Effects of Different Polymers on Thermal Inkjet Printing of Oral Thin Films: A Novel Approach

A project submitted

by

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ID: 13146043

Session: Spring 2013

to

The Department of Pharmacy

in partial fulfillment of the requirements for the degree of

Bachelor of Pharmacy (Hons.)

Dhaka, Bangladesh

September, 2018

This work is dedicated to my parents for their love and constant support.

Certification Statement

This is to certify that the project titled “Effects of Different Polymers on Thermal Inkjet Printing of Oral Thin Film: A Novel Approach” submitted for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.) from the Department of Pharmacy, BRAC University constitutes my own work under the supervision of Marzia Alam, Lecturer, Department of Pharmacy, BRAC University and that appropriate credit is given where I have used the language, ideas or writings of another.

Signed,

_____

Counter signed by the supervisor,

_____

Acknowledgement

All praise is for the Almighty who is the source of our life and strength of our knowledge and wisdom, has helped me to continue my study in full diligence which I hope will reflect in my project.

This research could not also have been completed without the support of many people who are gratefully acknowledged here.

I am thankful to my honorable supervisor, Marzia Alam, Lecturer, Department of Pharmacy, BRAC University, for her amiability to provide me with untiring guidance, whole cooperation and for her extensive knowledge in research that helped me in all the spheres to perform the project work.

I would like to put forward my most sincere regards and profound gratitude to Dr. Eva Rahman Kabir, Chairperson and Professor, Department of Pharmacy, BRAC University, for giving me the opportunity to conduct such an interesting project and for facilitating a smooth conduction of my study.

I also want to show my gratitude to Dr. Md Jasim Uddin, Assistant Professor, Department of Pharmacy, BRAC University, for his guidance and thoughtful suggestions that helped us a lot to conduct the research work.

I would also like to extend my thanks to all the research students in the lab, lab officers and other staffs of the Department of Pharmacy for their help and assistance, friendly behavior and earnest co-operation which enabled me to work in a very congenial and comfortable ambiance.

I owe special thanks to my family for their immense support, contribution and continuous motivation in my project work.

Thank you.

Abstract

The aim of this research was to use inkjet printing technology in formulation of personalized medicine. Thus in this research, an attempt was made to print OTF by TIJ printing. A placebo solution comprising of different polymers and polymer concentrations was used for TIJ printing on A4 paper. The formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12 and F13 were prepared with the following compositions: (20% Glycerin+0.5% CMC+H_2O), (30% Glycerin+4% CMC+H_2O), (20% Glycerin+ 2% CMC+H_2O), (20% Glycerin+2%Gelatin+H_2O), (18% Glycerin+4% Gelatin+H_2O), (21% Glycerin+3.5% Gelatin+H_2O), (20% Glycerin+2% HPMC K4 MCR +H_2O), (12.5% Glycerin+1.25% HPMC K4 MCR +H_2O), (9.5% Glycerin+0.5% HPMC K4 MCR +H_2O), (20% Glycerin+1% HPMC K4 MCR +H_2O), (0.05% HPMC K4 MCR +49.98% H_2O+ 49.98% Ethanol) and (1% HPMC K4 MCR +H_2O) respectively. The placebo formulations were prepared by using glycerin as plasticizer and three different polymers; Carboxymethyl Cellulose (CMC), Gelatin and Hydroxypropyl Methyl Cellulose K4MCR (HPMC K4MCR) in different concentrations as film forming agents. The plasticizer and polymers were dissolved in aqueous solvent to prepare each placebo formulation with which the printer cartridge was refilled. Printing was done with the formulations using Canon PIXMA ip2772 thermal inkjet printer. F1 and F4 formulations, prepared with CMC and gelatin provided better imprint on paper at concentrations 0.5% and 2%, respectively. However, formulations prepared with HPMC K4MCR at a concentration as low as 0.05%, could not be jetted through the nozzle of the cartridge and no imprint could be obtained. Thus, from the study it was found that viscosity of the ink solutions affected the imprint quality.

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List of Acronyms

OTF = Oral Thin Film

API = Active Pharmaceutical Ingredients

RH = Relative Humidity

LogP = Partition coefficient

CIJ = Continuous Ink-Jet

DOD = Drop On Demand

TIJ = Thermal Ink-Jet

TIJP = Thermal Ink-Jet Printing

PXRD = Powder X-Ray Diffraction

RSP = Riboflavin Sodium Phosphate

PH = Propranolol Hydrochloride

SC = Solvent Casting

ODF = Orally Dissolving Films

TF = Transparency Films

LOP = Loperamide hydrochloride

CAF = Caffeine

CMC = CarboxyMethyl Cellulose

HPMC = HydroxyPropyl Methyl Cellulose

CD = Compact Disc

cP = centi Poise

DSC = Differential Scanning Calorimetry

TGA = Thermogravimetric Analysis

DVS = Dynamic Vapor Sorption

HPLC = High-Performance Liquid Chromatography

SHG = Second Harmonic Generation

EDX = Energy-Dispersive X-ray Spectrooscopy

FTIR = Fourier Transform Infrared Spectroscopy

UV-vis = Ultraviolet-visible spectroscopy

XRD = X-Ray Diffraction

NIR = Near-Infrared spectroscopy

MS = Mass spectroscopy

TOF SIMS = Time-of-flight secondary ion mass spectrometry

dpi = dots per inch

Chapter 1: Introduction

The theory “one size fits all” is widely accepted and practiced across the pharmaceutical world. In spite of having the perks of easy dose calculations, this practice can bring forth challenges for drugs with narrow-therapeutic window or for drugs with remarkably changing pharmacokinetic or pharmacodynamic profiles. If each patient does not get correct dose due to the unavailability of personalized dose, underdosing with no therapeutic effect, or overdosing with adverse effects may occur. Personalization of dosage forms for individual patients have been proposed as a solution to this complication. In this system, drug doses are modified to fit each patient, according to their age, gender, weight and genetic background (Edinger, Bar-Shalom, Sandler, Rantanen, & Genina, 2018).

Such precision medicine seems difficult to achieve with conventional dosage forms. Moreover, oral route of administration has several disadvantages which include the degradation of enzymes in the gastrointestinal tract that restrains the administration of some specific classes of drugs like peptides and proteins to take orally (Khan, Boateng, Mitchell, & Trivedi, 2015).

A novel drug delivery system— Oral thin films has given hope of high prospects in replacing the conventional dosage forms. By providing efficient precision dosing in the form of extemporaneous preparations, oral thin films can greatly improve patient compliance. Currently several 2D+3D printed oral thin films are under formulation research worldwide (Zhang, Zhang, & Streisand, 2002).

1.1 Oral Thin Film (OTF)

Oral thin film is a promising novel drug delivery system. It is a strip of single or multilayered, mucoadhesive or non-mucoadhesive, thin polymeric film which is intended to deliver active therapeutic ingredients (drug) either locally or systemically in oral cavity through sublingual, buccal, palatal, or gastrointestinal absorption. Generally, films are known by several names such as orodispersible films, orally disintegrating films, orally dissolving films, rapid/fast/quick dissolving films, oral soluble films, oral thin films, strip films, quick disintegrating/dissolving films, buccal or buccal soluble film, mucoadhesive films, transmucosal films, sublingual films etc. Strip films or thin films

can be used as a common term for all kinds of film applications for oral, topical/transdermal, vaginal, etc. (Shanmugam, 2016)

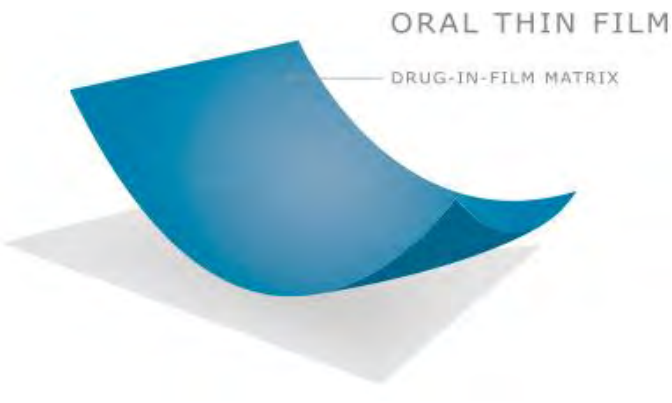


Figure 1.1 A: Oral thin film ("Oral Thin Films | ARx Drug Delivery Systems," n.d.)

Figure 1.1 B: Administration of oral thin film ("Rapidfilm® - tesa Labtec GmbH," n.d.)

OTF is fast-dissolving oral delivery system that disintegrates or dissolves immediately (in less than 1 minute) when it is placed in the mouth, without the help of drinking with water or chewing. (Cilurzo et al., 2011). This dosage form is particularly suitable for paediatric and geriatric use. No additional water is needed for drug administration because the films dissolve in saliva after application. (Garsuch & Breitkreutz, 2010)

1.2 History and background of formulation of OTF

The concept of orally disintegrating solid dosage forms was originated in 1970 as a result of patient's non-compliance with taking medicines because of difficulty of swallowing. Orally fast-dissolving thin film was first developed on the basis of the technology of transdermal patch (Nagarajan G, Shaik Mohammad Abdulla, Raja Amaranth P, Venu Madhav K, Jona Methusala R, 2015). According to Garg et al., (2010), oral thin films

were firstly used as confectionary and cosmetics products. Later, they have been started to be used as over the counter products, followed by as prescription drugs finally.

1.3 Special Features of OTF

According to Bala, Khanna, Pawar, & Arora, (2013); Patil & Shrivastava, (2014); Sharma et al., (2015); Arora & Chakraborty, (2017), OTFs should have following features:

- The oral thin film should be thin and elegant.
- It should be convenient in different size and shapes.
- It should not be obstructive in nature.
- The oral thin film should have excellent mucoadhesion properties.
- It should be disintegrated fast in oral cavity without the help of water.
- It should be released rapidly.
- It should not leave any residue in mouth.
- It should be less sensitive towards certain environmental conditions as temperature and humidity.

1.4 Advantages of OTF

Oral mucosa is extensively vascularized and so it helps in the rapid absorption of the drug. Moreover, it provides higher bioavailability, rapid onset of action and it bypasses the first pass effect. As a result, thin films get dissolved expeditiously compared to any other dosage forms (Arora & Chakraborty, 2017). Thin films do not get crumbled easily and it is also very easy to carry in contrast to any other dosage forms like tablets, syrup etc. In addition, there is no requirement of any secondary container to carry a single dose of strip individually (Karki et al., 2016). The thin films have greater stability. It has been also proved by research that OTFs have minimal side-effects than the other dosage forms used (Godbole, Joshi, & Sontakke, 2018).

OTFs have some unique attributes including high mechanical strength, less expensive lyophilization, rapid disintegration etc (Irfan et al., 2016). OTFs are designed in such a way that they can be administered without the help of water at anytime, anywhere. This dosage form of drug is suitable for geriatric and pediatric patients. It can also be given to

the mentally ill patients, non-cooperative patients or those who are nauseated. They provide constructive effects on these terms for example; motion sickness, in case of acute pain, sudden incident of allergic attack, specifically when there is a need of ultra rapid onset of action for the patient. As oral thin film is a novel dosage form, it provides new business opportunity in the manner of differentiation, promotion or extension of products (Bhyan, Jangra, Kaur, & Singh, 2011).

The other advantages includes that the acidic environment in the stomach can cause damage to the other oral dosage forms whereas OTFs can avoid such situation. If there is any required condition, the delivered drug can be relatively easily terminated. OTFs can provide site specific and local action. These are non-invasive in nature (Siddiqui, Garg, & Kumar Sharma, 2011).

1.5 Disadvantages of OTF

Oral thin films have several limitations. For instance, they cannot be used largely due to their minimal loading capacity of drugs. Usually OTFs have hygroscopic property. As a result, they require special precaution for longer storage (Karki et al., 2016). These films also require special packaging (Siddiqui et al., 2011) otherwise they tend to lose stability in environments with high RH (Relative Humidity) (Godbole et al., 2018).

Drugs, unstable at buccal pH cannot be administered via OTF. The techniques for the formation of these films are quite expensive compared to the oral dissolving tablets (Arora & Chakraborty, 2017). The drugs that irritate the oral mucosa cannot be administered via oral thin films (Godbole et al., 2018). In addition, the uniformity of dosage is a challenge technically in case of OTFs (Bhyan et al., 2011).

The use of combining multiple drugs simultaneously is a very challenging thing to do in terms of OTF formulation because it can cause hamper to both of the dissolution rate and the disintegrating time of the drugs in the oral film that have been administered concomitantly (Karki et al., 2016).

1.6 APIs suitable for OTF

According to Panda, Dey, & Rao, (2012), the drugs with lower loading doses and those with a rapid onset of action are preferable to incorporate into oral thin films. There are some ideal features for the drug candidates of OTFs:

- The APIs to be incorporate into OTFs should have lower loading dose which should not be greater than 40 mg.
- Drugs which have lower molecular weight are preferable to incorporate into OTFs.
- As the drug is directly administered into the oral cavity, it should retain pleasant taste.
- The drug should be easily soluble and should have stability both in water as well as in saliva.
- The drug should be moderately ionized at the pH of buccal cavity.
- It must possess the potential to pass through the oral mucosal tissue.

