Design and Optimization of 3D Printed Orodispersible Film

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.)

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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.
4. I have acknowledged all main sources of help.

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Approval

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Ethics Statement

The study does not involve any kind of animal and human trial.

Abstract

The oral route of drug administration is an alternative and preferable route over other available routes as it is considered to be the safest and effective route of administration. For this reason, the number of marketed oral medication is increasing day by day. The benefits of 3D printed oral medication are also emerging. As elderly patients and patients suffering from mental disorders and motion sickness cannot swallow oral tablets easily, orodispersible films are most suited for them. Orodispersible films are mainly similar to conventional tablets but very thin in appearance and consist of super disintegrants which allow them to dissolve in the mouth. These films are designed to attach to the buccal cavity in order to provide therapeutic action. 3D printing technology is a process through which three dimensional objects can be prepared from the aid of a digital file. This technology utilizes a virtual model to produce physical objects using controlled apparatuses. Several methods and different softwares can be used to formulate a 3D printed orodispersible film. Autodesk MAYA 2018 is a software that can effectively design orodispersible films with appropriate information and data. The present study incorporates the use of this software through which fifteen orodispersible films were designed. Therefore, this paper attempts to provide an overview of the methods and designing properties of 3D printed orodispersible films and their numerous applications and advantages.

Dedication

I would like to dedicate this research based project work to my supervisors Professor Dr. Eva Rahman Kabir, Dr. Hasina Yasmin and Dr. Md. Jasim Uddin.

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List of Acronyms

3D Three dimensional

ODF Orodispersible film

3DP Three-dimensional printing

ISO International Standard Organization

AM Additive manufacturing

RP Rapid proto-typing

TIJ Thermal inkjet printing

FDM Fused deposition modeling

ODT Orally disintegrating tablet

API Active pharmaceutical ingredient

HCl Hydrochloric acid

HBr Hydrobromic acid

FDA Food and Drug Administration

PMA Premarket approval

PMN Premarket notification

Chapter 1

Introduction

1.1 Introduction

During the past few years, there has been significant development in innovative drug delivery system to assure adequacy, security and patient compliance. As discovery and improvement of a medicinal agent is a complex, expensive and tedious procedure, current movements are sliding toward designing and creating innovative drug delivery system for existing medications. In order to accomplish greatest patient acceptance, the pharmaceutical industry has directed their research to the improvement of innovative delivery systems. In general, different drug dosage forms have different limitations such as, suspensions require shaking for accurate dosing, solutions need measurement tools like spoon or cup for accurate dosing, tablets and capsules are difficult to swallow for elderly patients and children, parenterals and rectal dosage forms require assistance of others and transdermal formulations can cause skin irritation (Webster, Camilleri, & Finn, 2016). Regarding this issue, oral films have been declared as a promising approach amongst the most encouraging methodologies as a modern drug delivery system for oral administration, demonstrating incredible interest and a market opportunity (Bilal et al., 2016) .

Administration of drug through oral route is a most convenient route because of its ease of administration, attractiveness, flexibility and patient compliance. Concerning drug administration through oral route, numerous alternatives have persistently been exhibited by using current novel technologies for pediatrics, geriatrics, sick and resistant patients (Chougule, Bhat, & Chimkode, 2017). Bioadhesive mucosal dosage forms including adhesive tablets, gels and patches are results of advancement in technology. Among different dosage forms, the use of polymeric films for delivering drug into buccal cavity has showed

great potential. Orally disintegrating films (ODFs), when put on tongue, promptly hydrates by soaking in saliva following disintegration and discharging active therapeutic agent from the dosage structure. ODFs are preparations which are ordinarily prepared utilizing hydrophilic polymers facilitating fast disintegration upon contact with salivation (Irfan et al., 2016).

Inexpensive lyophilization, high mechanical quality, fast disintegration, and decreased swallowing difficulty are the quality characteristics of ODFs. ODFs have accomplished astounding magnitude in pharmaceutical industry as they have remarkable properties and fast disintegration time spanning from seconds to one moment (Trenfield et al., 2018). ODFs design enables to incorporate a variety of drug into the film depending on their pharmacological effect e.g., antitussive, antiepileptic, anti-asthmatic, expectorant, and so forth (Irfan et al., 2016).

