustom the drug release as per the anticipated qualifications. Additionally, by providing nanoparticle complexes of ciprofloxacin – polysaccharide with naproxen/PEG 3350 solid dispersion and polyethylene – glycol, inkjet printing provide an abundant scope of progressing the dissolution property of some poorly water soluble drugs (Raijada et al., 2013). This process brings new way to regulate the crystallization of a specified drug substance and thus altering its characteristics beginning new predictions to advance novel pharmaceutical systems. Direct deposition of solutions of drug- polymer on top of numerous substrates, this was mainly attained. Different crystallization characteristic of the compounds were noticed due to the permeation of the materials into the porous substrates after comparing it with the printing on unpenetratable substrates (Vuddanda et al., 2018a). Gaisford et al. showed evident regarding the ease of the process to formulate medicine where an old-fashioned inkjet printer was customized to print salbutamol films on a paper tray. They adapted a Hewlett Packard cartridge printer where aqueous drug solutions were used instead of the ink. The individualized cartridge of the printer was modified to print highest resolution and highest quality drug when the printed templates were being designed by software, WORD 2007. TIJ is being established as an appropriate technology for printing low-dose drugs (Scoutaris, Ross, et al., 2016)**.**

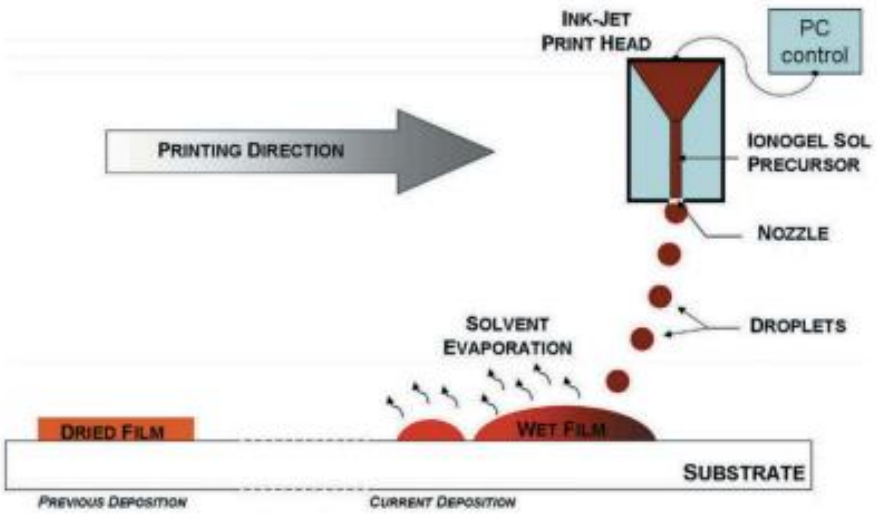

Figure 2illustration of inkjet printing process (Sina Azizi Machekposhti,2019)

1.4 Types of inkjet printing

Inkjet printing depends on the Lord Rayleigh's uncertainty hypothesis that clarifies the breaking of a fluid stream or jet into droplets created in 1878. The idea was utilized to create nonstop jet (CJ) and drop on demand (DOD) printing, these two are usually utilized in conventional production. CJ printing uses a pressurized stream is being used in CJ printing to create a nonstop stream of droplets that are charged after leaving the spout, to be guided by electrostatic plates to the substrate or to waste for recirculating (Kyobula et al., 2017a). DOD is viewed as increasingly exact and less inefficient as it can deliver low bead volumes, 1– 100 pL at high speeds, which is required. The two best kinds of activation with DOD printing are thermal (once in a while called air pocket) and piezo-electric. micro electro electro-mechanical (Prasad, Smyth, Prasad, & Smyth, 2016). A thermal print head uses a resistor with endless supply of electrical pulse which quickly heats and shapes a vapour in the ink reservoir (Prasad and Smyth, 2016).This air pocket powers ink from the print head; the air pocket then breaks, delivering a negative pressure to draw ink from the repository to fill-up the chamber (Prasad & Smyth, 2016).

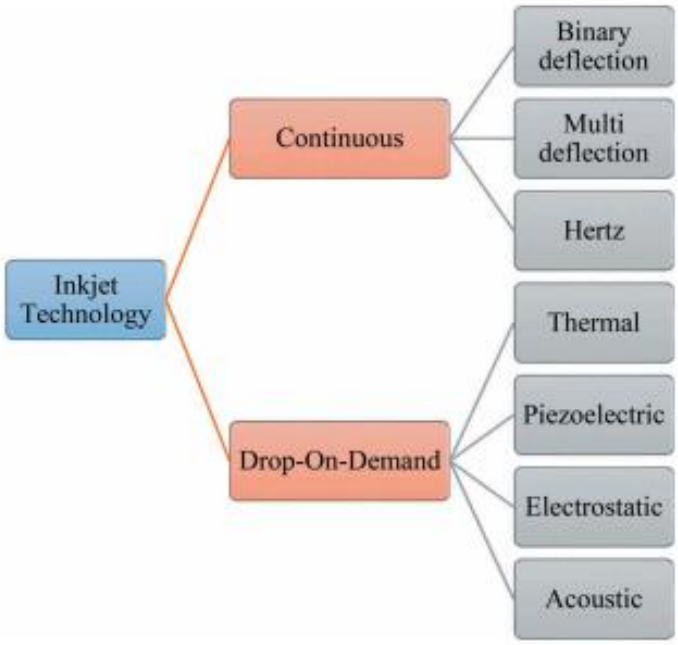

Figure 3classification of inkjet printing (Sina Azizi Machekposhti, 2019)

1.4.1 Electrostatic inkjet printers

Drops are supplied and directed by electrostatic fields in electrostatic inkjet printing. Mechanical driving forces are straightforwardly connected to the liquid chamber to cause an displacing. Since it does not use heat for producing droplets, this is viewed as good with cell consisting inks. The altitude of the nozzle should be balanced for every layer, to print distinctive layers of a hydrogel structure; it usually causes a decrease in printing resolution by adjusting the electric field round the nozzle tip. This insufficiency can be tended to by introducing a terminal ring between the nozzle tip and the target (Lim, Kathuria, Tan, & Kang, 2018).The plausibility of utilizing electrostatic inkjet printers to print bovine vascular endothelial cells onto culture circles was examined by Nakamura et al.This kind of printers was utilized for printing embodied B50 neuroblastoma rodent cells in an alginate hydrogel for getting an insight of the supplement (Azizi Machekposhti, Mohaved, & Narayan, 2019).

1.4.2 Electro hydrodynamic inkjet printers

To drive ink along the opening, electro hydrodynamic type of inkjet printers utilizes electricity. Voltage difference of (0.5-20kv) in between the nozzle and substrate supplied by the electric power helps to defeat the surface strain of the opening and expels the drops. Its downsides are high voltage requirements and ink streaming rate. If the ink is in constant flow in this type of process, then it is called cone-jet mode. If low voltage is given in this method, then a dripping mode and individual drop occurs (Azizi Machekposhti et al., 2019).

1.4.3 Thermal inkjet printing

TIJ framework attached over a print head contains a supply of fluid to be stream. The print head contains various little chambers, loaded up with fluid supply and connected with a resistor, delivered with photolithography (Buanz, Saunders, Basit, & Gaisford, 2011).

A sudden rise of temperature occurs when current is pulsating through the component of the printer which causes the portion of the fluid to vaporize, nucleate and extend of the vaporized bubble. As a result of the extension of vaporized bubble some fluid comes out of the chamber to shape a drop. At last the vaporized bubble breaks down to cause a vacuum loaded up with liquid from the supply. This process then recurrences by controlling the current and it formulates droplets- on-demand (DOD) (Alomari et al., 2018; López-Iglesias et al., 2019).

The resistor system usually occupies a temperature of about 300°C which causes bubble enlargement up to 3-10 μs and expels drop at a speed of 10 m s^{-1}, with droplet volume limit of 2–180 pL approximately. This has been observed that preparations of protein (human growth hormone and insulin) remained unchanged by TIJ (Buanz et al., 2011).

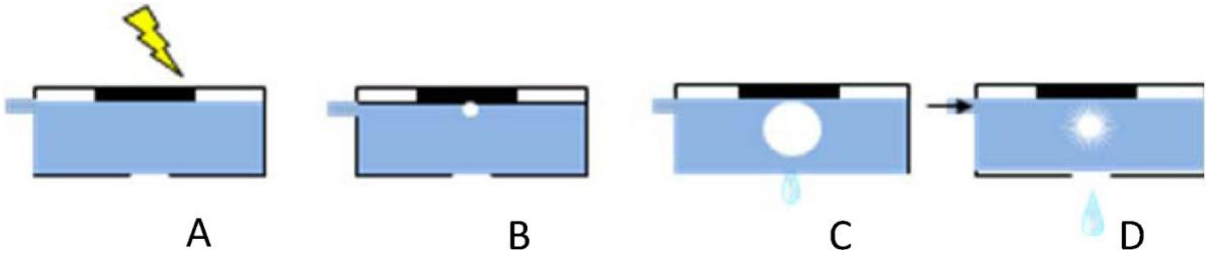

Figure 4Thermal ink-jet drop generating chamber((Alomari, Mohamed, Basit, & Gaisford, 2015)

(A) Rising of the resistor temperature upon receipt of an electrical pulse (B) nucleation due to formation of superheated vapour bubble (C) growth of the bubble and deposition of a droplet and (D) collapse of the bubble and refilling.

1.4.4 Continuous inkjet printing

Here the fluid ink is being led by a pump giving high pressure through a hole diameter of 50-80 µm which makes a constant ink stream. A piezoelectric crystal makes the fluid stream to break into drops at a particular speed and shape and time. The fluid stream is broken down into drops at a particular speed, shape and time by the piezoelectric crystal and these parameters are controlled by making an electrostatic field .In this way, the drops get charge and isolate via "drops of guard" in order to limiting the electrostatic repugnance among them. The charged droplets then lead to the substrate for the electrostatic field that was made. Then the charged drops move forward to the substrate owing to the created electrostatic field. Here, the drops are focused continually grounded on a counter-system of injection on demand, for this they are removed while needed (Konta, García-Piña, & Serrano, 2017; Vakili, Wickström, Desai, Preis, & Sandler, 2017).

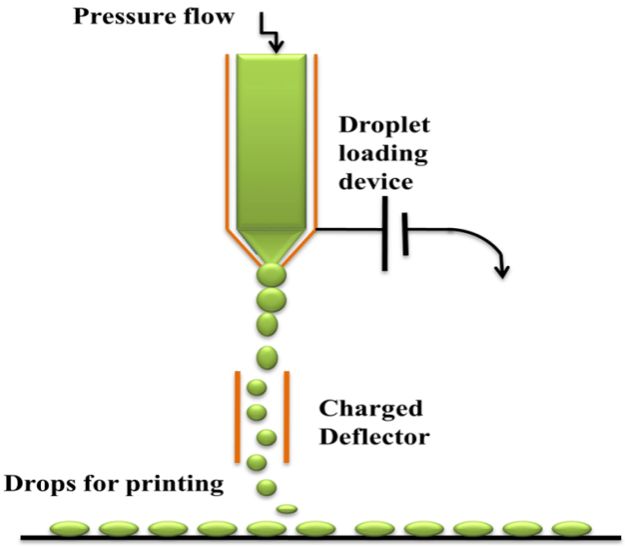

Figure 5continuous inkjet printing (Konta et al., 2017)