The APIs with lower molecular weight are more suitable to be incorporated into the Oral Thin Films. Some of the examples of APIs are mentioned below:

Table 1.1: APIs suitable for incorporation into OTFs

API	Molecular weight	LogP	Solubility
Formeterol	344.405 g/mol	2.2	In water: 1.12 X 10^4 mg/L at 25°C
Galantamine	287.359 g/mol	1.8	In water: fairly soluble; In alocohol, acetone, & chloroform: freely slouble In benzene and ether: Less soluble
Hydralazine	160.176 g/mol	1	In ether & alcohol: very slightly soluble
Loxapine	327.812 g/mol	3.77	In water: 1.03e-01 g/L
Carbamazepine	236.269 g/mol	3.39	In water: 17.7 mg/L In alcohol, acetone & propylene glycol: soluble
Quinapril	438.516 g/mol	3.2	In water: 1 mg/L
Bumetanide	364.417 g/mol	2.6	In water: >20 mg/ml
Dobutamine	301.38 g/mol	3.6	In water: 1.37e-02 g/L
Clopidogrel	321.82 g/mol	2.5	In water: 50.78 mg/L

Adopted from ("Formoterol | C19H24N2O4 - PubChem," n.d.), ("Galantamine | C17H21NO3 - PubChem," n.d.), (Kandler, Mah, Tejani, & Stabler, 2010), ("Dobutamine | C18H23NO3 - PubChem," n.d.; "Loxapine | C18H18ClN3O - PubChem," n.d.; Kieback, Felix, & Reffelmann, 2009; Lang, Kampf, & Matzger, 2002; Number, n.d.)

1.7 Formulation of OTF

Oral thin films have an area of about 5 to 20 cm^2 (depending on the drug and drug loading) in which the drug is consolidated in matrix form by using hydrophilic polymer (Irfan et al., 2016). A maximum dose of 30 mg of drug can be loaded into a single dose

(Siddiqui et al., 2011). There are some risks during the manufacturing of the oral films like, flaking of the films during slitting, cracking at the cutting stage etc. (Sharma et al., 2015)

Table 1.2: A typical composition of an oral thin film (Siddiqui et al., 2011)

Content	Quantity
Drug	5% to 30% w/w
Water soluble polymer	45% w/w
Plasticizers	0-20% w/w
Surfactants	q.s
Sweetening agent	3 to 6% w/w
Saliva stimulating agent	2 to 6% w/w
Fillers, colors, flavors etc.	q.s

The polymers used in the film forming, need to be selected very cautiously as it is a critical component for developing a film formulation successfully. A single polymer or a combination of some polymers can be used to prepare film with desired properties. These polymers are selected according to their physicochemical properties.

Properties of various types of polymers that are used for the formulation of OTFs are given following:

Table 1.3: Various types of polymers and their properties (Bala et al., 2013)

Polymer	Water solubility	pH	Moisture (% loss on drying)	Molecular weight (kDa)
Hydroxypropyl cellulose	Soluble in water	5-8	1.6	50000-1250000
Hydroxypropyl methyl cellulose	Soluble in cold water	5-8	1.6	50000-1250000
Sodium carboxymethyl cellulose	Viscous colloidal solution	6-8	10	90000-700000
Polyvinyl alcohol	Readily soluble	5-8	5	20000-200000
Polyethylene oxide	Readily soluble	8-10	<1	Variable
Kollicoat	>50% in water	6-7		About 45000
Pullulan	Readily soluble	5-7	6	100-250
Sodium alginate	Readily soluble, forming viscous solution	7.2	15	
Pectin	Soluble in water	6-7.2	10	30000-100000
Gelatin	Swell in water and soften	3.8-6.0	10	15000-250000
Maltodextrine	Swell in water and soften	4-7	6	Variable

1.8 Formulation Methods of OTF

There are two major methods which are usually used to formulate oral thin films; Solvent casting method and another one is hot melt extrusion method (Borges, Silva, Coelho, & Simões, 2015). There are some other methods that can be used for preparing oral thin films like semisolid casting, solid dispersion extrusion or rolling (Mahajan et.

al., 2011). Inkjet printing is an innovative method that has been described additionally. This method comprises of printing the medication substances onto a placebo thin film in a particular manner (Borges et al., 2015).

1.9 Inkjet Printing Technology

Printing technology has been used in the pharmaceutical industry for the purpose of identification or labelling the pharmaceutical dosage forms. However, this technology has initiated to be accustomed recently for loading the drugs. In the 1980's, Anhauser, Klein and Nick used screen printing and pad printing for loading drug substances on transdermal patches. Now, the inkjet printing method has started to be used as a reliable and proper process for preparing dosage forms with potent drugs (Borges et al., 2015).

Inkjet printing technology is a non-contact technique which helps to prepare 1-100 pL droplets of liquid into 2D or 3D framework. This method implicates the API of interest to be dissolved or dispersed into a liquid phase to form an ink. The ink is ejected from a micrometer scale nozzle. Droplets are formed by heating the ink liquid to a temperature greater than that of the boiling temperature of the liquid (in case of TIJ). Inkjet printing is usually alluded to as a tool-less approach because as it works only by movement of the nozzle or by the movement of substrate that allow precise and reproducible formation of the desired structure (Boehm, Miller, Daniels, Stafslien, & Narayan, 2014).

The basics of inkjet printing method were first discussed by Lord Rayleigh in the 19th century, explaining break of liquid flow into the droplets, which is called 'jet'. This concept has established two technologies, which are continuous ink-jetting (CIJ) and drop-on-demand (DOD). Among these two methods, DOD printing is more acceptable and often used due to lower cost, high precision and above all its simplicity (Alomari, Mohamed, Basit, & Gaisford, 2015).

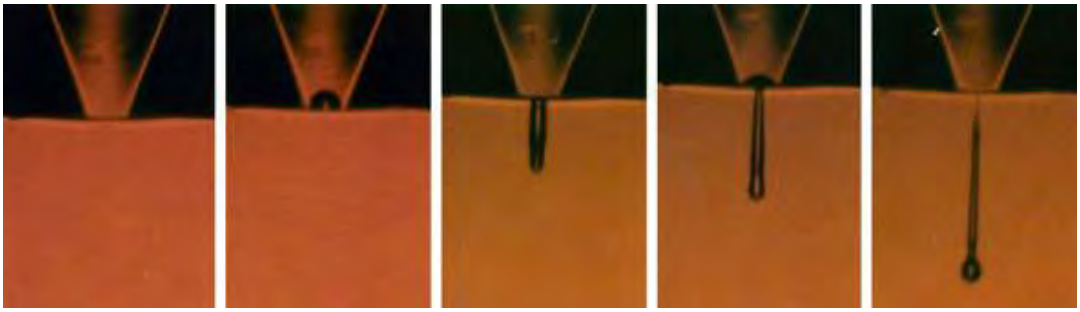


Figure 1.2: Schematic illustration of drop-on-demand mode jetting (Tarcha et al., 2007)

There are two major technologies of DOD printers; one is Piezoelectric and the another one is thermal inkjet printer (Alomari et al., 2015).

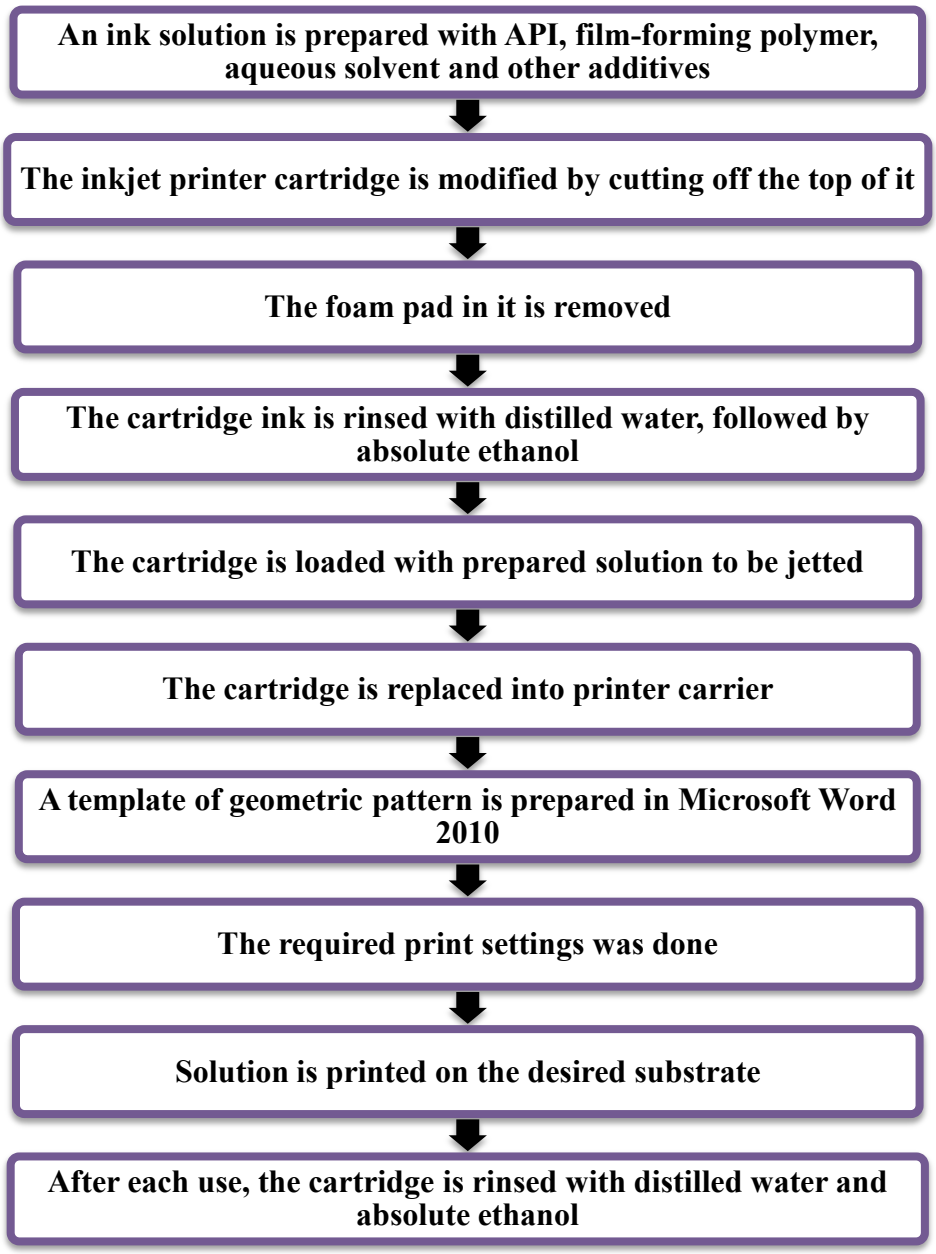
1.10 Thermal Inkjet Printing

The thermal inkjet printing (TIJP) is a method for printing where the ink heated and forms a vapor bubble rapidly expand which consecutively ejects the ink throughout the nozzle (Nicolaos Scoutaris, Ross, & Douroumis, 2016).

In this method, the API is deposited on the desired substrate. TIJP is capable of depositing very small volumes of droplets (containing 5–15 picoliter or pL in each droplet) with high accuracy. This technology has been used by printing droplets of solution on the surface of a substrate for preparing modified-release dosage forms. This method involves deposition of API solutions onto a substrate, instead of dispersing the solutions within the substrate. As a result, it is acceptable to consider that the imprinted films by TIJP should retain similar mechanical characteristics as the free film. Subsequently, this method offers significant advancements to that of solvent casting method as it ensures long-term stability of the prepared film (Buanz et al., 2015).

In TIJ printing, different substrates can be used to deposit the API solution. For the formulation of drug dosage forms, potato starch paper, rice paper, polymer film etc can be used potentially (Karki et al., 2016).

The flowchart of the steps of dispensing drug solution onto the substrate film is given below:



Adopted from (Buanz, Saunders, Basit, & Gaisford, 2011)

1.11 Evaluation of OTF by TIJ printing

There are a number of evaluation techniques used in the characterization of OTF by TIJ printing (Daly, Harrington, Martin, & Hutchings, 2015). The characterization techniques and their objectives are given following:

Table 1.4: Evaluation techniques used in the characterization of OTF by TIJ printing

Characterisation technique	Objective
Differential Scanning Calorimetry (DSC)	Verify crystallinity
Thermogravimetric Analysis (TGA)	Water content analysis
Dynamic Vapor Sorption (DVS)	Crystallisation behavior under humidity
High-Performance Liquid Chromatography (HPLC)	Drug release rate
Content analysis	Quantity of API in printed area
Second Harmonic Generation (SHG)	Analysis of the surface of crystal forms
Energy-Dispersive X-ray Spectrooscopy (EDX)	Distribution of API in sample
Fourier Transform Infrared Spectroscopy (FTIR)	Confirming co-crystal formation
Ultraviolet-visible spectroscopy (UV-vis)	Verify dose in real time
Raman spectroscopy	Polymer identification
X-Ray Diffraction (XRD)	Polymer identification
Near-Infrared spectroscopy	Verify dose in real time
Mass spectroscopy (MS)	Analysis of degradation products
Time-of-flight secondary ion mass spectrometry (TOF SIMS)	Analysis of chemical heterogeneities

Adopted from (Daly et al., 2015)

1.12 Advantages of using thermal inkjet printing for OTF

As long as thermal inkjet printing has fine control over deposition of liquid, this technology can be used to prepare pharmaceutical applications. The desktop thermal inkjet printers are designed in such a way that they are suitable to deposit liquid solutions onto flat substances, for example on oral and buccal films. TIJP provides instant preparation of specific doses in context of personalized dose medicine. This might be done by varying the concentration of the solution to be ejected as ink, tailoring the area of the films, or changing the print passing number over the film (Buanz et al., 2011).