The patient-driven drug development has been under significant consideration over the last few years. It was centered on novel dosage forms of medicine and innovative procedures. Increasing interest for personalized devices integrated with an extension of technological advancement, drives the significant development in customized drug, expressed for example by the creation of little arrangement of exclusively chosen portions and customized prostheses that meet the anatomical needs of patients (Ventola, 2013). Three-dimensional printing (3DP) is accepted to be the most progressive and amazing among the numerous discoveries launched into pharmaceutical and biomedical market. This method is perceived as an adaptable device that can assemble different devices accurately. It works technologically by preparing novel dosage forms, tissues and organs designing and disease modeling (Jamróz, Szafraniec, Kurek, & Jachowicz, 2018).

Three-dimensional printing is one of the fastest developing branches of technology, discipline and development currently. The term three-dimensional printing was characterized by

International Standard Organization (ISO) as: “fabrication of devices by utilizing materials that are discharged, with the aid of a print head, nozzle, or another printer technology”. It differs from routinely used subtractive process and developmental assembling procedures; this system is one of the techniques for additive manufacturing (AM) in which the parts are developed from the data obtained from 3D model software while the materials are combined in a layer by layer manner. The practical approach of this manufacturing process is called rapid prototyping (RP) and its positive sections include the decrease of prototyping time and costs, simple adjustments of an item at a designed dimension, the likelihood of assembling of little structures, individualized item arrangement or structures that are difficult to be shaped with subtractive procedures (Jamróz et al., 2018). Three-dimensional printing process mainly depends on computer supported designs to accomplish unparalleled adaptability, efficient, and excellent assembling capacity of pharmaceutical goods. The procedure includes 3D proto-typing of layer-by-layer creation (using computer-aided design models) to incorporate medicinal agent into the dosage form which is required (Alhnan et al., 2016). 3DP is increasing expectations in pharmaceutical formulation development as a viable system to overcome the challenges of traditional pharmaceutical unit operations. For example, the conventional manufacturing unit task including processing, blending, granulation and compression can result in divergent characteristics of the finished products concerning drug loading, drug discharge, drug stability and stability of pharmaceutical dosage form (Oyewumi, M.O. 2015).

ODFs are typically introduced to the patient as stamp-like strips, either in single-portion sachets or contained in multi-portion packs. Ideally, ODFs ought to be sealed individually so as to improve stability and decrease the probability of overdosing because of films sticking together. Potentially, advanced multi-dose dispensers could be utilized where the ideal dose is

attained by the patient or caregiver by cutting strips of fitting length from a tape-like supply (Lopez, Ernest, Tuleu, & Gul, 2015).

1.2 Overview of Mucosal Lining of Oral Cavity

The oral mucosal lining contains a layer of stratified squamous epithelium as the outermost layer which is followed by a base membrane then a lamina propria and lastly the innermost layer or sub mucosa. Permeability of the buccal mucosa is higher than skin. It is approximately 4-4000 times higher comparing to the permeability of the skin, which is different in each region. The order of permeability is such that: sublingual > buccal > palate according to the keratinization and thickness properties of these regions. Throughout the oral mucosa there are two permeation routes available for passive drug delivery. One of them is Para-cellular pathway and the other in Trans-cellular pathway. The nature of cytoplasm and the intercellular spaces is hydrophilic which helps hydrophilic drugs to penetrate while cellular membrane is lipophilic in nature which allows the permeation of drugs lipophilic in nature. Oral mucosal lining is tolerant to potential allergens due to having high blood supply, robustness, lack of Langerhans cell and requiring short time to recover after stress and damage. The pH of buccal mucosa is 6.28 +/- 0.36. There is one major limitation associated with buccal mucosal drug delivery which is the low flux leading to low drug bioavailability of some specific drugs for those addition of a permeation enhancer might be needed (Hanif, Zaman, & Chaurasiya, 2015).

1.3 3D Printing Technologies for Oral Drug Delivery

There are various techniques for the 3D printing for orodispersible films, which have been described below.