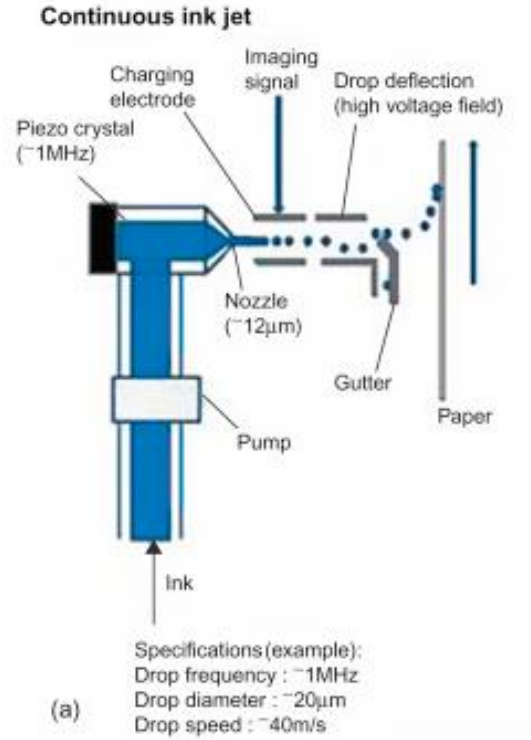

Figure 6continuous inkjet printing process (Dario Natali,2016)

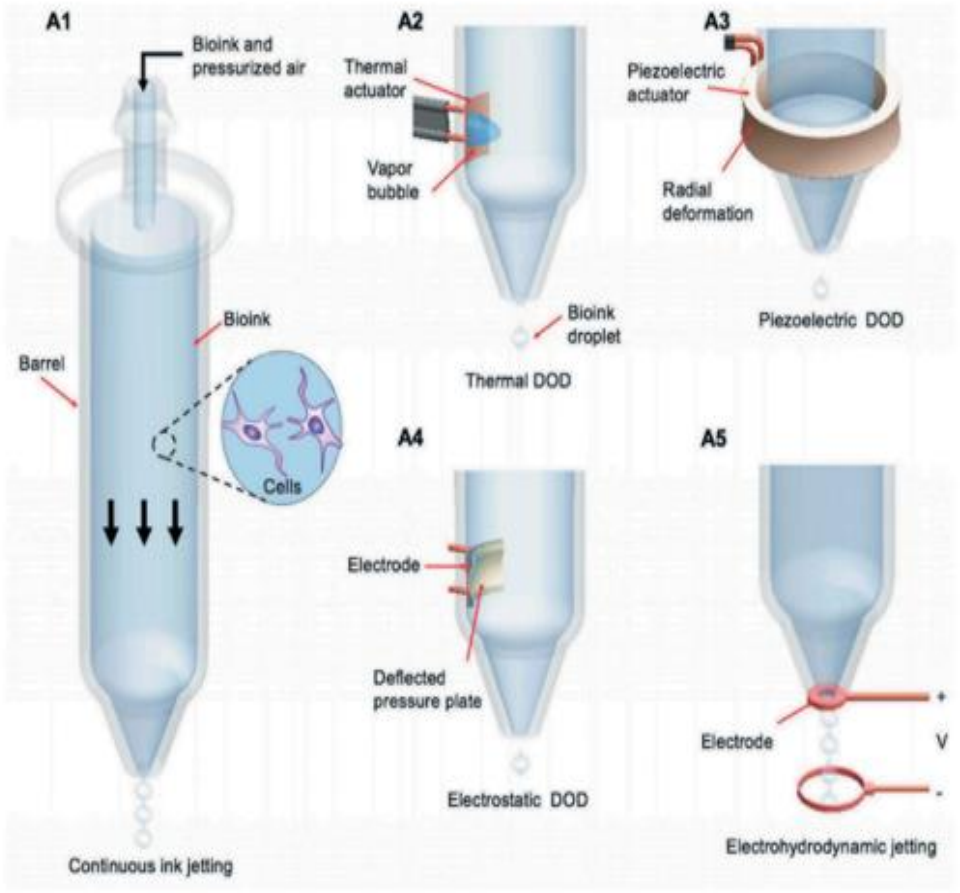

Figure 7various type of inkjet printing (Sina Azizi Machekposhti, 2019)

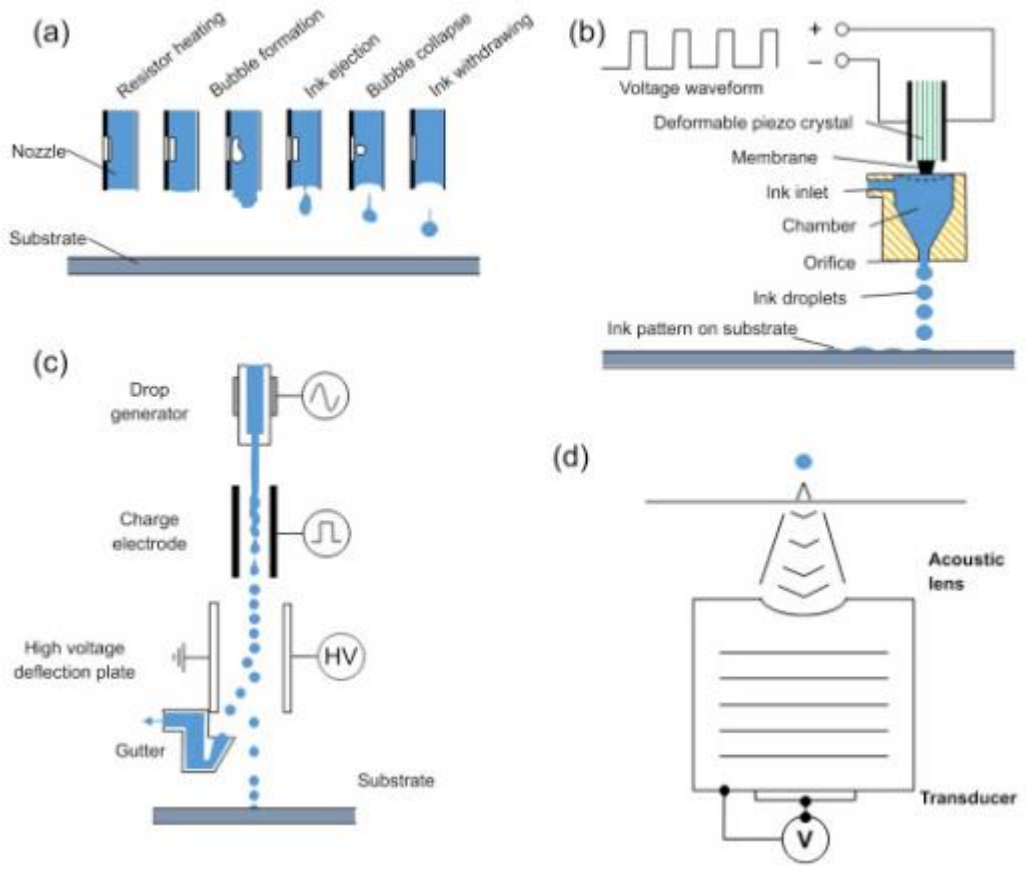

Figure 8various type of inkjet printing (L. Gonzalez-Macia,2017)

1.4.5 Drop-on-demand inkjet printing

IJP is broadly employed in routine printing of reports and pictures in office. Continuous and drop-on-demand (DOD) are two of the distinct kind of procedures of IJP. It is a probable empowering innovation not only for dependable assembling of medicines but also for customized prescription, yet the utilization of this remains frequently confined to low-viscous preparations and Nano-suspensions (Kolakovic et al., 2013). Drop-on-demand inkjet printing advances enable little portion of a fluid to be re-producible allotted in a single drop and precisely placed onto a substrate without contacting. adaptability of this methodology has been demonstrated in designs printing, and it is progressively being linked with mechanical uses The methodology has been adapted in designs printing and progressively in mechanical uses (Singh, Haverinen, Dhagat, & Jabbour, 2008).It is a computerized strategy

which is likewise appropriate for short run production and for this the printing pattern and spreading of fluid is alterable without changing the manufacturing line. This is a possible empowering innovation for disseminated manufacture and customized prescription: which ensures the adaption of the dose or mixtures of APIs for specific individual. This technique has been examined by different studies as a strategy for creating customized dosage form of medications (Buanz et al., 2011; Raijada et al., 2013). to modify the doses of controlled release drugs (Genina, Janßen, et al., 2013), to upgrade the disintegration behavior of ineffectively soluble medications, for example, ciprofloxacin (Cheow, Kiew, & Hadinoto, 2015), piroxicam (Raijada et al., 2013) and felodipine (Scoutaris, Ross, et al., 2016), and indomethacin (Varan, Wickström, Sandler, Aktaş, & Bilensoy, 2017) and for thinking about the solid state changes related with these processes (Hoath, Harlen, & Hutchings, 2012; Kollamaram, Hopkins, Glowacki, Croker, & Walker, 2018; Planchette et al., 2016).

There are two classes of DOD system one is drop-on-drop deposition and another is drop-on solid deposition These two process have the benefit of utilizing numerous kind of elements and colors as it is capable of printing multiple pieces at a time in layers and in the shortest time. In the drop-on-drop deposition system, the drop interposition produces the different layers of the RP. On the other hand, the drop-on-solid deposition, known as “powder bed fusion” is based on the projection of drops directly on the solid material. the drop-on-drop deposition framework, the drop mediation delivers the diverse layers of the RP. Whereas, the drop-on-solid deposition which is recognized as "powder bed fusion" depends on the projection of drops straightforwardly on the solid. It is ideal for a wide scope of active ingredients, permitting the control of the medication release process relying upon the characteristics of the binders (Kollamaram et al., 2018; Konta et al., 2017).

Point to consider for thermal inkjet printer

TIJ is capable of producing high temperatures close to the resistive component. It still needs special consideration for thermal decomposition, though there is minimal contact time and area of the ink with this component. Moreover, the print head needs volatile materials that for this pharmaceutical applications has been limited (Kyobula et al., 2017a; Prasad et al., 2016).

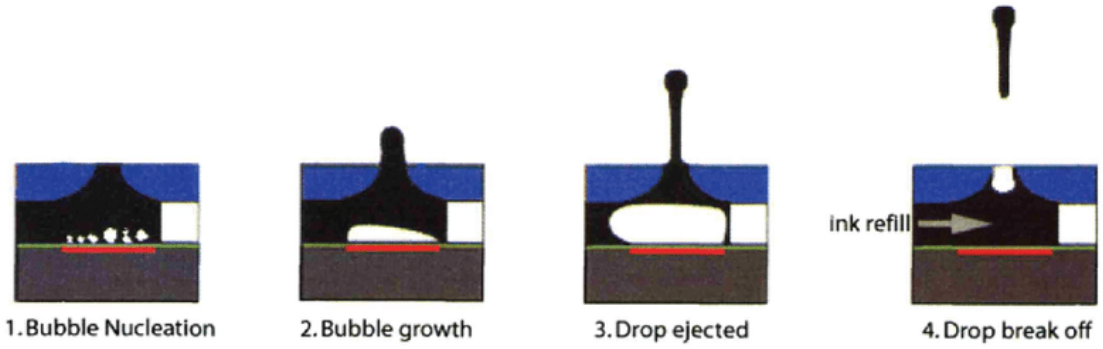

Figure 9thermal inkjet printing process (Dario Natali,2016)

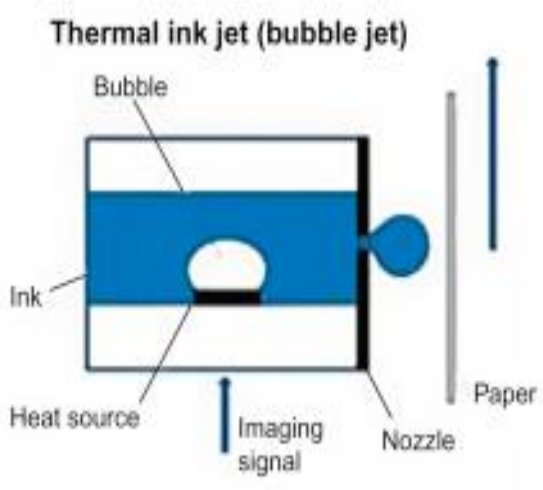

Figure 10droplet formation in a thermal inkjet printer (adapted from kolakovic et al., 2013)

Point to consider for piezoelectric printer

A mechanical movement is yielded due to the applied voltage as the piezoelectric print head uses a material either crystal or ceramic. The fluid is jetted from the nozzle due to the pressure created by the distortion of the material. This printing has been revealed to give more precisely controlled droplet and don't need heat for operating, which allows it to be used for drug improvement (Meléndez, Kane, Ashvar, Albrecht, & Smith, 2008a; Prasad & Smyth, 2016).