1.13 Future prospect of thermal inkjet printing

Printing technology to manufacture drug delivery systems in a customized process has advanced and still advancing towards improvement. The main challenge is delivering the advantages of TIJP technology to individual patient and to meet the future needs of the individuals (Kolakovic et al., 2013).

Since this method has been recently established as a process for deposition of drugs onto substrates, the next step will be expanding patient-acceptable edible substrates for developing individualized doses. The acceptability of this dosage delivery form is the main component in compliance to the therapy. Moreover, the safety and efficacy of therapy can be also influenced by this. The research on the substrate's capacity of choice to affect the releasing profile of the administered medicine could be the future opportunity, considering that the ingestible form of that medicine is produced.

In the future, the regulation procedures of this method should to be examined and then applied. This includes methods related to confirmed or exact dose and sterility procedures adopted while conducting the manufacturing and considering the factors that can affect dispensing or manufacture of OTF by TIJ printing. By means of avoiding these issues, TIJP technology may bring a new standard to the personalised medicines area (Alomari et al., 2015).

1.14 Rationale of the study

The aim of this study is:

- to make an approach towards the preparation of oral thin film by using the thermal inkjet printing technology
- to compare the effect of different polymers according to the obtained imprint quality
- to develop a placebo formulation of OTF which has a prospect to be used in future to develop OTF formulations of API.

1.15 Literature Review

The purpose of this section is to review the past analysis works that are identified with the present study. Since, literature review forms a bridge between the past and present study, which helps to justify the research work and to draw a satisfactory conclusion. The most relevant studies that have been conducted within the recent past related to the current work are introduced in this part.

In the research work of "Preparation of Personalized-dose Salbutamol Sulphate Oral Films with Thermal Ink-jet printing" published in 'Pharmaceutical Research' the use of TIJP method was evaluated for dosing of drugs onto oral films. The performance of the printer was determined as per the viscosity and surface tension of the solution. Viscosities of the solution within 1.1 to 1.5 mm^2s^{-1} were obtained to be favorable whereas the surface tension of the ink had no effect on the deposition of the ink. Then an oral film which was prepared from potato starch was deposited with Sulbutamol Sulphate using the printer. It had been found that the dose obtained by measuring was corresponding to the theoretical dose as the oral film was deposited with the doses in a single pass under the print head. On the other hand, for multiple passes under the print head, the measured dose was found considerably lower compared to that of the theoretical dose (Buanz et al., 2011).

In the research work of "Thermal Inkjet Application in the Preparation of Oral Dosage Forms: Dispensing of Prednisolone Solutions and Polymorphic Characterization by Solid-State Spectroscopic Techniques" published online in 'Journal of Pharmaceutical

Sciences' the practicality in case of the thermal ink-jet technology for preparation of solid dosage forms of drugs was examined. Different solutions of prednisolone were dispensed onto fiberglass films via thermal inkjet cartridges along with a printer and also with a micropipette for comparisonal analysis. The samples were dispensed and then analyzed by PXRD which was confirmed by Raman analyses. Raman mapping of both the samples dispensed by TIJ and the samples dispensed by micropipette showed a presence of both polymorphs which clarifies the existence of polymorphic nomenclature of prednisolone in the scientific literature (Melendez, Kane, Ashvar, Albrecht, & Smith, 2011).

In the study of "Tailoring controlled-release oral dosage forms by combining inkjet and flexographic printing techniques" published in 'European Journal of Pharmaceutical Sciences' the conventional technology of inkjet printing was merged with the flexographic printing method to manufacture drug delivery systems with precised doses with customized release of drug. Riboflavin sodium phosphate (RSP) and propranolol hydrochloride (PH) solutions were printed onto substrates with the help of an TIJP. The APIs (imprinted on substrates) were coated using water insoluble polymeric films of various thicknesses by flexographic printing. The two printing technologies were combined to allow the formulation of controlled-release oral dosage forms easily, while using just a single technique it is challenging to produce (Genina et al., 2012).

Scoutaris, Alexander, Gellert, & Roberts, (2011), in their research work "Inkjet printing as a novel medicine formulation technique" published in 'Science Direct' demonstrated the use of an ink-jet printer to manufacture controlled release dosage form of felodipine. Different solutions of Felodipine were dispensed using the print head of a piezoelectric 'ink-jet' onto a substrate that was hydrophobic in nature. Raman microscopy mapping in case of each micro-scale droplets helped to visualize the distribution of drug in the spots and assisting in identification of the drug release. The release of drug was changed by controlling the drug dispensing. This proof of single deposited micro-spot formulations demonstrated the possibility of inkjet printing technology for printing practical dosage forms.

In the research work of "Ink-jet printing versus solvent casting to prepare oral films: Effect on mechanical properties and physical stability" published in 'Science Direct', the mechanical properties and physical stabilities of the oral films of Clonidine

hydrochloride were compared and contrast which were prepared by TIJP method or solvent casting (SC) method. The printed films had similar mechanical properties as the free film, in contrast to the casted films were found considerably more brittle. In case of casted films, the drug was found to be crystallized out at the time of stress testing while the printed films stayed stable like before. It was found that the printed and the casted films had similar dissolution characteristics. The printing method resulted in a better film compared to that of casting method. The drug remained on the film which was prepared by printing, instead into the film where this could exert a plasticizing effect (Buanz et al., 2015).

In the study of "Evaluation of different substrates for inkjet printing of rasagiline mesylate" published in 'European Journal of Pharmaceutics and Biopharmaceutics' suitability of the orally dissolving films (ODF), porous copy paper sheets and water impermeable transparency films was evaluated to formulate the inkjet printed dosage form of Rasagiline mesylate. By evaluating the dosage forms, it was found that recrystalization of the API occured on the surface of TFs and ODFs. On the contrary, no crystals of drug were detected on the copy paper, because of ink absorption into the substrate matrix. The porous copy paper showed the best linear correlation between the drug dose and the printing layers number. On the other hand, the remaining two substrates exhibited poor linearity as well as unacceptable standard deviations of the printed drug substance because of inadequate absorption of drug soltuion into the carrier (Genina, Janßen, Breitenbach, Breitkreutz, & Sandler, 2013).

In the research work of "Behavior of printable formulations of loperamide and caffeine on different substrates—Effect of print density in inkjet printing" published in 'International Journal of Pharmaceutics', the suitability of inkjet printing in formulating personalized doses of Loperamide hydrochloride (LOP) and caffeine (CAF) was studied. Both of the APIs were investigated in terms of the characteristics of their prepared printable inks. The analysis exhibited that the printed LOP was not recrystallized on any of the substrates that was studied. On the contrary, there was a partial recrystallization observed in case of printed CAF, on all the carrier surfaces. It was found that the flexible doses of both APIs were obtained easily with adjusting the drop spacing of the deposition inks only. The obtained results were significant as to the theoretical content (Genina, Fors, Palo, Peltonen, & Sandler, 2013).

In the research paper “Combining inkjet printing and amorphous nanonization to prepare personalized dosage forms of poorly-soluble drugs” published in ‘European Journal of Pharmaceutics and Biopharmaceutics’ inkjet printing of drug nanosuspension was carried out for the first time on edible porous substrates in order to prepare personalized dosage forms of poorly soluble drugs. Amorphous drug–polysaccharide nanoparticle complex was used as the nanosuspension ink. Inkjet printing was performed with the ink, for both of the nanoplex sizes, it was found that by increasing the droplets dispensed number, the printed dose could be effectively increased. Print substrate having higher capacity of liquid uptake is required for increasing the payload closer to the therapeutic dose. The release of drug and non-cytotoxicity of the printed nanodrug were established successfully in vitro in this research (Cheow, Kiew, & Hadinoto, 2015).

Chapter 2: Methodology

2.1 Materials

Glycerin (Pharmaceutical grade) was obtained from Merck, Germany which was used as a plasticizer.

Three different polymers were used for the preparation of different ink solutions:

- Carboxy Methyl Cellulose (CMC) was obtained from Merck, India
- Gelatin was obtained from local source (Anchor Ltd.)
- Hydroxy Propyl Methyl Cellulose (HPMC K4 MCR) (it was gift from Eskayef Pharmaceutical Limited)

Distilled water prepared in the phytochemistry lab, BRAC University was used as the aqueous solvent and ethanol (reagent grade obtained from Merck, Germany) was used as the organic solvent. It was used so that this non-aqueous solvent can help to dissolve the polymers properly. While the aqueous solvent in the formulation will help to imprint on the paper or film, the non-aqueous solvent will instantly evaporate and leave a better imprint on the paper or film.

Raspberry color (reagent grade) was used as coloring agent to help the ink stain to be visible on the printed paper/film.

The TIJ components were a Canon PIXMA ip2772 inkjet photo printer (Canon Inc., Japan) and tricolor ink cartridge (model number: CL-811).

2.1.1 Mechanism of inkjet printing

In TIJP method, a fluid droplet is ejected through some fundamental events such are: (i) heating; (ii) bubble nucleation; (iii) bubble expansion; (iv) droplet ejection; (v) bubble collapse; and (vi) refilling of the TIJ-dispensing chamber.

Inside a thermal inkjet print head, each of the nozzles applies heat to the ink solution by using a micro-resistor that creates an explosion of vapor in the fluid. Then the resistor applies heat which can reach approximately 300℃ and last for only a few microseconds. However, only about <0.5% of the fluid can experience a rise of temperature due to the nucleation of vapor bubble and then it immediately start to expand over the following

3-10 micro-second (μs). In this way, the upper limit of temperature is confined by the boiling point of the solvent. Then the bubble that was expanding, forces the overlying fluid out through the orifice of the nozzle in order to yield an ejected droplet that had been moving nearly at 10 ms^{-1}. After that, the bubble gets collapsed and the additional fluid flows from the reservoir with a view to refilling the chamber again and prepare the resistor by cooling for the next event of thermal inkjet (Melendez et al., 2011)

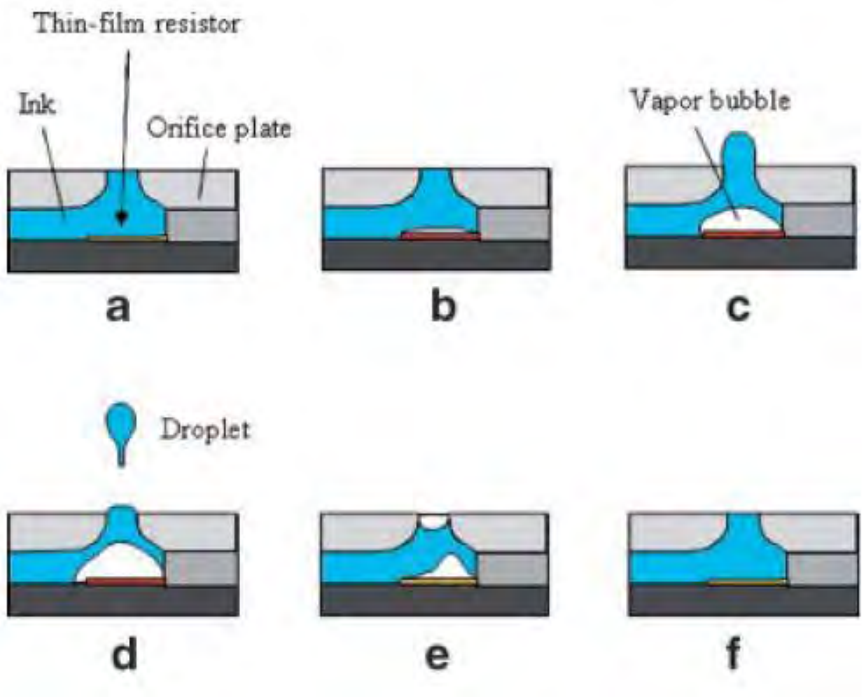


Figure 2.1: Schematic diagram of the development of a droplet ejected from a TIJ device: (a) Thermal Inkjet chamber before dispensing; (b) heating of a thin film of ink fluid by microresistor; (c) rapidly expanding vapor bubble pushing overlying fluid out through the nozzle, (d) the droplet separating and leaving the nozzle, (e) fluid flowing from the ink reservoir, (f) the thermal inkjet chamber is refilled again. (Melendez et al., 2011)

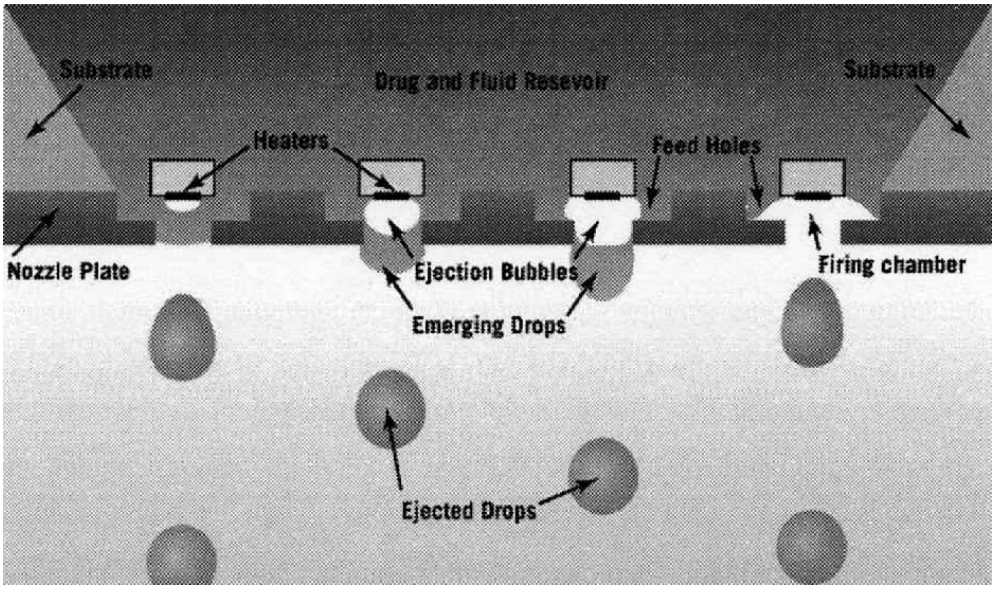


Figure 2.2: A close view of thermal inkjet ejection process (Goodall, Chew, Chan, Auriac, & Waters, 2002)

Each of the resistors can be separately controlled in the matter of voltage amount and the time of applied voltage or the dispensing frequencies number, or any other parameters. The parameters of dispensing are selected in accordance with the mechanical characteristics of the media, the fluid (for example, boiling point, viscosity etc), and also the desired behavior of the droplets that had been dispensed. Resultantly, groups of the nozzles dispense the droplets sequencially or concurrently and create the droplet patterns accurately and precisely. Furthermore, the control of the thermal inkjet events by computer and the location of the print head nozzles are correspondingly controlled to obtain accurate placement of droplets (Melendez et al., 2011).

The general specification for the Canon PIXMA iP 2772 is given below:

Table 2.1: General Specifications for Canon PIXMA iP 2772

General Specification	
Printing Resolution (dpi)	4800* (horizontal) × 1200 (vertical) *Ink droplets can be placed with a pitch of 1/4800 inch at minimum
Operating environment	Temperature: 5-35℃ Humidity: 10 to 90% RH (no condensation)
Storage environment	Temperature: 0-40℃ Humidity: 5 to 95% RH (no condensation)
Canon fine cartridge	Total 1472 nozzles (BK 320 nozzles, C/M/Y each 384 nozzles)

Adopted from ("iP Series | PIXMA iP7220 | Canon USA," n.d.)

Figure 2.3: Different parts of Canon PIXMA ip2772 thermal inkjet printer

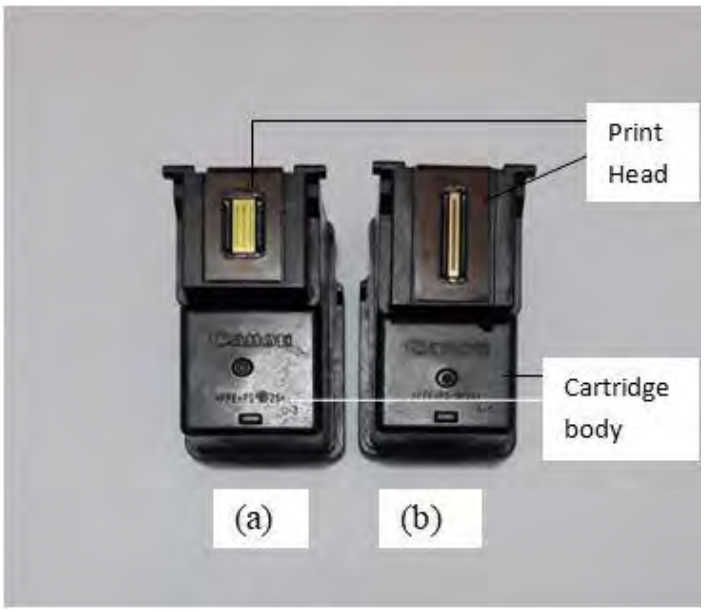


Figure 2.4: (a) print-head of tricolor cartridge, (b) print-head of black cartridge

2.2 Methods

2.2.1 Installation of the printer & printing software

First of all, the software for canon PIXMA ip2772 which was provided in a CD (available with the printer) was installed in the computer that was used for printing purpose. The USB cable was connected to the computer and the 'canon ip2700 series' printer was selected as default for printing.

2.2.2 Preparation of the template

A template was prepared in Microsoft Word 2010 (Microsoft Inc.). The template consisted of geometric shapes (20 squares of 0.8 inch × 0.8 inch). These squares were supposed to be cut into individual pieces after printing on desired substrate with ink solutions. The template (all squares) was colored into red as the tricolor cartridge was used for printing.

The template which was used for printing the solution is given following:

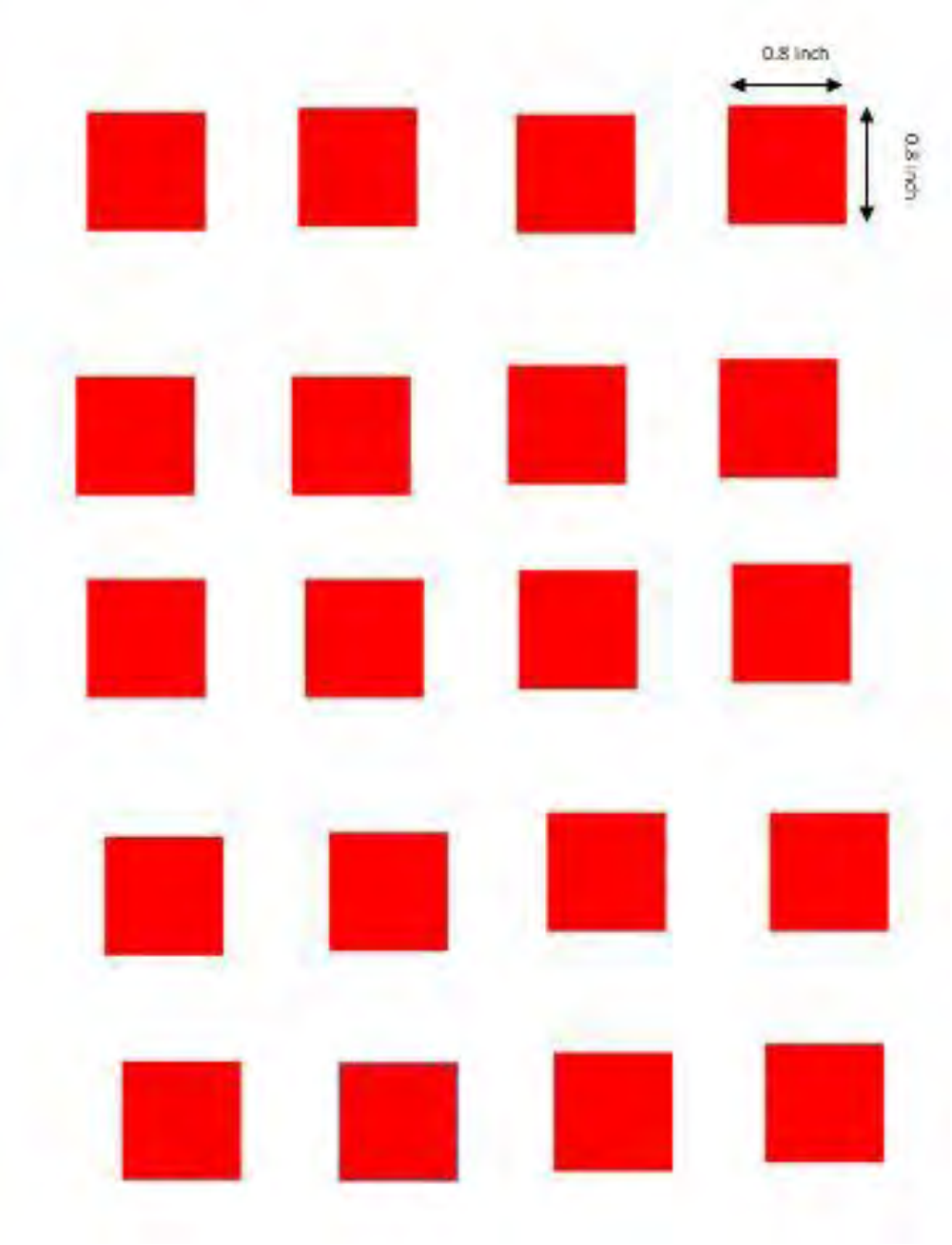


Figure 2.5: Template used for printing

2.2.3 Modification of the inkjet printer cartridge

The tricolor ink cartridge was modified for printing with the desired solution.

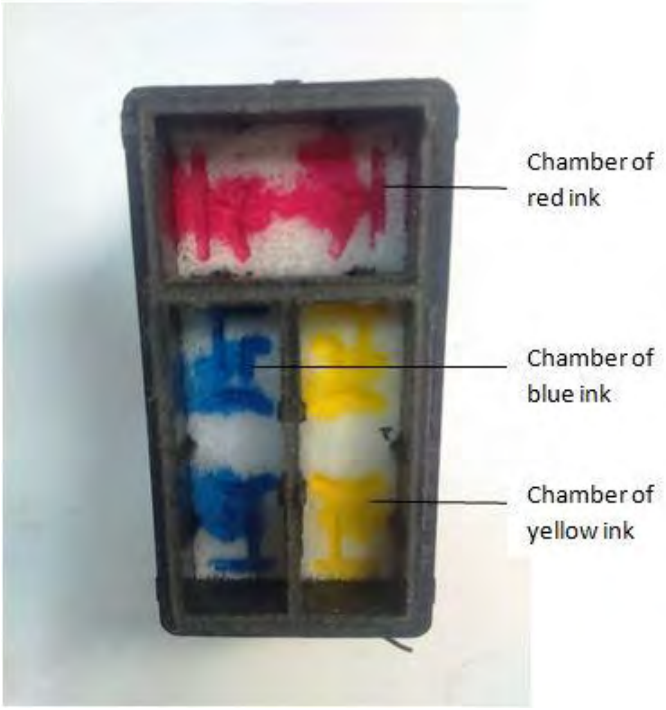
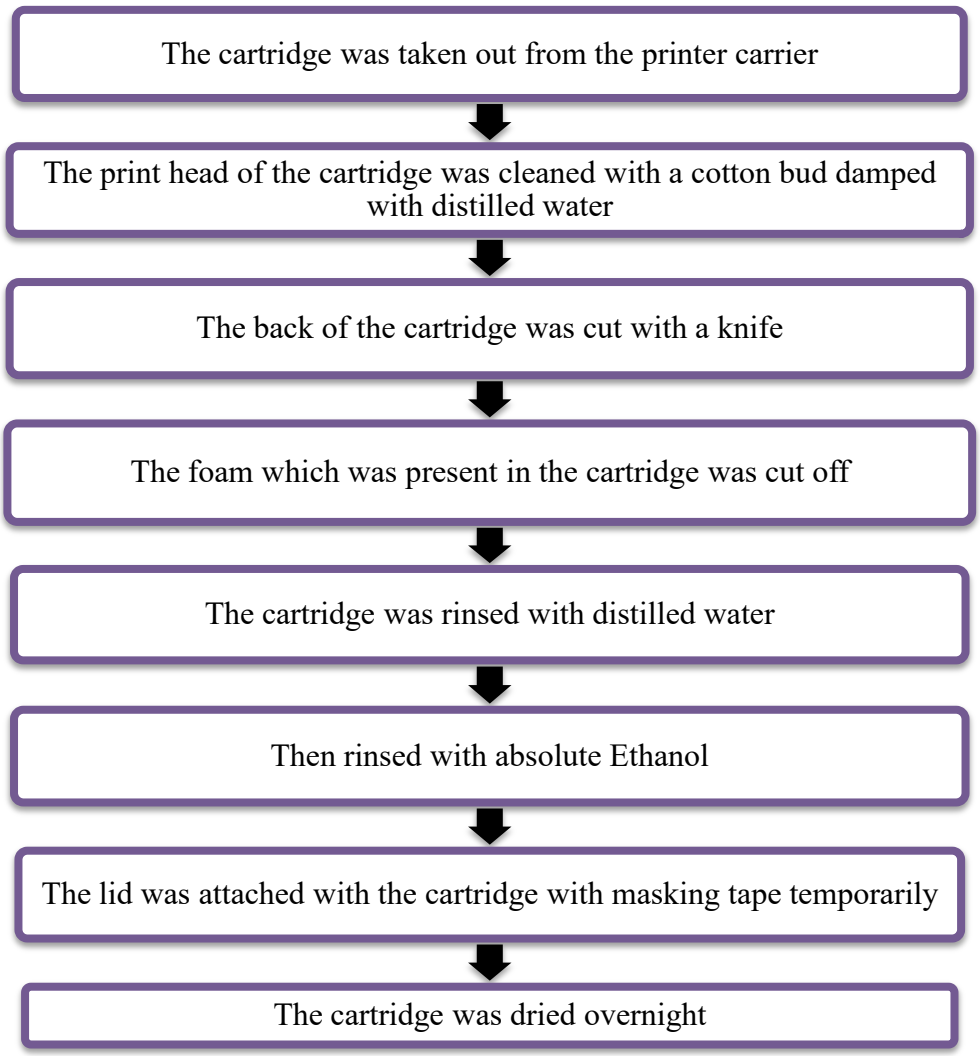


Figure 2.6 A: Inside of tricolor cartridge before cleaning

Figure 2.6 B: Inside of tricolor cartridge after cleaning

The following process was followed for modification of the cartridge.



During cleaning of the cartridge, touching of the circuit that is on the cartridge body was avoided. Otherwise there was risk of damage of the cartridge.