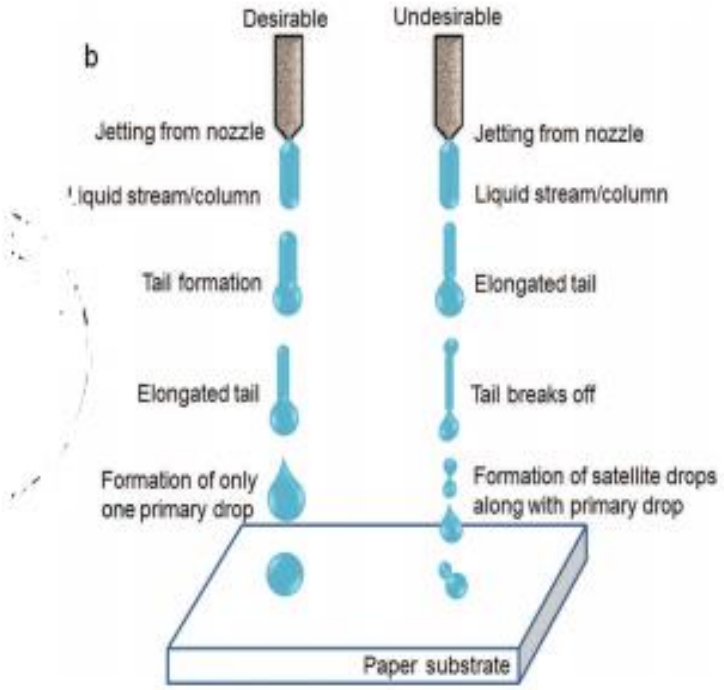

Figure 11drop formation in piezoelectric inkjet printing

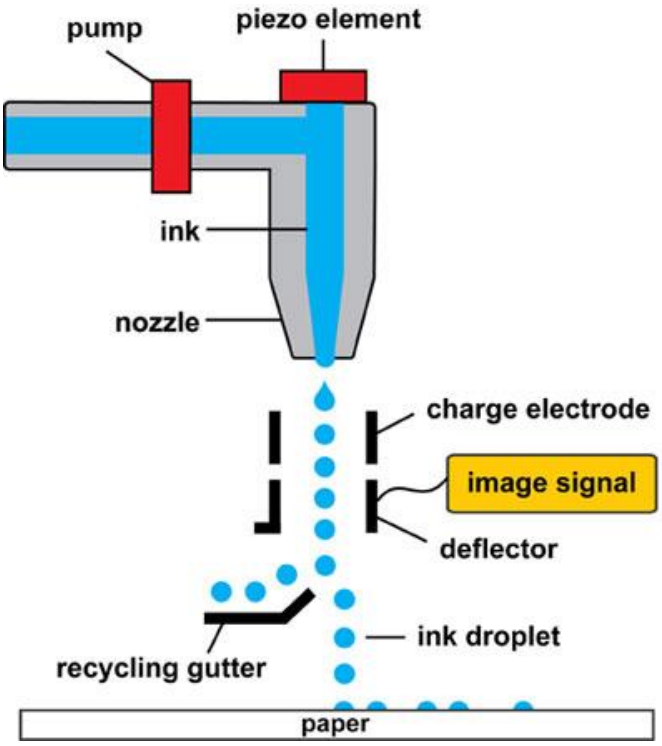

Figure 12 piezo inkjet printing process (Dario Natali,2016)

1.4.6 Other inkjet printing methods

Among various inkjet printing method, solenoid valve is one of them which contains pressurized ink which is jetted through a accurately adjusted solenoid valve and maintains consistency in droplet formation (Samson, Lee, & Song, 2018). In drop wise additive manufacturing (DAMPP), the ink is pushed by a one chambered, positive displacement pump which is capable of adjusting the drops volume by modifying the pump (Ajiro, Kuroda, Kan, & Akashi, 2015). They have same ink necessities like TIJ and PIJ which exhibit consistency in drop formation (Berg, Simonsen, & Svensson, 2018).

In Electro hydrodynamic printing (EHD) sufficient ink is packed in a nozzle which form the drop, where voltage is given to the electrode below the substrate to stretch ink and form the liquid bridge of nozzle and substrate.one droplet is formed in the substrate and the ink remains in the nozzle after the breaking of the bridge, this ink is further used for another turn (Palo et al., 2017).

This method has the potentiality to work with high viscous inks, which is comparable to other techniques and can form drops with proper consistency (Montenegro-Nicolini et al., 2018).

Films for buccal delivery has newly been suggested to be made by inkjet printing in two steps, first of all film manufacturing or substrate printing and then drug loading. Moreover, this technique could overcome the problem associated with solvent casting which usually causes dispersion of drug in the polymer of the film and changes some properties of the film for this reason now researchers has started adapting this technique for biologics specially (Alfadhel et al., 2018; Montenegro-Nicolini, Miranda, & Morales, 2017).

1.5 Type of printers and their uses in different printing techniques

There are two diverse business printers: HP Photo smart B010 and Epson Stylus SX 425W.HP uses warm inkjet print head and Epson piezoelectric inkjet print head. Be that as it may, from the earliest starting point the piezoelectric printer was observed to be incapable of printing any substance (Li, Ma, Higaki, Kamitani, & Takahara, 2018). The dissimilarity in these two innovations is that how the ink-droplet is framed. Thermal inkjet utilizes a heat component – a little resistor – to make heat as well as to vaporize the ink and to make an air pocket. At the point when the air pocket grows it pushes ink out of the nozzle. As the air pocket breakdown it makes a vacuum, more ink is pulled which makes the way from the cartridge into the print head (Square, Basher, & Buanz, n.d.; Takala et al., 2012).

Piezoelectric printer utilizes a little crystal at the back of the ink supply in every nozzle. Little electrical flow is directed to the precious stone, which makes the gem vibrate. At the point when the crystal grows, an ink bead is constrained out of the nozzle and when the crystal contracts, it pulls out more ink from the reservoir (López-Iglesias et al., 2019; Vakili et al., 2017).

Now and then the arrangement did not launch the cartridge into the print head gathering. There are different possible outcomes why they do not work however one significant issue could be fluid thickness. If the consistency is excessively high, the pharmaceutical ink cannot move through the printer head. At that point, if the thickness is excessively low, the pharmaceutical ink will come out of the print head even when it should not do so. There is no acknowledged data why it is so hard to print with piezoelectric printers (Mueannoom, Srisongphan, Taylor, Hauschild, & Gaisford, 2012; Prasad & Smyth, 2016).

1.6 Parameters to be considered during inkjet printing

Inkjet printing process is divided into three parts they are drop formation, drop impact and spreading and lastly drying of the droplet. For preparing pharmaceuticals in most of the drop on demand printing, piezoelectric actuation is used because thermal one needs vapour pressure or volatile elements. Moreover, drop formation being a critical process depends on many factors such as density, surface tension and fluid viscosity (Edinger, Jacobsen, Bar-Shalom, Rantanen, & Genina, 2018; Kolakovic et al., 2013).

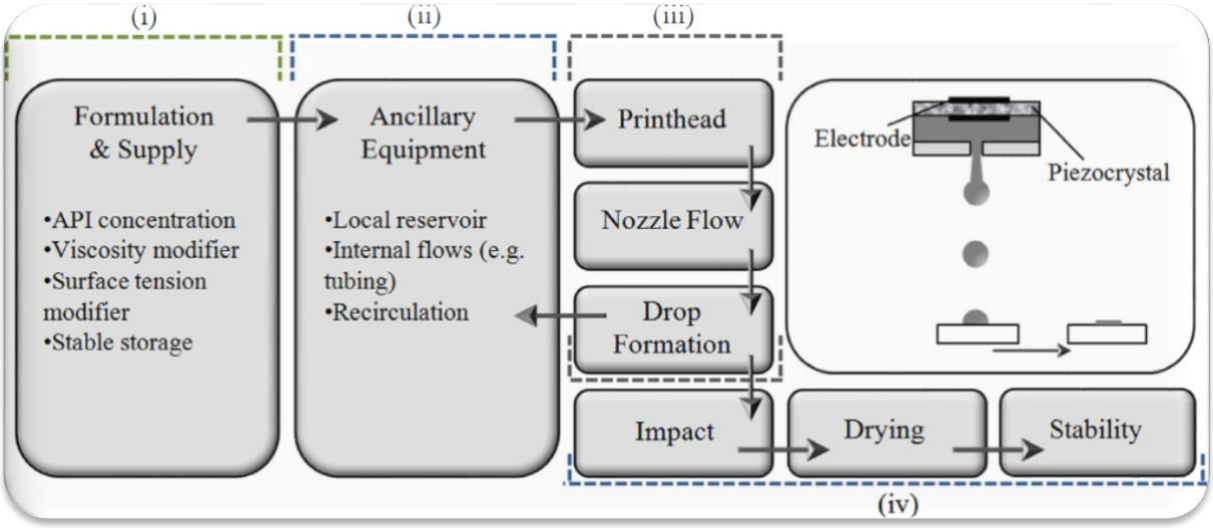

Figure 13Lifecycle of ink en route to printing (Palem, Gannu, Doodipala, Yamsani, & Yamsani, 2011)

(i) Formulation and supply to, (ii) Flow through ancillary equipment (iii) Transfer from print-head via nozzle to surface, (iv) Drop impact, drying and stable product formation.

While a suspension is used as the ink then some other factors need to be considered like suspension stability, effect on fluid rheology and particle size (Prasad et al., 2016).

The separation from nozzle to substrate is known as the standoff separate. This separation is generally limited to diminish the impacts of ecological wind current on bead direction; nonetheless, this esteem ought to likewise be adequate to permit appropriate drop development. Normally, a standoff separation of 2– 3mm is utilized with piezoelectric incitation (Raijada et al., 2013).

Drying or solidification has great effect on the behaviour of the final printed product. Drying usually happens through the evaporation of solvent so the selection of the solvent depends on the rate of evaporation of the solvent. By using ink tactically, the production efficiency of poorly soluble drugs can be enhanced in low doses and in very small volumes. Though the recrystallization from the print head fluid has an effect in the dosage form and their release pattern (Alomari et al., 2018).

Binder concentration is very crucial for the strength of the final product as increase concentration can lead to less porosity and enhances strength, though above 40% concentration structure distortion has been observed (Govindasamy, Kesavan, & Narasimha, 2013).For this reason, properties of the fluid used in the ink need to be supervised. Moreover particle soze is another factor that can have effect on the binder allocation and consequently final product's strength and porosity (Meléndez, Kane, Ashvar, Albrecht, & Smith, 2008b).

Usual layer thickness for inkjet printing can be in between 50-200 mm, thus mean particle size is conferred to be 50-150 mm (Lee, Samson, & Song, 2018; Meléndez et al., 2008a)

1.7 Characterization challenge of printed drug

Characterization of the printed dosage form is one of the main challenges of producing pharmaceuticals inkjet products due to the small sample requirements. Spatial characterization of the printed doses at nanometric scale and some classic techniques like DSC and XRD is required many times. Though a large variety of techniques have been utilized for the characterization of the printed drugs by using various methods (Li et al., 2018)

Atomic Force Microscopy (AFM) is one of them, which has been broadly utilized to figure out the crystalline characteristic of the product and for the identification of any phase partition of the materials. Furthermore, by using localized thermal analysis techniques such as scanning thermal microscopy, Nano-thermal analysis and transition thermal microscopy, thermal properties of the printed drugs are usually examined (El-Mahrouk, El-Gazayerly, Aboelwafa, & Taha, 2014; Uddin et al., 2015).

1.8 Applications of inkjet technology in bio-medicine new

New advancements, for example, IJP are being investigated to change the pharmaceutical production process and the start to finish production network. This is can be halfway ascribed

to the costly research costs, high-hazard, and capital-escalated scale-up in customary brought together clump fabricating (Daly, Harrington, Martin, & Hutchings, 2015). IJP, as a flexible strategy, has numerous applications in drug. Mammalian cells have been printed effectively utilizing this procedure (Mironov et al., 2006). This system has a potential use in medication advancement where it very well may be connected in medication screening and arrangement of pharmaceutical co crystals .Inkjets can likewise be utilized in clinical settings in the planning of customized medications for patients. Buanz and collaborators utilized the strategy to get ready customized dosages of salbutamol sulfate on oral movies (Buanz et al., 2011). IJP has applications in biomedical gadget fabricate. Orthopaedic specialists have replaced lost appendages with prosthetic appendages made by ink streaming. Medical devices with against bacterial properties have likewise been manufactured utilizing IJP. These were, notwithstanding, delivered utilizing the further developed three-dimensional (3D) printing procedure (Mertz, 2013, Sandler et al., 2014). In 3D printing, consecutive layers of material are stored and objects of any shape or geometry can be made. A PC helped structure show is utilized in the creation; numerous 3D printing innovations exist including stereo lithography, sintering, softening, and intertwined affidavit demonstrating (Borges, Silva, Coelho, & Simões, 2015).This printing innovation has been utilized in different territories of prescription including creation of tablets just as changed discharge drugs. IJP has been utilized in miniaturized scale molecule printing. Without excipient salbutamol sulfate and terbutaline sulfate for inward breath have been effectively planned by ink streaming into fluid nitrogen to create solidifies dried permeable particles. This generation procedure was a generally simplified approach contrasted with splash drying or micronization. thin film covering of restorative gadgets is another utilization of IJP. Moderate discharge dynamic pharmaceutical fixings (API's) can be connected to surfaces precisely. Coronary stents, for instance, expect coatings to guarantee immunosuppression and avoid coagulation and

obstructing. Microneedles – limited needles of the request of microns with lengths up to 1 mm which can puncture through the stratum corneum, however won't enter sufficiently profound into the skin to invigorate nerve receptors – have additionally been covered by means of ink streaming for transdermal conveyance of actives. Anticancer specialists like 5-fluororacil, curcumin and cisplatin have been exhibited for transdermal conveyance after ink streaming. Insulin microneedles have likewise been covered by means of inkjet printing (Preis, Breitkreutz, & Sandler, 2015a; Wening & Breitkreutz, 2011).

1.9 Advantages of inkjet printing

A crucial preferred viewpoint got from the utilization of IJP is the modest idea of inkjet printers. The bunch of uses to which these printers can be put and the generally minimal effort makes the innovation great incentive for cash – some inkjet printers cost as meager as £20. The ink jetting strategy has been portrayed as modest, yet, one that manages incredibly fine control of fluid droplets (Buanz, Belaunde, Soutari, Tuleu, & Gul, 2015).The capacity of some inkjet printers to work with as meagre as 20 µL of 'ink' makes the system valuable in medication revelation. Researchers can get results with minimal material, particularly, when materials being examined at this stage are constrained. Additionally, on the grounds that materials are conveyed precisely where they are required, there is less wastage of materials (Allain et al., 2004, Derby, 2008). IJP, as a non-contact strategy, offers the additional preferred standpoint of decreased contamination as the print head and the substrate don't collaborate physically. This, in the long run, prompts more work being done inside a given time as a purification procedure is decreased for most methodology (Ferris et al., 2013, Daly et al., 2015, Scoutaris et al., 2016c). IJP gives a high-throughput choice to leading logical investigations. The speed of the system enables a more extensive scope of concentrates to be directed inside a brief period. This is of significance in medication screening and improvement (Lemmo, Rose, & Tisone, 1998). Reproducibility of test volume is likewise

ensured under controlled conditions. With IJP being a mechanized system combined with the heartiness of ink jetting, the danger of blunders is decreased since the sum stored is steady, given the print head is in a decent condition. Inkjets have been depicted as economical robots that can constantly apportion minute measures of development factors and different proteins and even entire cells, in any example, inclination, or matrix that can be drawn (Montenegro-Nicolini et al., 2018; Scoutaris, Chai, et al., 2016).Inkjets have been accounted for to convey Pico litre droplets with a positional precision under 30 μm (Cook, Wang, & Derby, 2010; Cook et al., 2010).

1.10 Challenges of inkjet printing

The primary test related with the utilization of thermal inkjet printers is the hindering of the nozzle of the cartridge. The nozzle is essential, particularly in thermal inkjet printers, due to its role in droplet formation. Blockage can happen through drying of the 'ink' at the nozzle prompting either total or fractional blockage of the cartridge. Additionally, the salts found in culture media and physiological arrangement can likewise store at the nozzle and bring about obstruction (Lemmo et al., 1998). To limit the impact of this test, a few analysts incorporate ethylene dopamine tetra-acidic corrosive (EDTA) to their formulations as a result of its chelating properties. In spite of the fact that this methodology broadens the lifetime of the cartridge print head, the effect on cell suitability isn't known. Sonicating cartridges in water after use likewise helps clear blockages (Edinger, Jacobsen, et al., 2018; Verkouteren & Verkouteren, 2011). Another test presented by IJP is the confinement in dose creation. In spite of the fact that, IJP empowers on-demand producing and the adaptability of tailor-production prescriptions to suit patients' needs. It works best for exceptionally strong and little dosed formulation (Buanz et al.2011) required an expansive surface territory (13 – 26 cm2) to achieve the required measurements of salbutamol sulfate at the most astounding possible medication loading. Guaranteeing repeatable droplet arrangement is another test

particularly with pharmaceutical printing (Lemmo et al., 1998). A slight change in excipient may affect bead development. This can be checked by enhancing print settings and ink formulation. Printing under controlled situations likewise guarantees droplet reproducibility since it controls bead in-flight deviation because of streamlined impacts which can result in poor positions (Boehm, Miller, Daniels, Stafslien, & Narayan, 2014b; Cook et al., 2010; Daly et al., 2015; Mandeep, Rana, & Nimrata, 2013).

1.11 Inkjet Printing of Proteins

Peptides and proteins symbolize to a promissory gathering of particles utilized by the pharmaceutical business for medication treatment with incredible potential for progression. In any case, the administration of these molecules shows an evolution of challenges, making important the investigation of new choices like the buccal route of administration to enhance medicate treatment consistence (Tappa & Jammalamadaka, 2018). Drop on demand printing method has showed favourable results for smaller drugs but it couldn't exhibit much progress on introducing a proper delivery systems for biologics such as proteins and peptides. Along these lines, to survey the practicality of utilizing a thermal inkjet printing framework for dispensing lysozyme and ribonuclease-An as model proteins. To address the ingestion obstructions of a potential buccal use, a permeation enhancer (sodium deoxycholate) was likewise examined in details. They found that a customary printer effectively printed the two proteins, displaying high printing effectiveness (Montenegro-Nicolini et al., 2017).Besides, the protein structure was not influenced and minor impacts were seen in the enzymatic action after the printing procedure. Taking everything into account, it gives proof to the utilization of an economical, simple to utilize, solid, and reproducible thermal inkjet printing framework to dispense proteins solutions for potential buccal application. The examination essentially adds to show an option for assembling biologics conveyance frameworks, with prominence in buccal applications. Subsequent stages of improvements will be gone for the utilization of

new materials for printing, controlled discharge, and insurance methodologies for proteins and peptides (Boehm, Miller, Daniels, Stafslien, & Narayan, 2014a; Montenegro-Nicolini et al., 2017).

1.12 Inkjet Printable Nano medicines: the future of customized drug delivery

The acquaintance of printing advances with develop medication and different pharmaceuticals incorporates printing as optional manufacture technique for dose structures and medication conveyance frameworks and cell-based developments for diagnostics, embeds and notwithstanding for potential organ substitutions. The upsides of printing advances for various applications lay close by; printing empowers adaptable, quick and individual answers for numerous applications (C. C. Yu et al., 2016). It isn't just conceivable to print fluid materials onto surfaces (2D), yet in addition to fabricate 3D builds. A printing framework utilizing dynamic pharmaceutical fixings (APIs) opens up chances to create custom-made and redid tranquilize conveyance frameworks for individual patients. In spite of the fact that promoted items are yet to be set up, increasingly customized restorative items are advantageous specifically for unique patient gatherings (Lee et al., 2018; Rana, 2016). These incorporate for example the older, who frequently face multimorbidity and organization issues; and furthermore others, for example, youngsters. Since most of dynamic pharmaceutical fixings and, particularly new synthetic substances (up to 90%) have poor dissolvability, the exploration network around there is keen on beating solvency issues by utilizing new innovations. Consolidating an inkjet printing and medication nanonization method has been portrayed in ongoing writing, and besides, the utilization of nanosuspensions as inks has been effectively exhibited (Cheow et al., 2015). In these cases, the API itself has been planned as a nanosuspension, yet certain focal points could be normal by consolidating the API into a nanocarrier that is hence detailed into an ink, yet this is as yet

a moderately unexplored zone (Guillet, Flahaut, & Golzio, 2017; Hauzenberger et al., 2017; Luo et al., 2016; Preis, Breitkreutz, & Sandler, 2015b).

It ends up evident that the use of printing advances for prescription requires the improvement of exclusive expectation appropriate materials, which continue the procedure itself, yet additionally support keeping the dynamic fixings stable. Here, nanotechnology, that is, utilizing nanoparticle frameworks for either diagnostics or conveyance seems promising in such manner. Nanoparticles have been broadly investigated as medication conveyance frameworks for the most part went for parenteral organization in suspension structure, and a portion of the perceived favourable circumstances could be very much abused for printed definitions (Preis et al., 2015b). Exemplification of dynamic fixings into nano carriers is pointed toward improving the steadiness and dissolvability of the medication, shielding the medication from the earth (brutal pH in the GI tract, metabolic catalysts, and so forth, advancing adequate maintenance of the API inside the transporter all through the conveyance procedure lastly giving continued, controlled or even upgrades responsive discharge, especially at the objective site. Intersection of natural boundaries and cell take-up just as controlled intracellular dealing and discharge can likewise be promptly given by the nano system, if pertinent for the planned application. Thus, exact dosing of exceptionally strong, inadequately solvent medications or delicate biomolecules would increase clear advantages from being figured as nano-inks (i.e., API epitomized in a nanocarrier) (Kolakovic et al., 2013; Preis et al., 2015a).

1.13 Transdermal patches by inkjet printing

Conveyance of medications through the skin offers an appealing option in contrast to oral conveyance of medications because of its points of interest, for example, by-pass of the liver's first pass impact, decrease of pill load and enhanced patient compliance. The primary transdermal framework was produced in 1979, as a 72 h supported discharge fix to convey

scopolamine for hostile to movement disorder. Between year 2003 and 2007, another transdermal conveyance framework is endorsed each 7.5 months. It is assessed that more than one billion transdermal patches are at present made each year (Tabachnyk et al., 2016) Most of the current transdermal patches are manufactured as a solitary layer or different layers fix. A few techniques for manufacture exist today, for example, free film or roundabout Teflon form strategy. Covering of microneedles is likewise in fact testing particularly regarding keeping a known measure of medication onto the needle.3D printer with a piezoelectric driven material streaming capacity permits de-position of explicit measure of medication arrangement onto existing microneedles. Aside from precise dosing, it likewise enabled client to hold the supe-rior mechanical quality of existing microneedles, for example, that of metal microneedles.Utilizing a 2PP printer, which is as of now the most elevated goals printer, Gittard et al. and Doraiswamy et al. shown the manufacture of microneedles, which have very fine tip that permits great entrance of skin and conceivably cell focused on conveyance because of its Nano size (Karki et al., 2016; Lim et al., 2018; Pere et al., 2018).