2.2.4 Preparation of the placebo solutions for TIJ dispensing

13 different placebo solutions were prepared as ink solutions. The formulations are given below:

Table 2.2: Formulations prepared for using in TIJ printing

Formulation	Plasticizer (Glycerin)	Polymer			Water	Ethanol	Coloring Agent
		CMC	Gelatin	HPMC K4 MCR			
F1	20%	0.5%	-	-	q.s	-	q.s
F2	30%	4%	-	-	q.s	-	q.s
F3	20%	2%	-	-	q.s	-	q.s
F4	20%	-	2%	-	q.s	-	q.s
F5	18%	-	4%	-	q.s	-	q.s
F6	21%	-	3.5%	-	q.s	-	q.s
F7	20%	-	-	2%	q.s	-	q.s
F8	12.5%	-	-	1.25%	q.s	-	q.s
F9	9.5%	-	-	0.5%	q.s	-	q.s
F10	20%	-	-	0.1%	q.s	-	q.s
F11	-	-	-	0.05%	49.975 %	49.975%	q.s
F12	-	-	-	1%	q.s	-	q.s
F13	-	-	-	0.5%	q.s	-	q.s

2.2.5 Refilling of the cartridge

The tricolor cartridge was loaded with each formulaion to be jetted and replaced in the carrier of the printer. Each time the cartridge was filled up with about 5 ml of the placebo

solution very carefully using a syringe so that the ink solution do not spill outside, especially not into the printer as there is a chance that the printer can be damaged.

2.2.6 Printing of Placebo Ink Solutions

Each prepared placebo ink solution was printed on a normal A4 paper (80 gsm) and the previously prepared template was used for printing. The print settings were normal print quality, individual cartridge and highest resolution only. The tri color cartridge was used for printing in this experiment. The ink solutions were printed in squares of 0.8 inch × 0.8 inch in the template.

At first, the F1 formulation was taken into the cartridge and the cartridge was replaced into the carrier of the printer. This solution was printed on the paper once.

Then the F1 formulation was used again for printing on a different paper with the same template. But this time, this solution was reprinted on the same paper 4 times.

The F2 and F3 formulation was used for printing in the same way and 4-5 reprinting was done for each formulation.

The F1 formulation was taken again and used for printing with 5 reprints. As there was a problem with the imprints, so the problem was analyzed and troubleshooting was done. After that, F1 solution was reprinted on a paper for 5 times.

Then F4, F5 and F6 formulations were used for printing individually in the same manner and they were reprinted for 5, 3 and 5 times respectively.

F7, F8, F9, F10, F11, F12 & F13 formulations were refilled into the cartridge individually and set for printing and 5 times of reprints were done for each formulation.

After each time printing with an individual solution, the cartridge was rinsed with distilled water, and then by absolute ethanol. Then the cartridge was kept overnight to dry out.

2.2.7 Troubleshooting the Printer

Throughout the experiment, the printer was troubleshot for several times. Each time the cartridge was replaced into the carrier of the printer, the print-head of the cartridge was properly aligned with the carrier. Error 5200 was fixed by following the instructions of

the manual that was provided with the printer. Auto print head cleaning had to be done several times.

Chapter 3: Results and Discussion

3.1 Result

For each solution, the printed paper was inspected visually in a place where sufficient amount of light was present.For F1 formulation, the following imprint was obtained. The imprint was very light and several white bands were seen in the imprinted paper.

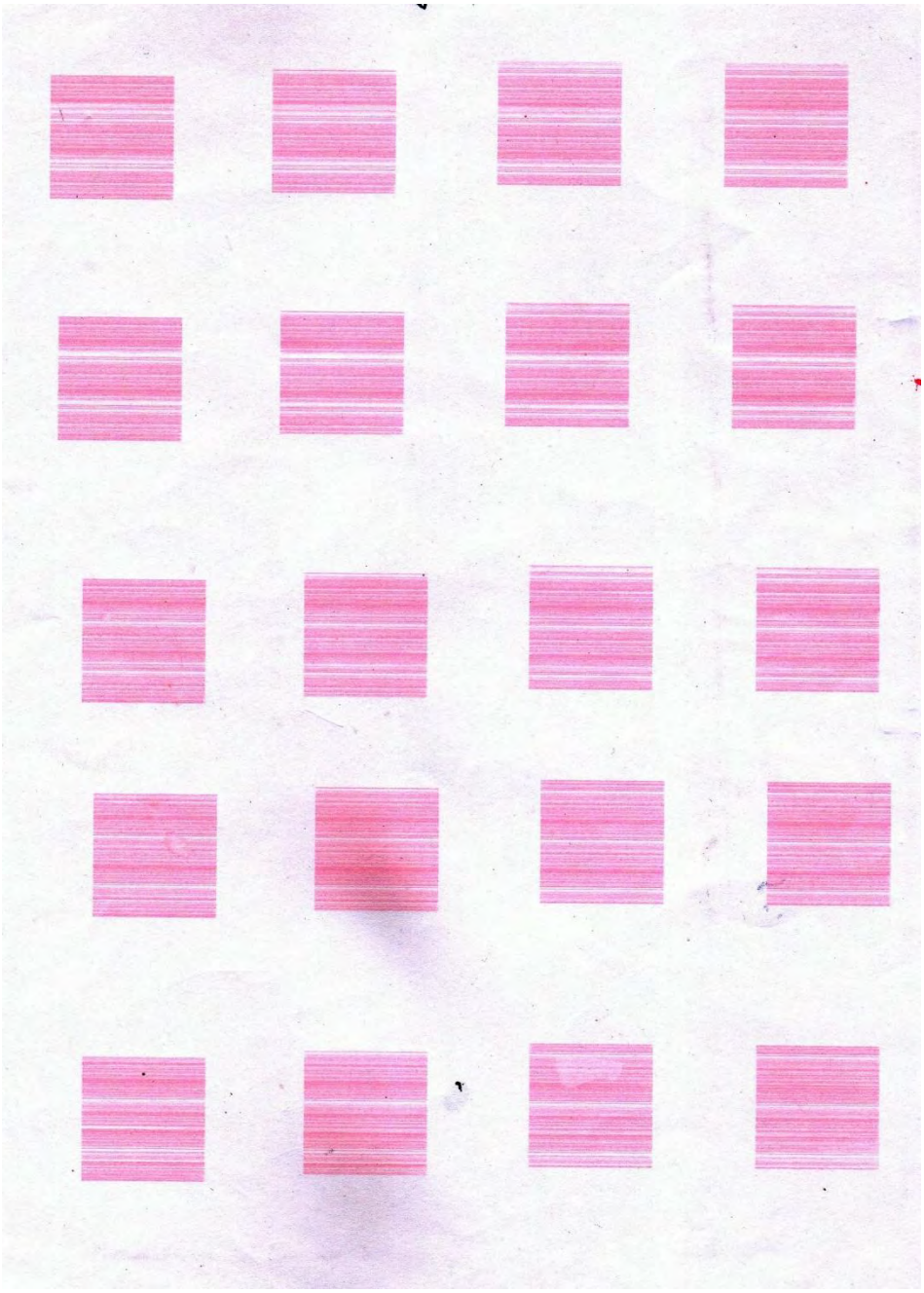


Figure 3.1: Inkjet printed paper for F1 formulation (no reprint)

F1 formulation was used again and reprinted for 4 times on the same paper as before to solve the problem of white bands. The printing quality was a lot better this time due to reprints. There were comparatively less number of bands were seen than before and the imprint was more prominent. The printed paper is given below:

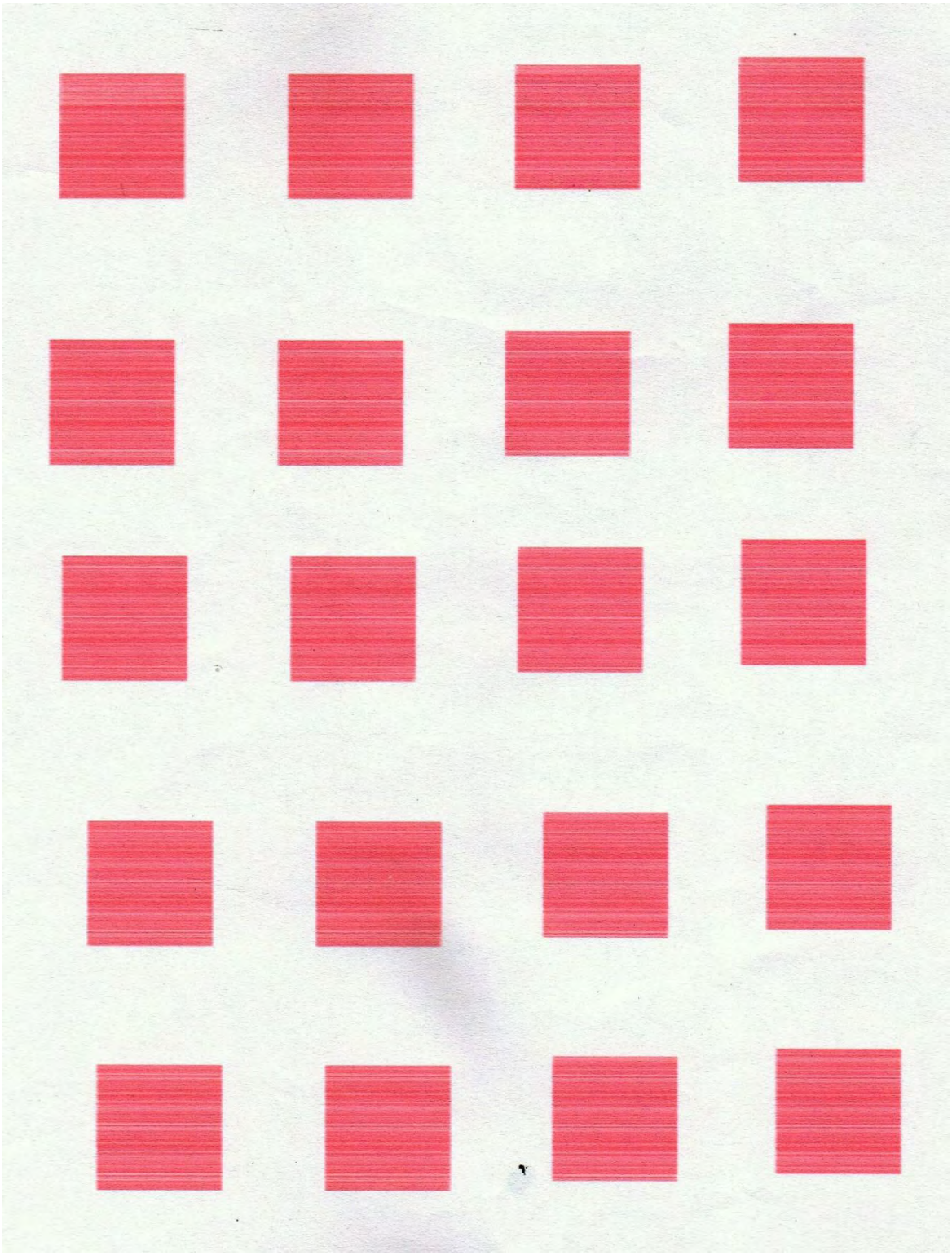


Figure 3.2: Inkjet printed paper for F1 formulation (4 reprints)

For F2 formulation, there was no visible line (no imprint) obtained on the paper. The printed paper was blank.

Likewise, the F3 formulation also did not show any visible lines on the paper. The printed paper was blank like the previous formulation (F2)

The F1 formulation was used again for printing and there were several white bands seen on the imprint. The printed paper is given below:

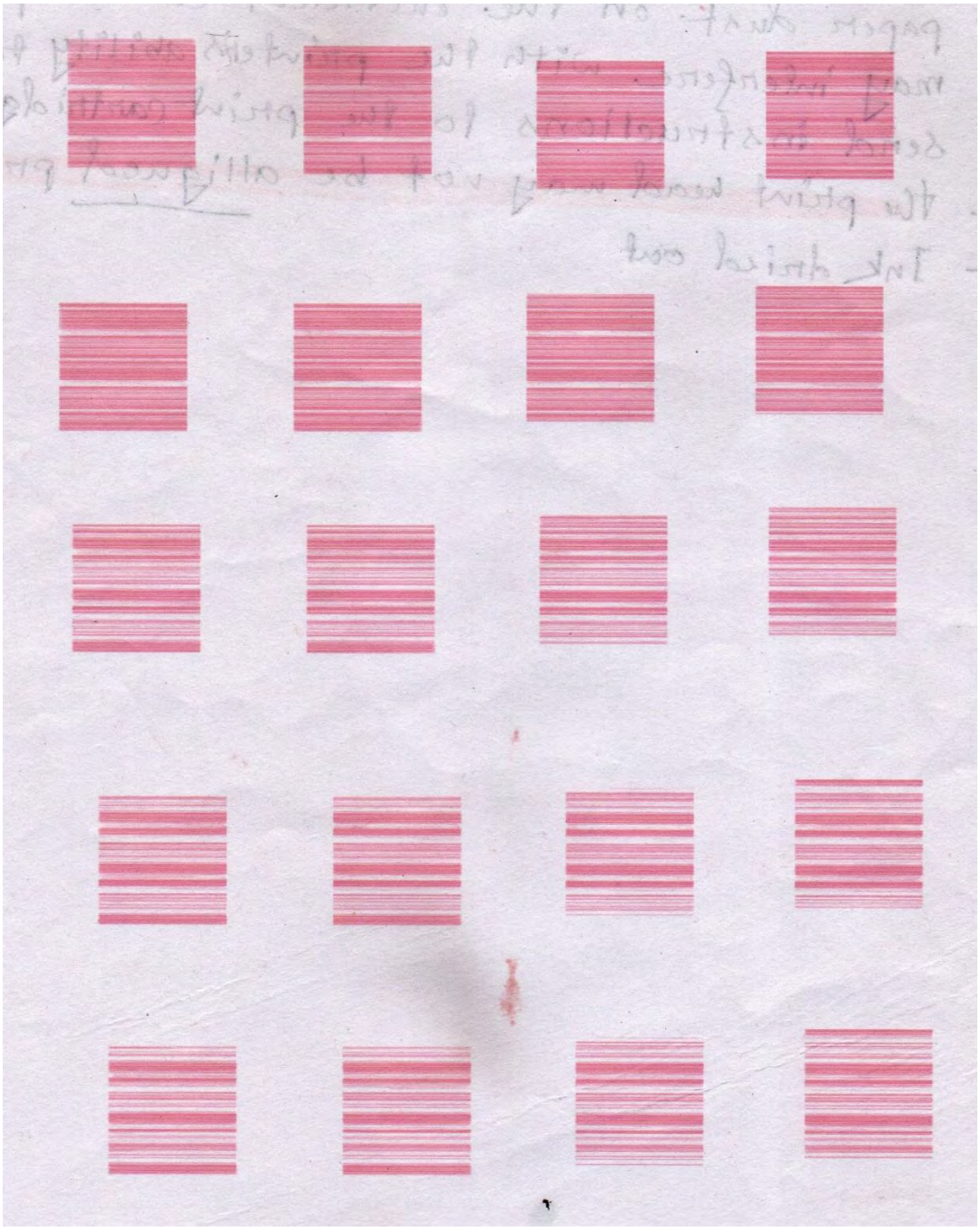


Figure 3.3: Inkjet printed paper for F1 formulation (white bands are visible)

The reasons behind those bands were searched. After troubleshooting, the same F1 formulation was used and 5 reprints were done on the same paper. The imprint was darker this time and there was comparatively less number of white bands on the prints. The printed paper is given below:

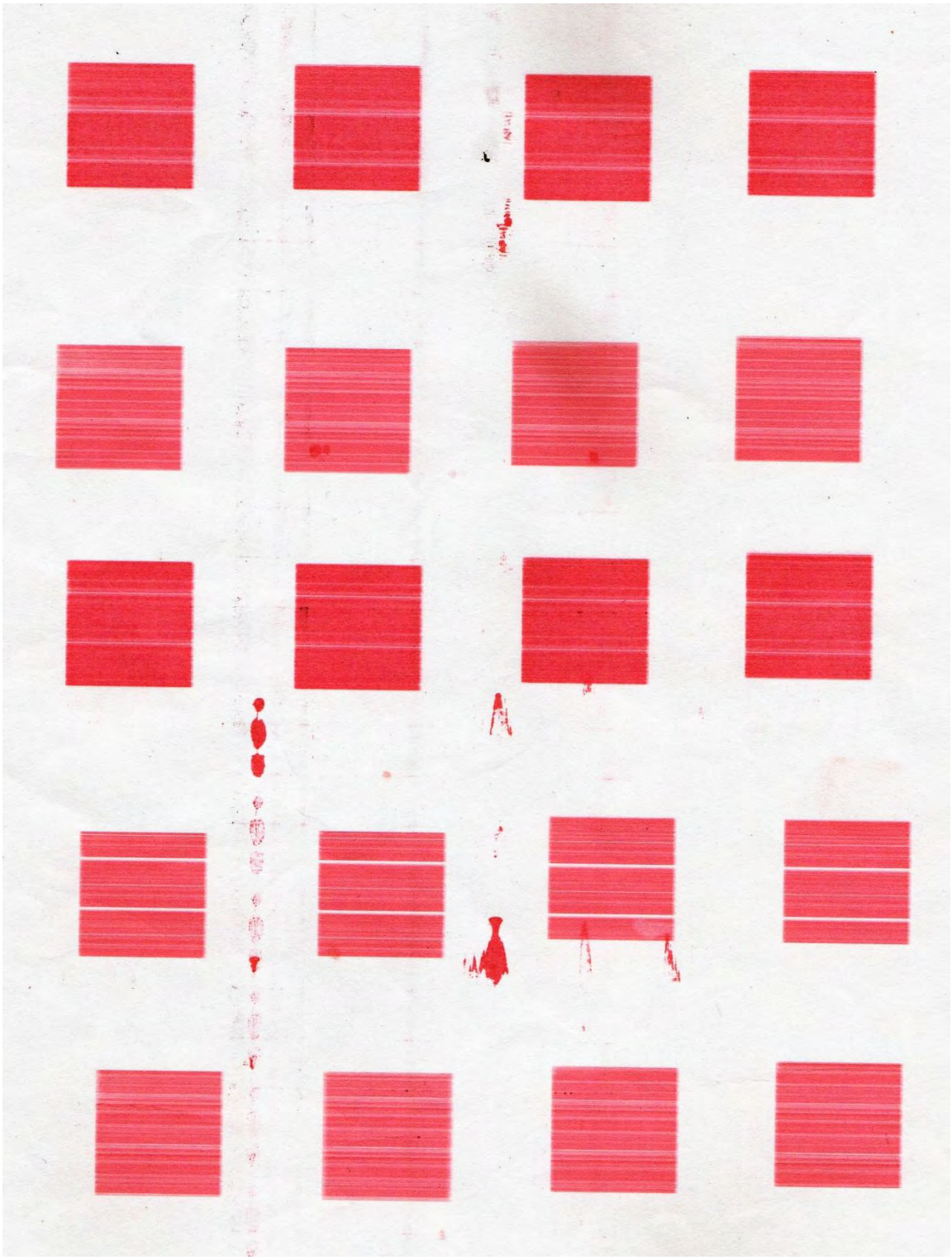


Figure 3.4: Inkjet printed paper for F1 formulation (5 reprints)

For F4 formulation, 5 reprints on the paper showed almost no visible white bands on the imprint and the color of the imprint was also prominent visibly. The printed paper is given below:

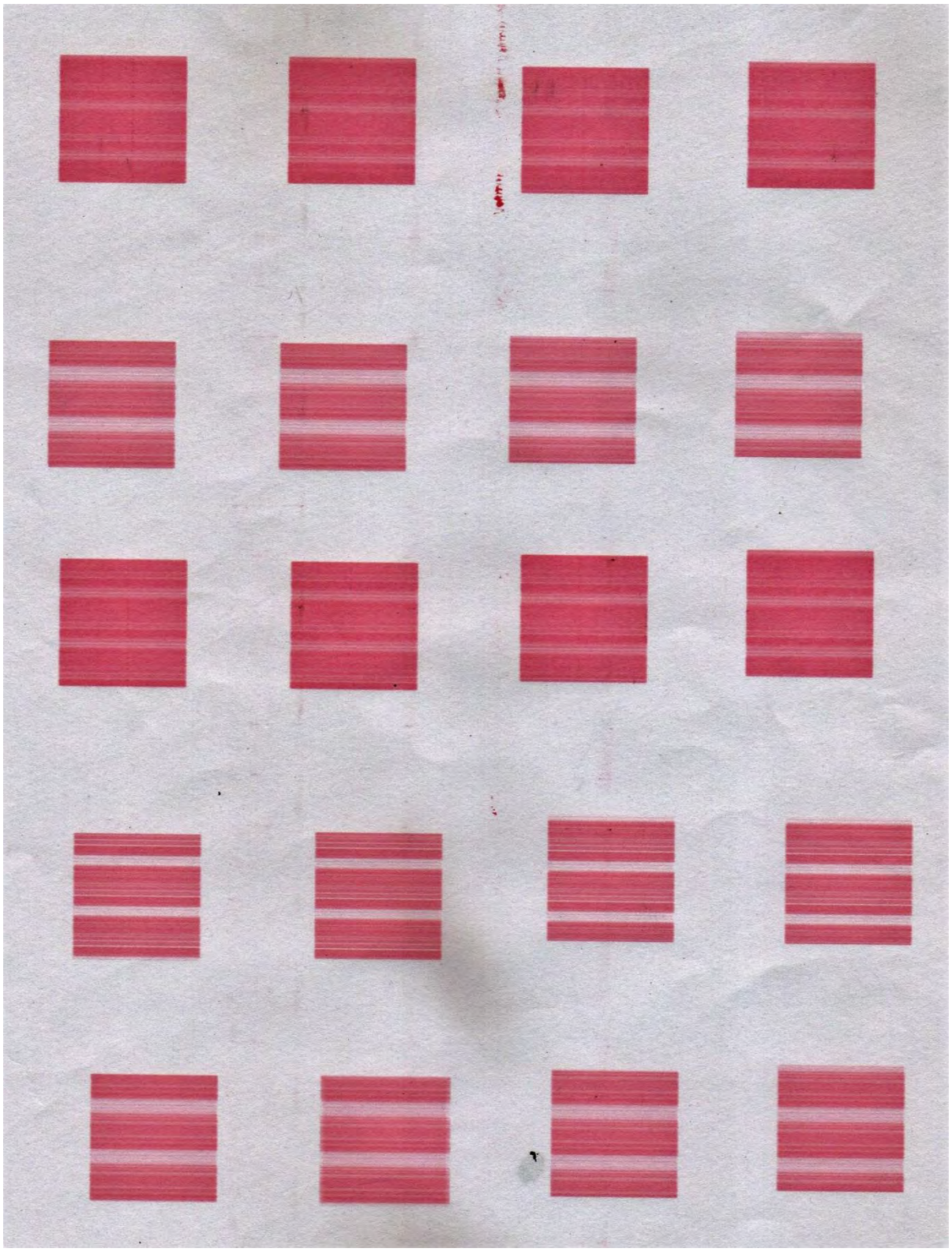


Figure 3.5: Inkjet printed paper for F4 formulation (5 reprints)

The F5 formulation did not show any good result. The printed lines were hardly seen even after 3 reprints on the printed paper. The printed paper is given below:

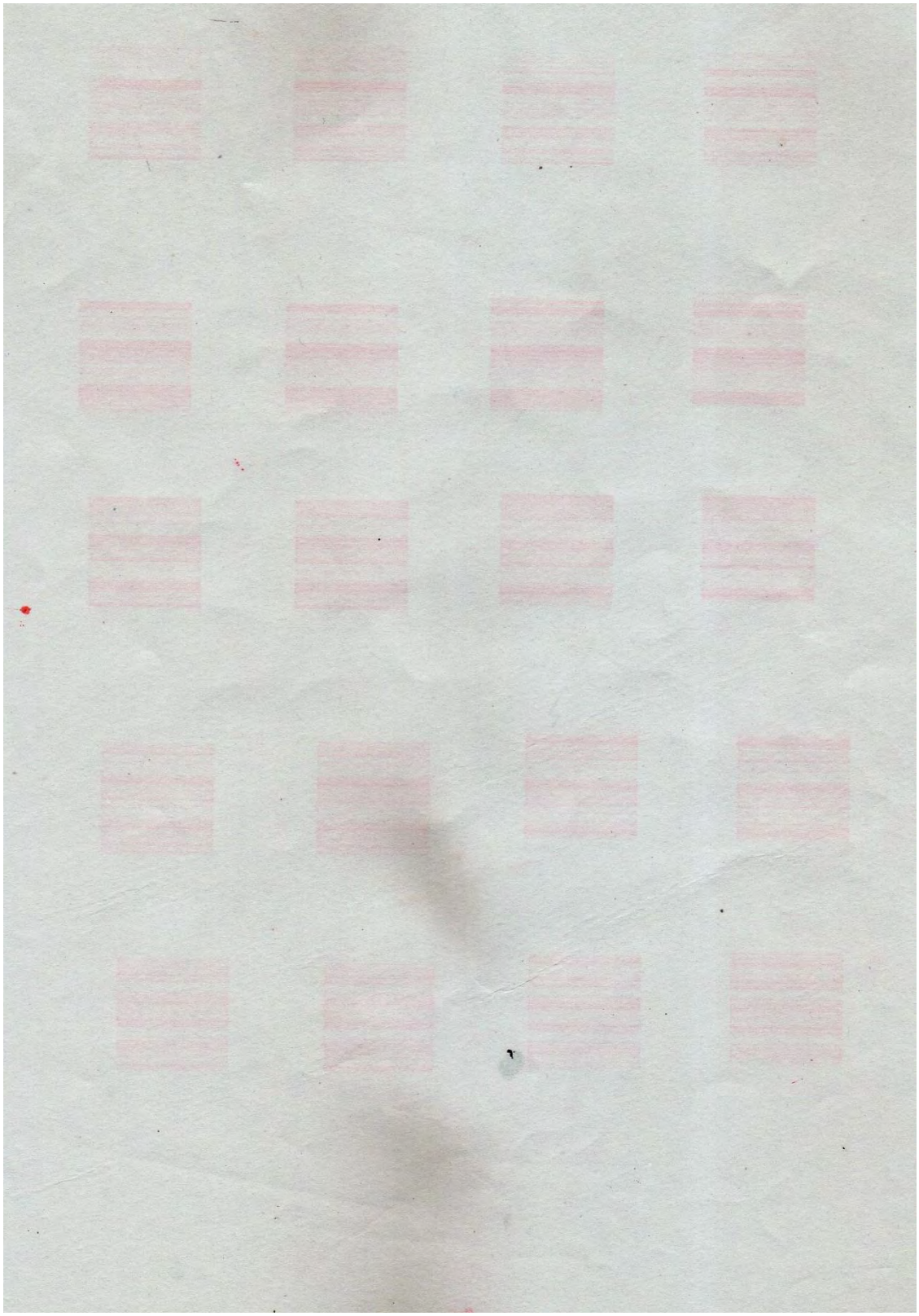


Figure 3.6: Inkjet printed paper for F5 formulation (3 reprints)

The F6 formulation showed very light imprint on the paper even after 5 reprints. The printed paper is given below:

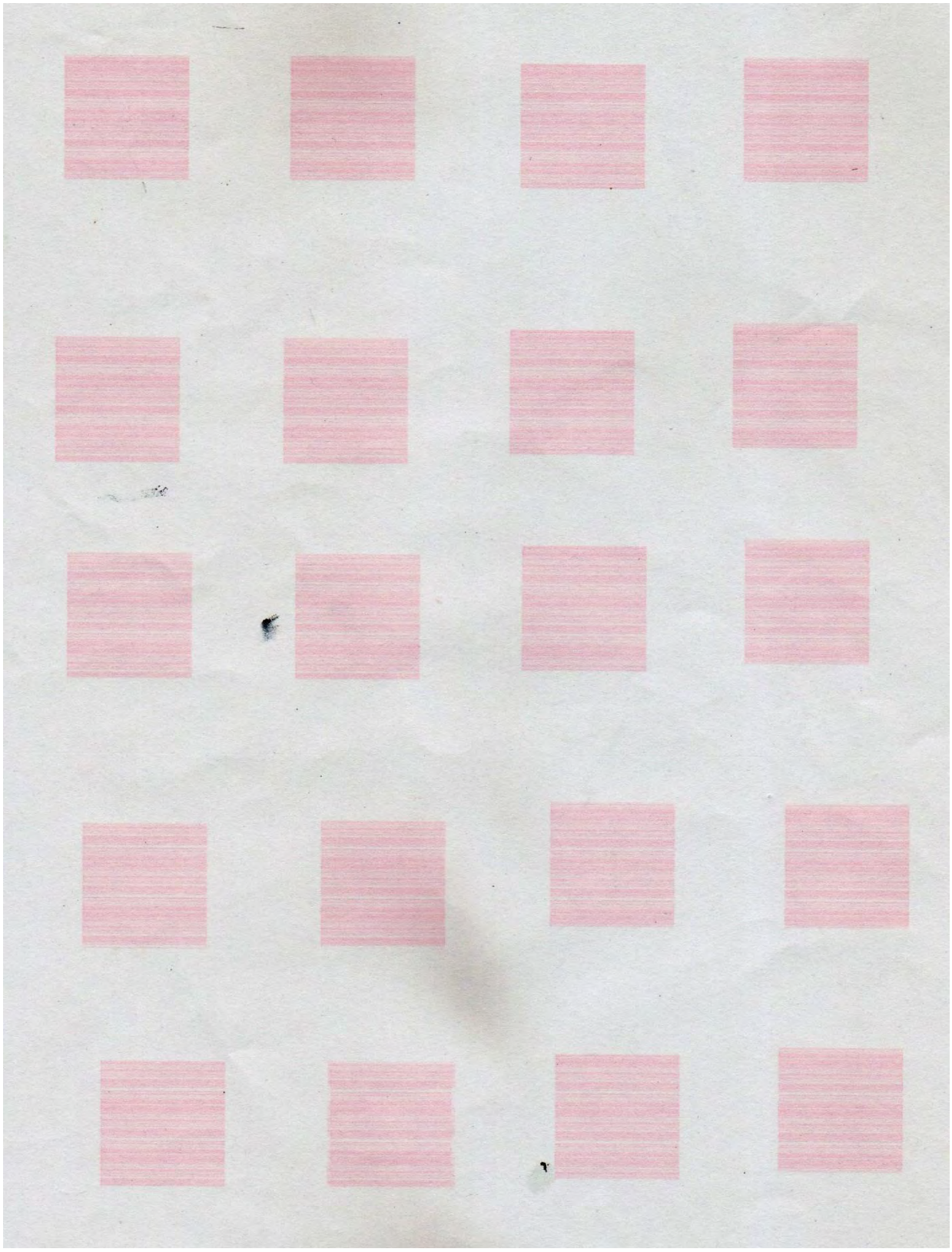


Figure 3.7: Inkjet printed paper for F6 formulation (5 reprints)

For F7 formulation, there was no visible line (no imprint) obtained on the printed paper. Then F8 formulation was prepared which was less viscous than the F8 formulation. But yet, there were no visible lines (no imprint) obtained on the printed paper with this ink solution.

Then again, F9 formulation was prepared which was less viscous even than the F8 formulation and there was only a few lines found on the printed paper with this ink solution. The imprint was too light that the printed lines could hardly be seen. The imprinted paper is given following:

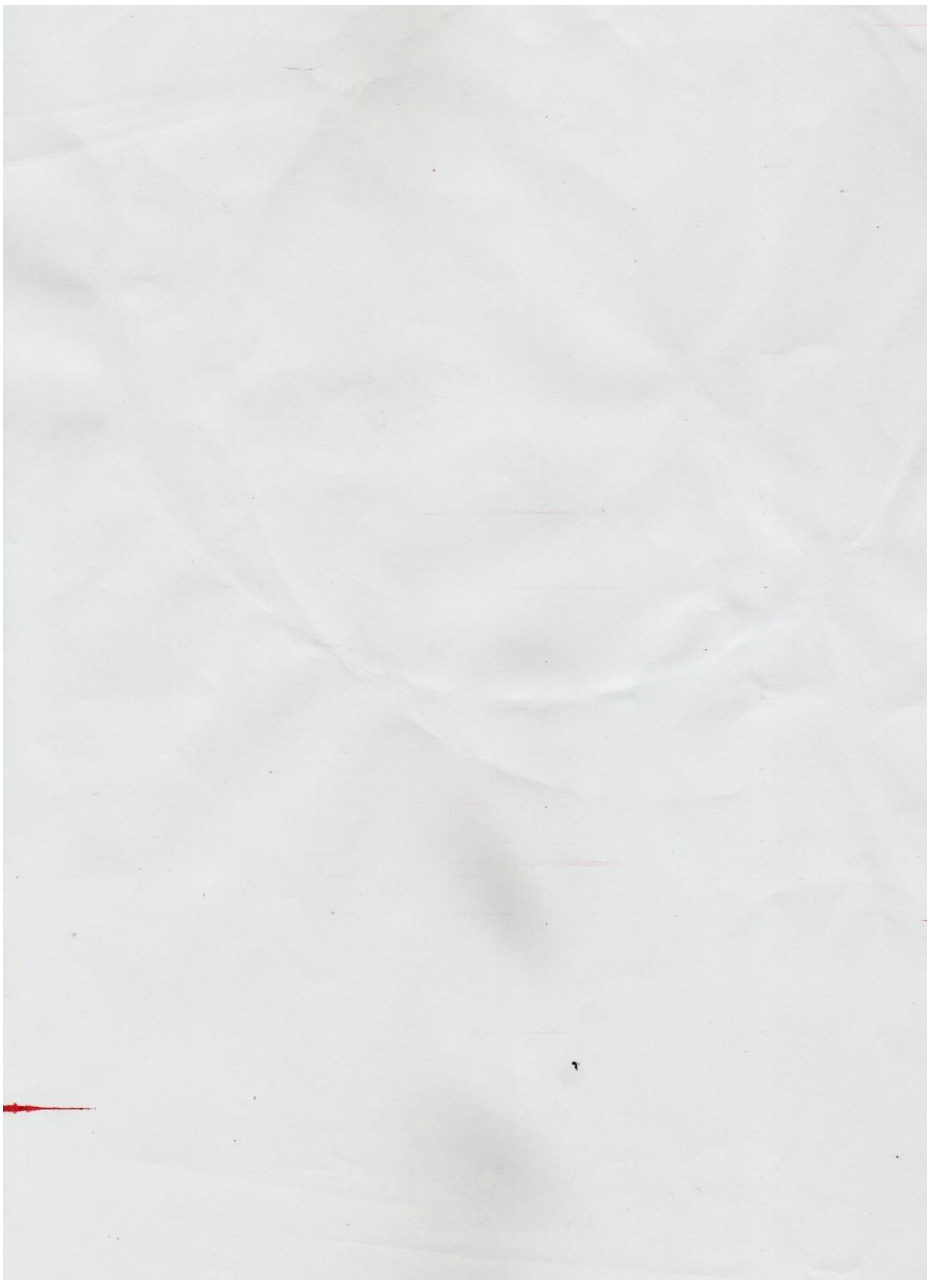


Figure 3.8: Inkjet printed paper for F9 formulation (5 reprints)

The F10 formulation that was less viscous than F9 formulation, was prepared which even gave a poor imprint, only a few lines were found on the printed paper. The imprint was also too light that the printed lines could hardly be seen like before. The imprinted paper is given below:

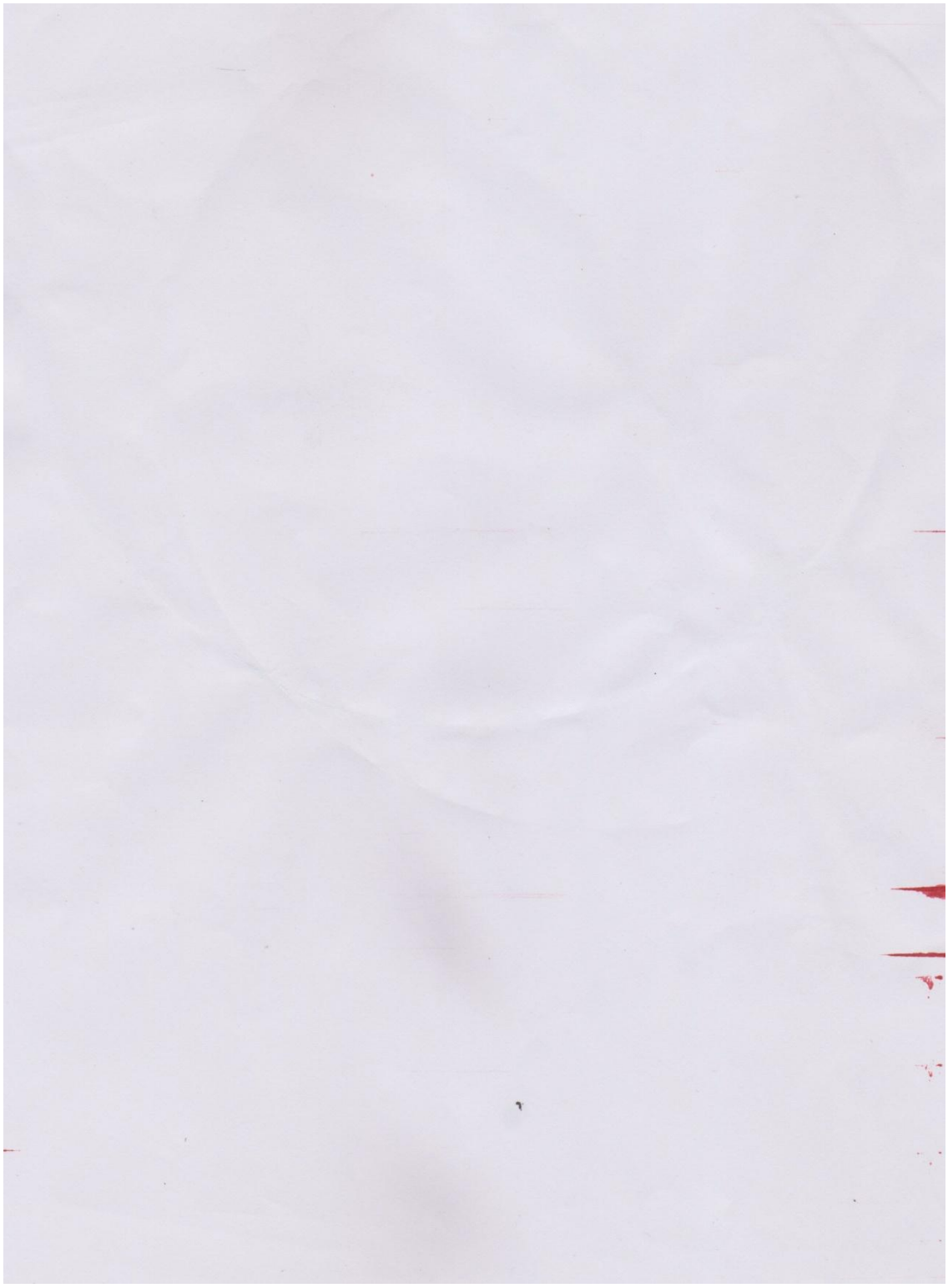


Figure 3.9: Inkjet printed paper for F10 formulation (5 reprints)

For F11, F12 and F13 formulation, no result was obtained and the printed paper was found blank (no visible lines) even after 5 reprints on the paper.

Table 3.1: A summary of the results obtained

Formulation	No. of reprints	Imprint quality
F1 (1st time)	0	Not satisfactory
F1 (2nd time)	4	Good
F2	4-5	No result
F3	4-5	No result
F1 (3rd time)	5	Not satisfactory
F1 (4th time)	5	Very good
F4	5	Satisfactory
F5	3	Not satisfactory
F6	5	Not satisfactory
F7	5	No result
F8	5	No result
F9	5	Not satisfactory
F10	5	Not satisfactory
F11	5	No result
F12	5	No result
F13	5	No result

3.2 Discussion

The F1 formulation gave a moderate imprint the first time and good imprint second time while printing.

It was observed that F2 & F3 formulation did not give any imprint on paper because of their increased viscosity. This explained that the viscosity of these formulations were so high that the print-head of the cartridge could not pass the solution and as a result the printed paper was blank even after 4-5 reprinting.

Although the F1 formulation gave a good imprint the second time while printing, the third time the imprint quality was not good and several white bands were observed in the printed squares. The reason behind such band formation was searched. Non-alignment of the print head was found as the reason. After troubleshooting, with the same F1 formulation, the obtained imprint was good and only a few number of white bands were obsereved.