Table 1Patented inkjet printing pharmaceuticals:

Article name	**inventor**	**Patented by**	**Drug type(delivered)**
System and methods for administering bioactive compositions	Christopher vitello Stephen welkley Andrew evans John greeven	United states of America	
Pharmaceutical form for oral administration of a highly controlled and stable dose of	Javier Octavio Morales Montecinos Miguel Montenegro Nicolinifelipe Aaron Campano	European patent Office	Nanoparticles or bio macromolecule

Article name	**inventor**	**Patented by**	**Drug type(delivered)**
nanoparticles or bio macromolecule suspensions	Hantscheruk		
System and a method for producing layered oral dosage forms	Iddys Figueroa Orlando Ruiz	United states of America	Oral medication
Inkjet Printing of Tissues and Cells	Tao Xu James J. Yoo Anthony	United states of America	Tissues and cells

Table 2Articles list with techniques and outcomes on inkjet printing of pharmaceuticals (for last 5 years)

Article name	**Author year**	**Drug used**	**Technique used**	**Result**
Inkjet printing-based photo-induced electron transfer reaction on parchment paper using riboflavin as a photosensitizer.	Annie Agnes Suganya Samson et all_2018	Dismutase	Inkjet printing	more competent to determine the radical scavenging potential of natural plant products.
Inkjet printing of paracetamol and indomethacin using electromagnetic technology: Rheological compatibility and polymorphic selectivity	Gayathri Kollamaram et al_2018	Paracetamol and Indomethacin	Inkjet printing	Suspension ink along with hy-droxypropyl cellulose gives good adhesive property of the drug indomethacin on HPMC focuses the requirement of customizing the binder.
Combining inkjet printing and amorphous nanonization to prepare personalized dosage forms of poorly-soluble drugs	Wean Sin Cheow et al_2015	Ciprofloxacin	Inkjet printing	Ostwald ripening growth, super saturation generation competency and high colloidal stability are not exhibited by amorphous drug nanoplex,and make it model for using.
Inkjet printing of PCL nanoparticles and cyclodextrin inclusion	Cem Varan et al_2017	Cyclodextrin and PCL nanoparticles	Inkjet printing	expansion of antiviral or anticancer drugs combination for

Article name	Author year	Drug used	Technique used	Result
complexes on bio adhesive film for cervical administration				mucosal administration can be printed by this technology
Application of a handheld NIR spectrometer in prediction of content of drug in inkjet printer orodispersible formulations containing prednisolone and levothyroxine.	Hossein Vakili et al_2017	Prednisolone and levothyroxine	Inkjet printing	Square shaped units of 4 cm^2 were printed in different resolutions to achieve an escalating drug dose by highly accurate and uniform displacement of droplets in Pico liter range from the print head onto the substrates
Continuous inkjet printing of enalapril maleate onto orodispersible film formulations	Thabet Y, et al_2018	Enalapril maleate	Inkjet printing	A more related therapeutically fixed dose combination was obtained by printing on HCT ODFs

1.14 Supervisory considerations

The US Food & Drug Administration (FDA) has described varieties of considerations which includes different types of development phases along with production Process, Process validation, Semi- finished & finished device testing for the manufacturing process of both Additive and inject printing. In the drug discovery & application the whole process of using inject bio printing technology can be characterized in the following steps-

Designing consideration-, several steps are required for building up a device. FDA recommends making a flow diagram that will be summing up all the steps from initial device design to final device. Moreover, to have a better impression regarding the suitability of this process to have desired application FDA recommends to make a comparison among the required resolution & feature size of final finished device to the minimum possible feature size of the available inkjet printing process & manufacturing tolerances that is associated with. These will be helpful in all other phases while developing the products and analyses the Possible failure of the device (Daly et al., 2015).

#Material control- The accuracy & the functionality of the Process and the bioprinted structure highly depends on the raw materials being used as it has important role in changing physical and biological properties as well. For the assurance of the consistency for both the raw material & final Product. According to the FDA, manufacturers must keep documentation for the feedstock materials, suppliers of materials, specifications of incoming material, and certificates of material analysis. However, FDA also suggests to describe the process of material's reuse if the materials are being used in the process of bio printing technology. There are some parameters for the specification of the document, for fluids the parameters are viscoelasticity, pot life & viscosity. For polymer or monomer parameters are composition, purity, molecular formula & weight, molecular weight distribution, water content, chemical structure, glass transition temperature, crystallization point and melting point (Lim et al., 2018).

Validation of process- According to the FDA regulation critical analysis is required for parameters such as, Bio printing process, process step &Feedstock materials to ensure the quality of printed feature. Moreover, if there is any kind of changes in manufacturing or materials revalidation is must (Azizi Machekposhti et al., 2019).

Post processing- Based on FDA recommendation, all the steps of post processing & there effects on the final Structure should be documented as post processing technique have impact on the accuracy and resolution of printed feature (Azizi Machekposhti et al., 2019).

1.15 Aim of the project

The aim of this study is to highlight the suitability of Thermal inkjet printing as a novel manufacturing technology by focusing its application in printing of proteins and poorly soluble drugs, low dosage medication and the parameters required for successful printing.

Chapter 2

Methodology

Renowned journals, published research papers and research databases such as Science Direct PubMed, Scopus, Academic Search, and Web of Science etc. have been searched to collect information regarding inkjet printing. Searches were also performed with filters and specific MeSH terms. Information was also gathered from official sites and a book.

I have gone through all the articles for writing a review on the thermal inkjet printing technology along with focusing the other film formulation techniques, because administration of drug through this delivery system has emerged as a new incentive for developing drug delivery system. From around 70 articles regarding inkjet printing technology associated with different dosage form delivery, I have sorted out all of them to focus on the outcome of this immense emerging technique, to give an insight.

Chapter 3

Discussion

Buanz *et al.* Revealed that numerous studies have discussed regarding the formulation of single drugs on different substrate, following the deposition of very potent drug (salbutamol sulphate; 40 μg/cm2 per print pass) on the edible potato starch film. then a narrow therapeutic index drug, theophylline appropriate for child (2-12yrs old) was printed by Sandler *et al.* (Sandler et al., 2011). In a description it was mentioned that for the treatment of hypothyroidism, a ODFs (orodispersible film) of T4 was being printed by using piezoelectric inkjet printing method (Kalyan & Bansal, n.d.; Karki et al., 2016; Mahboob, Riaz, Jamshaid, Bashir, & Zulfiqar, 2016; Vakili et al., 2017; Varan et al., 2017). A key advantage of the TIJ is that it can deposit different solutions to make dose variation which has been used by Wickström *et al*. to make a ODF of Vitamins B1, B2, B3 and B6 combinations. Though for this a multi component solution was made first and then dispensing of the vitamins occur as per their ratios. Therefore, this method cannot change the doses of vitamins individually.in addition, a description of Kollamaram. *et al.* mentioned the inkjet printing of two distinct drugs (indomethacin and paracetamol)(Kollamaram et al., 2018; Pere et al., 2018; J. Yu et al., 2017).

For formulating combinations of doses, different solutions are individually dispensed from individual cartridges, this idea has been used to prepare bioadhesive films of two anticancer drugs indicated to be used for cervical local application (Edinger, Jacobsen, et al., 2018; Takala et al., 2012; Varan et al., 2017).

Though printing of different layers by numerous cycles can lead to the distortion of the substrate and damage of the drug, for overcoming this problem a study proposed the Y-value concept which allows to print large amount drugs in one cycle and that too reduce risk of

distortion along with maintained dose accurately (Alomari et al., 2018). Inkjet printing plays a vital role in drug development by helping in screening of different candidates formulation and also provide high throughput. Thus Scoutaris et al. utilize this technique to screen various drug loads for a felodipine-PVP formulation using thermal analysis,ATR-IR, and confocal Raman microscopy in order to find out the homogeneity and crystalline characteristic of the printed drugs.in which the outcomes were constant in small scale screening and ensure the acceptance of inkjet printing for formulation (Acosta-Vélez, Linsley, Craig, & Wu, 2017; F & Velez, 2016; Kyobula et al., 2017b; Zheng et al., 2011). Being a technological attraction, inkjet printing is also used for preparing mono dispersible particles, especially Drop on demand method gives a way to dispense polymer on the substrate in way so that a uniform microsphere can be prepared, which allows extensive particle size control compared to conventional production techniques. Microspheres are newly demandable because they provide good control of drug release profile and of duration. Printing technology also offer an alternate to fabricate of micro particles for the development of inhalation dosage form with greater effectiveness and consistency (Buanz et al., 2015; Buanz, Telford, Scowen, & Gaisford, 2013; Edinger, Jacobsen, et al., 2018; Gao et al., 2015; Prasad & Smyth, 2016).

Despite the fact that TIJ is a high-temperature aerosolization framework, it has been demonstrated that formulations can be readied that will enable labile proteins to be exposed to the aerosolization conditions without limiting of their structure or activity. It has similarly been demonstrated that the innovation can be designed to make a respirable aerosol, permitting the further improvement of the innovation for pneumonic medication delivery (Dodoo, Alomari, Stapleton, & Gaisford, n.d.; Vuddanda et al., 2018b; J. Yu et al., 2017).

For creating a digital aerosol inhaler for the inhalation of therapeutics for both by local and systemic route, TIJ is being used extensively, though this technique requires high temperature generation and vaporization of the ink to form the drops, still by conducting a thorough study

for developing drug formulation for permitting the production of therapeutic proteins containing aerosols except degrading the proteins by using inkjet printing. Human growth hormone protein and insulin protein were being formulated and aerosolized. After assaying the physiochemical and biological properties of the aerosol of the proteins, earlier and later of aerosolization, no noteworthy alteration was detected for this process of aerosolization, giving testimony of the use of this TIJ method for aerosolization of protein therapeutics (Goodall, Chew, Chan, Auriac, & Waters, 2002a).

At the end of the day, the inkjet LbL (layer by layer) framework has the value of having the option to control stereo complex development by changing the total cycles. In any case, one drawback of inkjet frameworks is the evaporating of the solvent system, which causes blockage of the head. It happens as often as possible bringing about uneven release and more often collapsing of LbL film creation. Conversely, being more stable the aqueous system was used for inkjet printing and for this in the experiment they extended the PLA streocomplex in aqueous medium through a block of copolymer with the hydrophilic moiety. Here PEG has been taken as the block polymer for its biocompatibility. The fact remains that the use of heat may become a threat for decomposition of many compounds like biologics. Though, from the evidence of many studies it is proven that peptides and proteins exhibit less or not at all degradation in case of thermal inkjet printing, this is because of exceedingly short heating time and further discharging of the drop (Buanz et al., 2011; Goodall, Chew, Chan, Auriac, & Waters, 2002b; Montenegro-Nicolini et al., 2017, 2018; Vuddanda et al., 2018a).

Printing systems were observed to be fruitful for evaluating PET response on non-created surface, which was viably accomplished by utilizing four-to five-, arranges less response volume as compared to other technique. In this manner, this inkjet printing based estimation comprises an effective endeavor to contemplate photochemical-based free extreme scrounger examination. The outcomes got without bright light affirm that nonlinear and inconsequential

sign were delivered in both printing and well-plate strategies. The benefits of this detailed technique incorporates a lesser example utilization and a shorter examination time, just as a superior cost viability and a sensational minimization of work escalated steps. Especially, these issues are basic in the medication disclosure process. This inkjet printing-based PET examine exhibits the reasonable utilization of a traditional four-cartridge inkjet printing framework as a summed up stage for assessing free radical rummaging action of mixes on the non-manufactured paper surface (Tabachnyk et al., 2016; Thabet, Sibanc, & Breitkreutz, 2018).

Inkjet printing has shown potential for orthopedic implants to be coated with antibiotics to inhibit bacterial proliferation. At this time, coating cover the entire surface of the implants and considerably delay and interfere with the Osseo implementation until the coating have been dreaded for several months. By disparity, standard hydroxyapatite (Hap) and phosphate calcium coatings, designed and used initially for their osteo-conductive behavior, also have very constrained monitored ability to free antibiotics. As for example, antibiotics can be loaded on porous bio-mimetic appetite coatings. However, these techniques of delivery usually show original bursts followed by very low release rates in due course antibiotic depletion within several hours (El-Mahrouk et al., 2014; Preis et al., 2015a).

An inject printing method was created to overcome the drawbacks, to generate micro-patterns consisting of biphasic calcium phosphate (BCP) nanoparticles and rifampicin (RFP) nanoparticles dispersed in a biodegradable matrix of poly (D, L-lactic–co-glycolic) acid (PLGA). The character of the RFP nanoparticles is to ensure sustained release of antibiotics over a few weeks and permit killing bacteria close to the alloy implant surface preventing the formation of Staphylococcus epidermidis biofilm colonies (Govindasamy et al., 2013) At the same time, the micro-patterned titanium alloy surface, new bone tissue is expected to grow explicitly and fast by reason of

a) the osteo-conductive properties of the Ti alloy surface
b) availability of calcium phosphate required to recruit and mineralize osteoblast cells and
c) the micro scale dimensions of the patterned features (scoutaris,2016)

Inkjet printing has discovered floor in tissue engineering and regenerative medications' where cell-based 3D bio printing has been used. By depositing various cell types, in particular, 3D tissues can built that can resemble and replace eventually real living tissues contributing to manage the storage of organ donors (Langer R, Vacanti JP, 1993). Bio-manufacturing approaches currently require the deposition of cells at specific locations at high spatial resolution that can be attained using standard deposition approaches. During the printing of 3D structures, there has been a lot of disapproval about the cell viability owing to the shear forces exerted. Researchers have shown that most of the cells remain active and in good physical shape, while there are no significant differences between printed and non-printed cells in apoptosis (Luo et al., 2016).

In terms of inkjet printing technology for bio-printing devices, thermal inkjet printers are preferred relative to piezoelectric print heads due to sheer frequency of vibration which might lead to disruption of the cell membrane. In thermal inkjet printing the local nozzle temperature is raised up to 300°C and duration of the cell printing can be done in few microseconds. Consequently, the ejected mammalian cells are heated for only 2μs with a temperature rise of 4–10°C above ambient follow-on an average cell viability of 90 per cent. However, there is distributed work affirming great cell feasibility when piezoelectric gadgets were utilized (Ajiro et al., 2015; Nagaraju et al., n.d.; Thabet, Lunter, & Breitkreutz, 2018).

A study compared and contrasted some mechanical and physical properties of oral films, which were prepared with TIJP, and solvent casting respectively. They chose a low therapeutic index drug, clonidine and cellulose polymers were used for making the films. By

evaluating the mechanical testing it was showed that the new printed film had alike tensile strength and young's moduli values like free film, but casted films were considerably fragile. Stress testing showed that the casted films are crystalizing out while the printed one persisted unaffected. Due to the fast disintegration of the polymer used, dissolution properties were same for both of them. They came to the decision that printing films are better films than the casted one as the drug remains on the film not in the film, so as to give plasticity impact (Acosta-Vélez et al., 2017; Buanz et al., 2013; C. C. Yu et al., 2016).

With regards to customized prescriptions, TIJ could be utilized to print an assortment of individualized doses onto a consumable substrate, for example, orodispersible films (ODFs). This idea was exhibited by Buanz. et al., whereby a profoundly strong medication (salbutamol sulphate; 40 μg/cm2 per print pass) was imprinted onto a palatable potato starch film (Buanz et al., 2011). Nonetheless, financially accessible TIJ printers are just ready to store exceptionally low dosages (around a limit of 35 μg/print cycle). So, this innovation is as of now reasonable for planning very strong medications .This gives a test when endeavoring to detail restricted restorative list tranquilizes that commonly require dosing inside the milligram go, for example, warfarin. Scientists have been tried to expand medicate deposing by means of various methodologies, such as by utilizing different printing cycles (Edinger, Jacobsen, et al., 2018; Genina, Fors, Palo, Peltonen, & Sandler, 2013) and higher feed fixations (Raijada et al., 2013). Be that as it may, challenges encompassing non-linearity of medication testimony and crystallization of APIs were found (Vuddanda et al., 2018a). For broadening the utilizations of TIJ, obviously a novel technique to expand the measure of medication is needed. In that capacity, this investigation depicts the adjustment of a business TIJ printing framework to plan modified warfarin ODFs (up to milligram measurements). The subsequent ODFs were portrayed and assessed for medication substance and strength (Alomari et al., 2018; Montenegro-Nicolini et al., 2018).

Biologics samples, for example, cells and anti-toxins were imprinted on various substrates by a changed business TIJP. It demonstrated that live bacterial cells can be dependably kept to exact positions on a structured surface, making it conceivable to make denser cell array and sophisticated design in a completely computerized and reproducible way (Pere et al., 2018) For instance, for application, anti-infection arrangements were taken as bio-ink for antimicrobial examines. The accuracy of inkjet printing innovation was estimated and demonstrated to be sufficiently high even contrasted with the customary cup plate dispersion strategy (Tabachnyk et al., 2016).By means of the flexible print setup, including shading and dark scale, it was effectively decided the intensity of amikacin. Here, the different layer inkjet printing strategy were presented and combined with slope printing for the affirmation of microbes and anti-infection agents, and after that built up a novel methodology for an antimicrobial vulnerability test and anti-microbial MIC assurance. This new technique has potential applications for the assessment of novel medications and assurance of lethal synthetic compounds. In a word, with trademark points of interest of inexpensiveness, comfort, expediency, full mechanization, and high accuracy, inkjet printing innovation could be an incredible asset to be connected in genomics, biosensors, tissue designing, and medication exposure (J. Yu et al., 2017; Zheng et al., 2011).

Inkjet printer Nano drug on consumable permeable substrate was effectively arranged and described unexpectedly for possible use as customized measurement types of ineffectively dissolvable medications (Tappa & Jammalamadaka, 2018).amorphous medication nanoplex, that showed very limited inclination toward Ostwald maturing development, great colloidal strength, and supersaturation age capacity, was utilized as the Nano suspension ink at two distinct shapes. An ideal ink for printing was methodically resolved to be of 0.25% (w/v) nanosuspension focus within the sight of 5% (w/v) PEG 8000. Inkjet printing of the Nano suspension ink was observed to be practical till the fluid acceptance edge of the substrate (for

example 3.33 lL/cm^2) beyond which the HPMC-substrate broke down because of unreasonable springing. While the reachable portion of the printed nano drug could be expanded by means of expanding, beads quantity administered, precise relationships between the feasible portion and the quantity of drops apportioned were not set up for the two Nano plex sizes. These outcomes alluded to the presence of spatial non-homogeneity in the Nano plex suspension focus free of the nanoparticle measure (Samson et al., 2018) By and by, the utilization of the littler noncomplex as the Nano suspension ink reliably brought about a greater payload, with the payload of 2.5 lg/cm^2. In spite of the nonappearance of careful relationships between the reachable portion and the quantity of beads administered, the payload was found to show tasteful clump to-cluster dose consistency (%CV < 6%) indicating the consistency of the method. In conclusion, it was discharged unreservedly from the substrate and the non-cytotoxicity of the drug was effectively settled. The forthcoming heading of the exploration will be to build up a permeable print substrate having a higher fluid take-up limit that will allow us to expand the payload to restorative portion (Borges et al., 2015).The advancement of better print substrates is vital as expanding the payload by bringing the Nano suspension focus up in the ink is less inclined to prevail because of physical confinements of the inkjet printing process(for example spout blockage at higher suspension fixation). At the end, readiness of print substrates arranged by crosslinking of polysaccharides which has high swelling limits is as of now progressing in our research facility (Cheow et al., 2015; Kalyan & Bansal, n.d.).

Categorical innovations and inkjet challenges have been presented; while there is at present a different writing on the point, there are two key factors that ought to be considered as the network move ahead. Initially, as there are restricted combinations of excipients, bearer liquids and APIs, a characterization approach ought to be investigated dependent on the fundamental API science to empower a progressively reasonable correlation of research

discoveries and viable interpretation to assembling. Also, and considerably increasingly basic to the eventual fate of the pharmaceutical inkjet printing vision, examine must start to consider at a prior stage the exact generation is focused on (Goodall, Chew, Chan, Auriac, & Waters, 2002c). The investigation of details related to a proper print head is fundamental in light of the distinctive definition and streaming parameter necessities related with every gadget. This audit has joined the fundamental research difficulties with the assembling and business reviews. The patterns distinguished here will ideally empower the world to drive a fast, engaged and coherent interpretation of pharmaceutical inkjet printing to the assembling scale (Clark et al., 2017; Mandeep et al., 2013; Verkouteren & Verkouteren, 2011).

The capacity of electromagnetic (valve jet) inkjet printing for the deposition of pharmaceutical formulations included a wide variety of particle sizes more than 2 μm and viscosities, has been confirmed by using hydroxypropyl cellulose (HPC), paracetamol (PML) and indomethacin (IND) as typical inks. The manufacturing and printing requirements of the used inks are usually material specified as well as they need to be calibrated on the basis of the physiochemical characteristics of APIs which are on observation. A more thorough study revealed that using of solution ink might give effect on the rheology of the substrate and its relation in post printing state of APIs solid-state changes (Boehm et al., 2014b; Hoath et al., 2014).

Chapter 4

Conclusion

Three-dimensional printing has turned into a valuable and potential device for the pharmaceutical sector, leading to customized prescription concentrated on the patients' needs. It offers various advantages, such as expanding the cost proficiency and the assembling speed, since a RP should be possible in only minutes. In any case, there is as yet a critical hindrance to guarantee that 3D printed meds have a similar viability, wellbeing, and security as the pharmaceuticals routinely made by the Pharmaceutical Industry. With respect to foundation of rules, laws, quality frameworks and wellbeing of utilization and utilization of 3D printed medications, it is an extraordinary test for the administrative experts involving incredible hindrances, given the conventional necessities by the pharmaceutical sector. However, the point of view of the administrative specialists is adjusting quick to this present reality and patient's needs. The FDA created in 2016 another direction entitled "Specialized Considerations for Additive Manufactured Devices" so as to give the FDA's underlying reasoning on specialized contemplations related with AM procedures, and proposals for testing and the Bioengineering 2017, 4, 79 14 of 16 portrayal for gadgets that incorporate in any event one AM creation step. This is only the start of the unrest of medication producing procedures. This survey has analyzed the business motivating forces, current advancements and future difficulties engaged with inkjet printing of pharmaceuticals. Unmistakably this field has been being worked on for a noteworthy time be that as it may, likewise with the improvement of business inkjet printing, there have been incredible walks in understanding the hidden innovation and ink plans over ongoing years. A scope of advancements has been inspected here that empowers inkjet printing to take on a few unique jobs inside the pharmaceutical assembling inventory network, from driving fast medication disclosure to

creation of materials for medication delivery, assembling of customized prescriptions and improving item security through bundling developments.

Chapter 5

Future direction

Following are two future possibilities of inkjet printing pharmaceuticals:

- The coming of conventional measurements shapes with scarcely any, recognizing (or confounding) qualities, forces issues identified with their acknowledgment by patients. As such, end users can experience issues in distinguishing their very own prescription. IJP empowers creation of the prescription in a remarkable example of for example snappy reaction (QR) codes, that contain the medication itself and data pertinent to the purchaser (Edinger, Jacobsen, et al., 2018). A customary cell phone outfitted with a standardized identification scanner can be utilized by end-clients to recognize and follow the medicine, and by that improve medication security and adherence (Mira et al., 2015; Tseng and Wu, 2014), and limit visits to social insurance experts (Rathbone and Prescott, 2017). Another inadequacy of customary tablets or containers is their basic structure that can be anything but difficult to fake.

- Dissemination of fake drugs is an overall issue these days (WHO, 2017). Assembling of dose frames by IJP near the end-client in a novel example, e.g., scanner tag, can improve the following of medications from the assembling to the end-clients with a diminished hazard for duplicating (Preis et al., 2015). This is additionally significant for internet requesting of medications, where the instances of conveying fake medication items were identified. The scanner tag, for example, QR code or other cell phone meaningful examples, can really encode a secret phrase ensured URL that would require the way to affirm the inventiveness of medication, and offer access to the required data. The key could be sent to end clients' close to home cell phone in the wake of requesting the prescription (McGuigan, 2018). This would guarantee that

unique and right medication was gotten by the end-user (Cook et al., 2010; Edinger, Bar-Shalom, Sandler, Rantanen, & Genina, 2018).