For F7 formulation, there was no visible lines (no imprint) on the printed paper because the viscosity of the solution was too high. So after diluting it for once, F8 formulation was prepared but yet, there was no visible lines (no imprint) obtained on the printed paper with this ink solution. Then again the solution was diluted (2^{nd} time) and F9 formulation was prepared and there was only a few lines found on the printed paper with this ink solution. The solution was diluted again (3^{rd} time) considering that the F9 formulation was still too viscous to be ejected through the cartridge nozzle and F10 formulation was prepared which even gave a poor imprint, only a few lines were found on the printed paper. For F11, F12 and F13 formulation, no result was obtained as the printed paper was found blank (no visible lines) even after several reprints on the paper.

This explained that HPMC K4 MCR is a polymer which was not suitable in case of this thermal inkjet printing as the prepared ink solution was too viscous and the cartridge nozzle could not pass the solution to be jetted.

On the contrary, both of the polymers, CMC and gelatin helped the solution to imprint on the paper in a good manner. Several formulations with particular ratio of these polymers and the plasticizer showed very prominent imprint on the paper. Hence, these polymers could be used later for printing of drug on a film.

The physicochemical properties of CMC and gelatin were analyzed and it was found that CMC could be used for the OTF formulation in the best way as the molecular weight of CMC is relatively low. CMC also increases the viscosity of the solution in a controlled way that it can help the solution to pass through the print-head on the cartridge and make an imprint on the paper.

Table 3.2: The physicochemical properties of CMC and Gelatin

Properties	CMC	Gelatin	HPMC
Molecular weight	240.208 g/mol	15000-250000 g/mol (varies with different grades)	1261.45 g/mol
Solubility in water	20 mg/ml	67 mg/ml at 50°C	50 mg/ml
Viscosity	1500-3000 cP, 1% in H_2O	4.5-6 cP	2600-5600 cP, 2% in H_2O
Storage temperature	15-25°C	2-8°C	20-90°C
Stability	Stable, Incompatible with strong oxidizing agents.	Stable, Incompatible with strong oxidizing agents.	Stable, Incompatible with strong oxidizing agents.

Adopted from (National Center for Biotechnology Information., n.d.) ("Carboxymethylcellulose sodium salt High viscosity | Sigma-Aldrich," n.d.) (GIMA, 2012) ("Gelatin---Chemical Information Search," n.d.) ("Hydroxy propyl methyl cellulose | C56H108O30 - PubChem," n.d.)

The obtained specific formulations of CMC and gelatin can be used in future to prepare OTF with a particular API. For formulation of OTF, the API would have to be added into these placebo formulations and then printed on the required substrates in the same manner.

Since, there was no API used in this research, no evaluation tests were done in this work.

Chapter 4: Conclusion

The oral thin film drug delivery system fabricated by inkjet printing method can bring a tremendous and excellent scope for research as well as in the pharmaceutical production purpose. Moreover, the individual patients can have their personalized dosage forms in compliance with their age, gender, physical condition etc. From the present research, we can conclude that CMC and gelatin and glycerin can be used as polymers and plasticizers respectively for the formulation purpose of drug solution printing as these polymers can easily pass through the printer cartridge nozzle and the print head and also can provide a prominent imprint on the paper. However, further studies on drug-loaded formulation preparation, it's optimization, evaluation of mechanical properties, compatibility, stability, palatability, release kinetic studies are needed to be done to continue this research.

Chapter 5: Appendix

The F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12 & F13 formulations were prepared by using the following calculation:

The amount (w/w or w/v) of plasticizer or polymer to be added =

$$\frac{x \times total\ volume\ of\ solution}{100}$$

Here, x = percentage (w/w or w/v) of the plasticizer or polymer in the solution.

Chapter 6: References

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. https://doi.org/10.1016/j.ijpharm.2014.12.006

Arora, L., & Chakraborty, T. (2017). A review on new generation orodispersible films and its novel approaches. *Indo American Journal of Pharmaceutical Research*, *7*(01).

Bala, R., Khanna, S., Pawar, P., & Arora, S. (2013). Orally dissolving strips: A new approach to oral drug delivery system. *International Journal of Pharmaceutical Investigation*, *3*(2), 67. https://doi.org/10.4103/2230-973X.114897

Bhyan, B., Jangra, S., Kaur, M., & Singh, H. (2011). Orally fast dissolving films: Innovations in formulation and technology. *International Journal of Pharmaceutical Sciences Review and Research*, *9*(2), 50–57.

Boehm, R. D., Miller, P. R., Daniels, J., Stafslien, S., & Narayan, R. J. (2014). Inkjet printing for pharmaceutical applications. *Materials Today*, *17*(5), 247–252. https://doi.org/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. https://doi.org/10.1016/j.jconrel.2015.03.006

Buanz, A. B. M., Belaunde, C. C., Soutari, N., Tuleu, C., Gul, M. O., & Gaisford, S. (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. https://doi.org/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. https://doi.org/10.1007/s11095-011-0450-5

Carboxymethylcellulose sodium salt High viscosity | Sigma-Aldrich. (n.d.). Retrieved September 11, 2018, from

https://www.sigmaaldrich.com/catalog/product/sigma/c5013?lang=en&region=BD

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.https://doi.org/10.1016/j.ejpb.2015.08.012

Cilurzo, F., Cupone, I. E., Minghetti, P., Buratti, S., Gennari, C. G. M., & Montanari, L. (2011). Diclofenac fast-dissolving film: Suppression of bitterness by a taste-sensing system. *Drug Development and Industrial Pharmacy*,*37*(3),252-259.https://doi.org/10.3109/03639045.2010.505928

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. https://doi.org/10.1016/j.ijpharm.2015.03.017

Dobutamine | C18H23NO3 - PubChem. (n.d.). Retrieved September 12, 2018, from https://pubchem.ncbi.nlm.nih.gov/compound/36811

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. https://doi.org/10.1016/j.ijpharm.2017.11.052

Formoterol | C19H24N2O4 - PubChem. (n.d.). Retrieved September 12, 2018, from https://pubchem.ncbi.nlm.nih.gov/compound/3410

Galantamine | C17H21NO3 - PubChem. (n.d.). Retrieved September 12, 2018,fromhttps://pubchem.ncbi.nlm.nih.gov/compound/9651#section=2D-Structure

Garg, S., Goldman, D., Krumme, M., Rohan, L. C., Smoot, S., & Friend, D. R. (2010). Advances in development, scale-up and manufacturing of microbicide gels, films, and tablets. *Antiviral Research*, *88*(SUPPL.), S19–S29. https://doi.org/10.1016/j.antiviral.2010.09.010

Garsuch, V., & Breitkreutz, J. (2010). Comparative investigations on different polymers for the preparation of fast-dissolving oral films. *The Journal of Pharmacy and Pharmacology*, *62*(4), 539–545. https://doi.org/10.1211/jpp/62.04.0018

Gelatin---Chemical Information Search. (n.d.). Retrieved September 11,

2018,from:https://www.chemicalbook.com/ProductList_En.aspx?kwd=gelatin

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. https://doi.org/10.1016/j.ijpharm.2013.06.003

Genina, N., Fors, D., Vakili, H., Ihalainen, P., Pohjala, L., Ehlers, H., … Sandler, N. (2012). Tailoring controlled-release oral dosage forms by combining inkjet and flexographic printing techniques. *European Journal of Pharmaceutical Sciences*, *47*(3), 615–623. https://doi.org/10.1016/j.ejps.2012.07.020

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. https://doi.org/10.1016/j.ejpb.2013.03.017

GIMA. (2012). Gelatin handbook. *GIMA, Gelatin Manufacturers Institute of America*, *563*(888), 25. Retrieved from http://www.gelita.comhttp//www.nitta-gelatin.comhttp://www.gelatin.comhttp://www.rousselot.comhttp://www.weishardt.com

Godbole, A., Joshi, R., & Sontakke, M. (n.d.). ISSN : 2278-6252 ORAL THIN FILM TECHNOLOGY- CURRENT CHALLENGES AND FUTURE SCOPE ISSN : 2278-6252, *7*(2), 1–14.

Goodall, S., Chew, N., Chan, K., Auriac, D., & Waters, M. J. (2002). Aerosolization of protein solutions using thermal inkjet technology. *Journal of Aerosol Medicine : The Official Journal of the International Society for Aerosols in Medicine*, *15*(3), 351–357. https://doi.org/10.1089/089426802760292717

Hydroxy propyl methyl cellulose | C56H108O30 - PubChem. (n.d.). Retrieved September 12, 2018, from https://pubchem.ncbi.nlm.nih.gov/compound/57503849#section=Top

iP Series | PIXMA iP7220 | Canon USA. (n.d.). Retrieved September 16, 2018,from:https://www.usa.canon.com/internet/portal/us/home/products/details/printers/inkjet-single-function/ip-series/ip7220

Irfan, M., Rabel, S., Bukhtar, Q., Qadir, M. I., Jabeen, F., & Khan, A. (2016). Orally disintegrating films: A modern expansion in drug delivery system. *Saudi Pharmaceutical Journal*. https://doi.org/10.1016/j.jsps.2015.02.024

Kandler, M. R., Mah, G. T., Tejani, A. M., & Stabler, S. N. (2010). Hydralazine for essential hypertension. In M. R. Kandler (Ed.), *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd. https://doi.org/10.1002/14651858.CD004934.pub3

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. https://doi.org/10.1016/j.ajps.2016.05.004

Khan, S., Boateng, J. S., Mitchell, J., & Trivedi, V. (2015). Formulation, Characterisation and Stabilisation of Buccal Films for Paediatric Drug Delivery of Omeprazole. *AAPS PharmSciTech*. https://doi.org/10.1208/s12249-014-0268-7

Kieback, A. G., Felix, S. B., & Reffelmann, T. (2009). Quinaprilat: a review of its pharmacokinetics, pharmacodynamics, toxicological data and clinical application. *Expert Opinion on Drug Metabolism & Toxicology*, *5*(10), 1337–1347. https://doi.org/10.1517/17425250903282773

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. https://doi.org/10.1517/17425247.2013.859134

Lang, M., Kampf, J. W., & Matzger, A. J. (2002). Form IV of Carbamazepine. *Journal of Pharmaceutical Sciences*, *91*(4), 1186–1190. https://doi.org/10.1002/jps.10093

Loxapine | C18H18ClN3O - PubChem. (n.d.). Retrieved September 12, 2018, from https://pubchem.ncbi.nlm.nih.gov/compound/3964

Melendez Peter A., Kane Kevin M., Ashvar Claudine S., Albrecht Mary, S. P. A. (2011). Thermal Inkjet Application in the Preparation of Oral Dosage Forms: Dispensing of Prednisolone Solutions and Polymorphic Characterization by Solid-State Spectroscopic Techniques. *International Journal of Drug Development and Research*, *3*(2), 26–33. https://doi.org/10.1002/jps

Nagarajan G, Shaik Mohammad Abdulla, Raja Amaranth P, Venu Madhav K, Jona Methusala R, R. B. . (2015). Formulation and evaluation of topical nano emulgel of adapalene. *World Journal of Pharmaceutical Sciences*, (93).

National Center for Biotechnology Information. (n.d.). Carboxymethylcellulose sodium (USP) | C8H15NaO8 - PubChem. Retrieved September 11, 2018, from https://pubchem.ncbi.nlm.nih.gov/compound/23706213

Number, C. (n.d.). Clopidogrel Bisulfate (Cas No 120202-66-6) Clopidogrel Bisulfate, (120202), 3–6.

Oral Thin Films | ARx Drug Delivery Systems. (n.d.). Retrieved September 11, 2018, from https://arxpharma.com/drug-delivery-systems/oral-thin-films/

Patil, P., & Shrivastava, S. K. (2014). Fast Dissolving Oral Films : a Novel Drug Delivery System. *International Journal of Science and Research (IJSR)*, *3*(7), 2088–2093.

Rapidfilm® - tesa Labtec GmbH. (n.d.). Retrieved September 11, 2018, from http://www.tesa-labtec.com/eng/rapidfilm

Scoutaris, N., Alexander, M. R., Gellert, P. R., & Roberts, C. J. (2011). Inkjet printing as a novel medicine formulation technique. *Journal of Controlled Release*, *156*(2), 179–185. https://doi.org/10.1016/j.jconrel.2011.07.033

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

Shanmugam, S. (2016). Oral Films: A Look Back. *Clinical Pharmacology & Biopharmaceutics*, *05*(02), 2–4. https://doi.org/10.4172/2167-065X.1000e124

Sharma, D., Kaur, D., Verma, S., Singh, D., Singh, M., & Singh, G. (2015). Fast Dissolving Oral Films Technology : A Recent Trend For An Innovative Oral Drug Delivery System. *International Journal of Drug Delivery*, *7*(October), 60–75.

Siddiqui, N., Garg, G., & Kumar Sharma, P. (2011). A Short Review on " A Novel Approach in Oral Fast Dissolving Drug Delivery System and Their Patents " *Advances in Biological Research*.

Tarcha, P. J., Verlee, D., Hui, H. W., Setesak, J., Antohe, B., Radulescu, D., & Wallace, D. (2007). The application of ink-jet technology for the coating and loading of drug-eluting stents. *Annals of Biomedical Engineering*, *35*(10), 1791–1799. https://doi.org/10.1007/s10439-007-9354-2

Zhang, H., Zhang, J., & Streisand, J. B. (2002). Oral mucosal drug delivery: Clinical pharmacokinetics and therapeutic applications. *Clinical Pharmacokinetics*. https://doi.org/10.2165/00003088-200241090-00003