References

Acosta-Vélez, G., Linsley, C., Craig, M., & Wu, B. (2017). Photocurable Bioink for the Inkjet 3D Pharming of Hydrophilic Drugs. *Bioengineering*, *4*(4), 11. DOI: 10.3390/bioengineering4010011

Ajiro, H., Kuroda, A., Kan, K., & Akashi, M. (2015). Stereocomplex Film Using Triblock Copolymers of Polylactide and Poly(ethylene glycol) Retain Paxlitaxel on Substrates by an Aqueous Inkjet System. *Langmuir*, *31*(38), 10583–10589. DOI: 10.1021/acs.langmuir.5b03169

Alfadhel, A., Ouyang, J., Mahajan, C. G., Forouzandeh, F., Cormier, D., & Borkholder, D. A. (2018). Inkjet printed polyethylene glycol as a fugitive ink for the fabrication of flexible microfluidic systems. *Materials and Design*, *150*(2017), 182–187. DOI: 10.1016/j.matdes.2018.04.013

Alomari, M., Mohamed, F. H., Basit, A. W., & Gaisford, S. (2015). Personalised dosing: Printing a dose of one's own medicine. *International Journal of Pharmaceutics*, *494*(2), 568–577.DOI: 10.1016/j.ijpharm.2014.12.006

Alomari, M., Vuddanda, P. R., Trenfield, S. J., Dodoo, C. C., Velaga, S., Basit, A. W., & Gaisford, S. (2018). Printing T3and T4oral drug combinations as a novel strategy for hypothyroidism. *International Journal of Pharmaceutics*, *549*(1–2), 363–369. DOI: 10.1016/j.ijpharm.2018.07.062

Azizi Machekposhti, S., Mohaved, S., & Narayan, R. J. (2019). Inkjet dispensing technologies: recent advances for novel drug discovery. *Expert Opinion on Drug Discovery*, *14*(2), 101–113. DOI:10.1080/17460441.2019.1567489

Berg, A. K., Simonsen, A. B., & Svensson, J. (2018). Perception and Possible Causes of Skin

Problems to Insulin Pump and Glucose Sensor: Results from Pediatric Focus Groups. *Diabetes Technology & Therapeutics*, *20*(8), 566–570. DOI:10.1089/dia.2018.0089

Boehm, R. D., Miller, P. R., Daniels, J., Stafslien, S., & Narayan, R. J. (2014a). Inkjet printing for pharmaceutical applications. *Materials Today*, *17*(5), 247–252. DOI: 10.1016/j.mattod.2014.04.027

Boehm, R. D., Miller, P. R., Daniels, J., Stafslien, S., & Narayan, R. J. (2014b). Inkjet printing for pharmaceutical applications. *Materials Today*, *17*(5), 247–252. DOI: 10.1016/j.mattod.2014.04.027

Borges, A. F., Silva, C., Coelho, J. F. J., & Simões, S. (2015). Oral films: Current status and future perspectives: I — Galenical development and quality attributes. *Journal of Controlled Release*, *206*, 1–19. DOI: 10.1016/J.JCONREL.2015.03.006

Buanz, A. B. M., Belaunde, C. C., Soutari, N., Tuleu, C., & Gul, M. O. (2015). Ink-jet printing versus solvent casting to prepare oral films: Effect on mechanical properties and physical stability. *International Journal of Pharmaceutics*, *494*(2), 611–618. DOI: 10.1016/J.IJPHARM.2014.12.032

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*(10), 2386–2392. DOI: 10.1007/s11095-011-0450-5

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*(6), 1031–1035. DOI: 10.1039/C2CE26519B

Cheow, W. S., Kiew, T. Y., & Hadinoto, K. (2015). Combining inkjet printing and amorphous nanonization to prepare personalized dosage forms of poorly-soluble drugs.

European Journal of Pharmaceutics and Biopharmaceutics, *96*, 314–321. DOI: 10.1016/j.ejpb.2015.08.012

Clark, E. A., Alexander, M. R., Irvine, D. J., Roberts, C. J., Wallace, M. J., Sharpe, S., … Wildman, R. D. (2017). 3D printing of tablets using inkjet with UV photoinitiation. *International Journal of Pharmaceutics*, *529*(1–2), 523–530. DOI: 10.1016/j.ijpharm.2017.06.085

Cook, C. C., Wang, T., & Derby, B. (2010). Inkjet delivery of glucose oxidase. *Chemical Communications*, *46*(30), 5452. DOI: 10.1039/c0cc00567c

Daly, R., Harrington, T. S., Martin, G. D., & Hutchings, I. M. (2015). Inkjet printing for pharmaceutics - A review of research and manufacturing. *International Journal of Pharmaceutics*, *494*(2), 554–567.DOI: 10.1016/j.ijpharm.2015.03.017

Dodoo, C. C., Alomari, M., Stapleton, P., & Gaisford, S. (n.d.). Determination of Minimum Inhibitory Concentrations using Thermal Ink-jet Printing. Retrieved from https://www.ingentaconnect.com/content/ist/nipdf/2015/00002015/00000001/art00045

Edinger, M., Bar-Shalom, D., Sandler, N., Rantanen, J., & Genina, N. (2018). QR encoded smart oral dosage forms by inkjet printing. *International Journal of Pharmaceutics*, *536*(1), 138–145. DOI: 10.1016/j.ijpharm.2017.11.052

Edinger, M., Jacobsen, J., Bar-Shalom, D., Rantanen, J., & Genina, N. (2018). Analytical aspects of printed oral dosage forms. *International Journal of Pharmaceutics*, *553*(1–2), 97–108. DOI: 10.1016/j.ijpharm.2018.10.030

El-Mahrouk, G. M., El-Gazayerly, O. N., Aboelwafa, A. A., & Taha, M. S. (2014). Chitosan lactate wafer as a platform for the buccal delivery of tizanidine HCl: In vitro and in vivo performance. *International Journal of Pharmaceutics*, *467*(1–2), 100–112. DOI:

10.1016/j.ijpharm.2014.03.049

F, G., & Velez, A. (2016). 3D Pharming: Direct Printing of Personalized Pharmaceutical Tablets. *Polymer Science*, *2*(1), 1–10. DOI: 10.4172/2471-9935.100011

Gao, G., Schilling, A. F., Hubbell, K., Yonezawa, T., Truong, D., Hong, Y., … Cui, X. (2015). Improved properties of bone and cartilage tissue from 3D inkjet-bioprinted human mesenchymal stem cells by simultaneous deposition and photocrosslinking in PEG-GelMA. *Biotechnology Letters*, *37*(11), 2349–2355. DOI: 10.1007/s10529-015-1921-2

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*(2), 488–497. DOI: 10.1016/j.ijpharm.2013.06.003

Genina, N., Janßen, E. M., Breitenbach, A., Breitkreutz, J., & Sandler, N. (2013). Evaluation of different substrates for inkjet printing of rasagiline mesylate. *European Journal of Pharmaceutics and Biopharmaceutics*, *85*(3 PART B), 1075–1083. DOI: 10.1016/j.ejpb.2013.03.017

Goodall, S., Chew, N., Chan, K., Auriac, D., & Waters, M. J. (2002a). Aerosolization of Protein Solutions Using Thermal Inkjet Technology. *Journal of Aerosol Medicine*, *15*(3), 351–357. DOI: 10.1089/089426802760292717

Goodall, S., Chew, N., Chan, K., Auriac, D., & Waters, M. J. (2002b). Aerosolization of Protein Solutions Using Thermal Inkjet Technology. *Journal of Aerosol Medicine*, *15*(3), 351–357. DOI: 10.1089/089426802760292717

Goodall, S., Chew, N., Chan, K., Auriac, D., & Waters, M. J. (2002c). Aerosolization of

Protein Solutions Using Thermal Inkjet Technology. *Journal of Aerosol Medicine*, *15*(3), 351–357. DOI: 10.1089/089426802760292717

Govindasamy, P., Kesavan, B. R., & Narasimha, J. K. (2013). Formulation of unidirectional release buccal patches of carbamazepine and study of permeation through porcine buccal mucosa. *Asian Pacific Journal of Tropical Biomedicine*, *3*(12), 995–1002. DOI: 10.1016/S2221-1691(13)60192-6

Guillet, J.-F., Flahaut, E., & Golzio, M. (2017). A Hydrogel/Carbon-Nanotube Needle-Free Device for Electrostimulated Skin Drug Delivery. *ChemPhysChem*, *18*(19), 2715–2723. DOI: 10.1002/cphc.201700517

Hauzenberger, J. R., Hipszer, B. R., Loeum, C., McCue, P. A., DeStefano, M., Torjman, M. C., … Joseph, J. I. (2017). Detailed Analysis of Insulin Absorption Variability and the Tissue Response to Continuous Subcutaneous Insulin Infusion Catheter Implantation in Swine. *Diabetes Technology & Therapeutics*, *19*(11), 641–650. DOI: 10.1089/dia.2017.0175

Hoath, S. D., Harlen, O. G., & Hutchings, I. M. (2012). Jetting behavior of polymer solutions in drop-on-demand inkjet printing. *Journal of Rheology*, *56*(5), 1109–1127. DOI: 10.1122/1.4724331

Hoath, S. D., Vadillo, D. C., Harlen, O. G., McIlroy, C., Morrison, N. F., Hsiao, W.-K., … Hutchings, I. M. (2014). Inkjet printing of weakly elastic polymer solutions. *Journal of Non-Newtonian Fluid Mechanics*, *205*, 1–10. DOI: 10.1016/J.JNNFM.2014.01.002

Kalyan, S., & Bansal, M. (n.d.). *Recent Trends in the Development of Oral dissolving Film*. *International Journal of PharmTech Research CODEN* (Vol. 4). Retrieved from https://pdfs.semanticscholar.org/474a/5da6bc5d440c13187bc7553a41188041e1d1.pdf

Karki, S., Kim, H., Na, S.-J., Shin, D., Jo, K., & Lee, J. (2016). Thin films as an emerging platform for drug delivery. *Asian Journal of Pharmaceutical Sciences*, *11*(5), 559–574. DOI: 10.1016/j.ajps.2016.05.004

Kolakovic, R., Viitala, T., Ihalainen, P., Genina, N., Peltonen, J., & Sandler, N. (2013). Printing technologies in fabrication of drug delivery systems. *Expert Opinion on Drug Delivery*, *10*(12), 1711–1723. DOI: /10.1517/17425247.2013.859134

Kollamaram, G., Hopkins, S. C., Glowacki, B. A., Croker, D. M., & Walker, G. M. (2018). Inkjet printing of paracetamol and indomethacin using electromagnetic technology: Rheological compatibility and polymorphic selectivity. *European Journal of Pharmaceutical Sciences*, *115*(January), 248–257. DOI: 10.1016/j.ejps.2018.01.036

Konta, A., García-Piña, M., & Serrano, D. (2017). Personalised 3D Printed Medicines: Which Techniques and Polymers Are More Successful? *Bioengineering*, *4*(4), 79. DOI: 10.3390/bioengineering4040079

Kyobula, M., Adedeji, A., Alexander, M. R., Saleh, E., Wildman, R., Ashcroft, I., … Roberts, C. J. (2017a). 3D inkjet printing of tablets exploiting bespoke complex geometries for controlled and tuneable drug release. *Journal of Controlled Release*, *261*(June), 207–215.DOI: 10.1016/j.jconrel.2017.06.025

Kyobula, M., Adedeji, A., Alexander, M. R., Saleh, E., Wildman, R., Ashcroft, I., … Roberts, C. J. (2017b). 3D inkjet printing of tablets exploiting bespoke complex geometries for controlled and tuneable drug release. *Journal of Controlled Release*, *261*(June), 207–215.DOI: 10.1016/j.jconrel.2017.06.025

Lee, J., Samson, A. A. S., & Song, J. M. (2018). Inkjet printing-based β-secretase fluorescence resonance energy transfer (FRET) assay for screening of potential β-secretase inhibitors of Alzheimer's disease. *Analytica Chimica Acta*, *1022*, 89–95. DOI:

10.1016/j.aca.2018.03.033

Lemmo, A. V, Rose, D. J., & Tisone, T. C. (1998). Inkjet dispensing technology: applications in drug discovery. *Current Opinion in Biotechnology*, *9*(6), 615–617. DOI: 10.1016/S0958-1669(98)80139-0

Li, L., Ma, W., Higaki, Y., Kamitani, K., & Takahara, A. (2018). Organic-Inorganic Hybrid Thin Film Fabricated by Layer-by-Layer Assembly of Phosphorylated Cellulose Nanocrystal and Imogolite Nanotubes. *Langmuir*, acs.langmuir.8b03107. DOI: 10.1021/acs.langmuir.8b03107

Lim, S. H., Kathuria, H., Tan, J. J. Y., & Kang, L. (2018). 3D printed drug delivery and testing systems — a passing fad or the future? *Advanced Drug Delivery Reviews*, *132*, 139–168. DOI: 10.1016/j.addr.2018.05.006

López-Iglesias, C., Casielles, A. M., Altay, A., Bettini, R., Alvarez-Lorenzo, C., & García-González, C. A. (2019). From the printer to the lungs: Inkjet-printed aerogel particles for pulmonary delivery. *Chemical Engineering Journal*, *357*, 559–566. DOI: 10.1016/J.CEJ.2018.09.159

Luo, H., Li, H., Yang, X., Li, J., Zhang, X., & Wu, Z. (2016). A Nanoscale Polymeric Penetration Enhancer Based on Polylysine for Topical Delivery of Proteins and Peptides. *Journal of Pharmaceutical Sciences*, *105*(12), 3585–3593. DOI: 10.1016/j.xphs.2016.08.022

Mahboob, M. B. H., Riaz, T., Jamshaid, M., Bashir, I., & Zulfiqar, S. (2016). Oral Films: A Comprehensive Review. *International Current Pharmaceutical Journal*, *5*(12), 111–117. DOI: 10.3329/icpj.v5i12.30413

Mandeep, K., Rana, A. C., & Nimrata, S. (2013). Fast Dissolving Films: An Innovative Drug

Delivery System. *International Journal of Pharmaceutical Research & Allied Sciences*, *2*(1), 14–24. Retrieved from www.ijpras.com

Meléndez, P. A., Kane, K. M., Ashvar, C. S., Albrecht, M., & Smith, P. A. (2008a). 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*(7), 2619–2636. DOI: 10.1002/jps.21189

Meléndez, P. A., Kane, K. M., Ashvar, C. S., Albrecht, M., & Smith, P. A. (2008b). 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*(7), 2619–2636. DOI: 10.1002/JPS.21189

Montenegro-Nicolini, M., Miranda, V., & Morales, J. O. (2017). Inkjet Printing of Proteins: an Experimental Approach. *The AAPS Journal*, *19*(1), 234–243. DOI: 10.1208/s12248-016-9997-8

Montenegro-Nicolini, M., Reyes, P. E., Jara, M. O., Vuddanda, P. R., Neira-Carrillo, A., Butto, N., … Morales, J. O. (2018). The Effect of Inkjet Printing over Polymeric Films as Potential Buccal Biologics Delivery Systems. *AAPS PharmSciTech*, (5). DOI: 10.1208/s12249-018-1105-1

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*(1), 149–155. DOI: 10.1016/J.EJPB.2011.09.016

Nagaraju, T., Gowthami, R., Rajashekar, M., Sandeep, S., Mallesham, M., Sathish, D., & Shravan Kumar, Y. (n.d.). Comprehensive Review On Oral Disintegrating Films. Retrieved from

https://www.ingentaconnect.com/content/ben/cdd/2013/00000010/00000001/art00016

Palem, C. R., Gannu, R., Doodipala, N., Yamsani, V. V., & Yamsani, M. R. (2011). Transmucosal delivery of domperidone from bilayered buccal patches: In vitro, ex vivo and in vivo characterization. *Archives of Pharmacal Research*, *34*(10), 1701–1710. DOI: 10.1007/s12272-011-1014-2

Palo, M., Kogermann, K., Laidmäe, I., Meos, A., Preis, M., Heinämäki, J., & Sandler, N. (2017). Development of Oromucosal Dosage Forms by Combining Electrospinning and Inkjet Printing. *Molecular Pharmaceutics*, *14*(3), 808–820. DOI: 10.1021/acs.molpharmaceut.6b01054

Pere, C. P. P., Economidou, S. N., Lall, G., Ziraud, C., Boateng, J. S., Alexander, B. D., … Douroumis, D. (2018). 3D printed microneedles for insulin skin delivery. *International Journal of Pharmaceutics*, *544*(2), 425–432. DOI: 10.1016/j.ijpharm.2018.03.031

Planchette, C., Pichler, H., Wimmer-Teubenbacher, M., Gruber, M., Gruber-Woelfler, H., Mohr, S., … Khinast, J. (2016). Printing medicines as orodispersible dosage forms: Effect of substrate on the printed micro-structure. *International Journal of Pharmaceutics*, *509*(1–2), 518–527.DOI: 10.1016/J.IJPHARM.2015.10.054

Prasad, L. K., & Smyth, H. (2016). 3D Printing technologies for drug delivery: a review. *Drug Development and Industrial Pharmacy*, *42*(7), 1019–1031. DOI: 10.3109/03639045.2015.1120743

Prasad, L. K., Smyth, H., Prasad, L. K., & Smyth, H. (2016). 3D Printing technologies for drug delivery : a review 3D Printing technologies for drug delivery : a review, *9045*. DOI: 10.3109/03639045.2015.1120743

Preis, M., Breitkreutz, J., & Sandler, N. (2015a). Perspective: Concepts of printing

technologies for oral film formulations. *International Journal of Pharmaceutics*, *494*(2), 578–584. DOI: 10.1016/j.ijpharm.2015.02.032

Preis, M., Breitkreutz, J., & Sandler, N. (2015b). Perspective: Concepts of printing technologies for oral film formulations. *International Journal of Pharmaceutics*, *494*(2), 578–584. DOI: 10.1016/J.IJPHARM.2015.02.032

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*(10), 3694–3704. DOI: 10.1002/jps.23678

Rana, V. (2016). Therapeutic Delivery. *Ther. Deliv*, *7*(2), 117–138. DOI: 10.4155/tde.15.92

Samson, A. A. S., Lee, J., & Song, J. M. (2018). Inkjet printing-based photo-induced electron transfer reaction on parchment paper using riboflavin as a photosensitizer. *Analytica Chimica Acta*, *1012*, 49–59.DOI: 10.1016/j.aca.2018.02.004

Scoutaris, N., Chai, F., Maurel, B., Sobocinski, J., Zhao, M., Moffat, J. G., … Douroumis, D. (2016). Development and Biological Evaluation of Inkjet Printed Drug Coatings on Intravascular Stent. *Molecular Pharmaceutics*, *13*(1), 125–133. DOI: 10.1021/acs.molpharmaceut.5b00570

Scoutaris, N., Ross, S., & Douroumis, D. (2016). Current Trends on Medical and Pharmaceutical Applications of Inkjet Printing Technology. *Pharmaceutical Research*, *33*(8), 1799–1816. DOI: 10.1007/s11095-016-1931-3

Singh, M., Haverinen, H. M., Dhagat, P., & Jabbour, G. E. (2008). Inkjet Printing-Process and Its Applications. DOI: 10.1002/adma.200901141

Square, B., Basher, A., & Buanz, M. (n.d.). *UCL SCHOOL OF PHARMACY Pharmaceutical*

Applications of Thermal Inkjet Printing. Retrieved from

Tabachnyk, M., Karani, A. H., Broch, K., Pazos-Outón, L. M., Xiao, J., Jellicoe, T. C., … Friend, R. H. (2016). Efficient singlet exciton fission in pentacene prepared from a soluble precursor. *APL Materials*, *4*(11), 1–28. DOI: 10.1063/1.4968518

Takala, M., Helkiö, H., Sundholm, J., Genina, N., Kivikuoma, P., Widmaier, T., … Kuosmanen, P. (2012). Ink-jet printing of pharmaceuticals. *8th International DAAAM Baltic Conference "Industrial Engineering,"* (April), 6.

Tappa, K., & Jammalamadaka, U. (2018). Novel biomaterials used in medical 3D printing techniques. *Journal of Functional Biomaterials*, *9*(1). DOI: 10.3390/jfb9010017

Thabet, Y., Lunter, D., & Breitkreutz, J. (2018). Continuous inkjet printing of enalapril maleate onto orodispersible film formulations. *International Journal of Pharmaceutics*, *546*(1–2), 180–187. DOI: 10.1016/j.ijpharm.2018.04.064

Thabet, Y., Sibanc, R., & Breitkreutz, J. (2018). Printing pharmaceuticals by inkjet technology: Proof of concept for stand-alone and continuous in-line printing on orodispersible films. *Journal of Manufacturing Processes*, *35*, 205–215. DOI: 10.1016/J.JMAPRO.2018.07.018

Uddin, M. J., Scoutaris, N., Klepetsanis, P., Chowdhry, B., Prausnitz, M. R., & Douroumis, D. (2015). Inkjet printing of transdermal microneedles for the delivery of anticancer agents. *International Journal of Pharmaceutics*, *494*(2), 593–602. DOI: 10.1016/j.ijpharm.2015.01.038

Vakili, H., Wickström, H., Desai, D., Preis, M., & Sandler, N. (2017). Application of a handheld NIR spectrometer in prediction of drug content in inkjet printed orodispersible formulations containing prednisolone and levothyroxine. *International Journal of*

Pharmaceutics, *524*(1–2), 414–423.DOI: 10.1016/j.ijpharm.2017.04.014

Varan, C., Wickström, H., Sandler, N., Aktaş, Y., & Bilensoy, E. (2017). Inkjet printing of antiviral PCL nanoparticles and anticancer cyclodextrin inclusion complexes on bioadhesive film for cervical administration. *International Journal of Pharmaceutics*, *531*(2), 701–713. DOI: 10.1016/j.ijpharm.2017.04.036

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*(15), 9644–9653. DOI: 10.1021/la201728f

Vuddanda, P. R., Alomari, M., Dodoo, C. C., Trenfield, S. J., Velaga, S., Basit, A. W., & Gaisford, S. (2018a). Personalisation of warfarin therapy using thermal ink-jet printing. *European Journal of Pharmaceutical Sciences*, *117*(January), 80–87. DOI: 10.1016/j.ejps.2018.02.002

Vuddanda, P. R., Alomari, M., Dodoo, C. C., Trenfield, S. J., Velaga, S., Basit, A. W., & Gaisford, S. (2018b). Personalisation of warfarin therapy using thermal ink-jet printing. *European Journal of Pharmaceutical Sciences*, *117*, 80–87. DOI: 10.1016/j.ejps.2018.02.002

Wening, K., & Breitkreutz, J. (2011). Oral drug delivery in personalized medicine: Unmet needs and novel approaches. *International Journal of Pharmaceutics*, *404*(1–2), 1–9. DOI: 10.1016/J.IJPHARM.2010.11.001

Yu, C. C., Baek, J. D., Su, C. H., Fan, L., Wei, J., Liao, Y. C., & Su, P. C. (2016). Inkjet-Printed Porous Silver Thin Film as a Cathode for a Low-Temperature Solid Oxide Fuel Cell. *ACS Applied Materials and Interfaces*, *8*(16), 10343–10349. DOI: 10.1021/acsami.6b01943

Yu, J., Qian, C., Zhang, Y., Cui, Z., Zhu, Y., Shen, Q., … Gu, Z. (2017). Hypoxia and H_2O_2 Dual-Sensitive Vesicles for Enhanced Glucose-Responsive Insulin Delivery. *Nano Letters*, *17*(2), 733–739. DOI: 10.1021/acs.nanolett.6b03848

Zheng, Q., Lu, J., Chen, H., Huang, L., Cai, J., & Xu, Z. (2011). Application of inkjet printing technique for biological material delivery and antimicrobial assays. *Analytical Biochemistry*, *410*(2), 171–176. DOI:10.1016/j.ab.2010.10.024

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