1.3.1 Inkjet Printing

Distinctive blends of active agents and excipients (ink) are accurately sprayed in little droplets (desired amount of drug) or continuous jet method in fluctuating sizes, layer by layer into a non-powder substrate in this method. This method mainly includes powder-based 3D printing that utilizes a powder base (powder substrate) for the sprayed ink where it hardens into a solid dosage form (Oyewumi, 2015).

1.3.2 Direct-Write Printing

Direct-write is an optimistic method amongst the most encouraging methodologies as it offers adaptability in material determination, ease of construction, and capacity to develop complex 3D structure. It utilizes a computer directed translational stage that moves as a pattern-generating device so as to obtain, layer-by-layer, 3D microstructure. This facilitates the composition to be differed throughout the 3D structure that provides a level of control which is not accessible with traditional fabrication (Oyewumi, 2015).

1.3.3 Zip Dose Printing

This method gives a customized dose regardless of the delivery of a high medication load with high dissolution and disintegration levels by assembling exceedingly porous material (Oyewumi, 2015).

1.3.4 Thermal Inkjet (TIJ) Printing

TIJ technique comprises of a micro scale resistor that warms a thin film of ink liquid (situated in the ink reservoir) configuring a vapor bubble that nucleates and grows to shove the ink drop out of a nozzle. TIJ manages the process through which solutions of medication or preparations are administered into 3D films or drug careers (Oyewumi, 2015).

1.3.5 Fused Deposition Modeling (FDM)

This procedure is mainly used for different dosage forms where polymers are used as a major component of the structure, for example, inserts, zero-order release tablets, multi-layered tablets and quick dissolving devices. In the process, the desired polymer is dissolved and expelled through a movable nozzle which is heated. The layer by layer discharge of the polymer is repeated along x-y-z stage, trailed by hardening to make a shape recently characterized by the computer directed design models. The advantages of this technique are most reduced expense and great mechanical strength. The only problem is that thermoplastic materials can't be utilized and API can deteriorate because of the high temperature (Oyewumi, 2015).

1.4 Types of Oral Film

Depending upon the design and disintegration time, there are different types of oral film. These are:

i. Fast dissolving oral film
ii. Sustained-release oral film
iii. Mucoadhesive film
iv. Oral patch

Mucoadhesive films and oral patches are generally available as buccal sustained release dosage forms. Local or systemic treatment can be accomplished with different kinds, whereby especially for mucoadhesive films systemic treatment might be acknowledged for the most part by methods for absorption of the API through the oral mucosa. Different application areas are also possible. ODFs are generally administered onto the tongue. Mucoadhesive films are normally placed onto the cheeks, yet the palate or sublingual are possible (Hoaffmnn, Breitenbach, & Breitkreutz, 2011).

1.5 Ideal Characteristics ODF

i. Film should be thin and exquisite (Bala, Khanna, Pawar, & Arora, 2013).

ii. Accessible in different size and shapes (Sheoran, 2018).

iii. Unobstructive (Bala et al., 2013).

iv. It should stick to the oral cavity effectively (Liew, Peh, & Fung Tan, 2013).

v. Should be able to disintegrate without water (Irfan et al., 2016).

vi. Modified discharge (Bala et al., 2013).

vii. There should be minimum or no residue left in the mouth afterwards (Abdulraheman Z.S., Patel, 2015).

1.6 Advantages of ODF

This dosage form has some special advantages over other oral formulations, such as,

1. Quick disintegration in the oral space is achievable due to accessibility of greater surface area that enhances the onset of action, reduce the dose, and upgrade the effectiveness and wellbeing profile of the medicine (Sheoran, 2018).
2. Most ODTs are delicate and fragile, which need exceptional packaging for ensuring safety throughout stocking and transportation. On the other hand, ODFs are adaptable, they are not as delicate as oral tablets, transportation, and managing and storage are simpler (Liew et al., 2013).
3. ODFs offer fast, accurate dosing in a safe, efficacious format that is convenient and portable, without the need for water or measuring devices. This is one of the reasons why the pharmaceutical companies and consumers have adopted ODFs as a practical and accepted alternative to traditional over the counter medicine forms such as liquids, tablets, and capsules (Abdulraheman Z.S., Patel, 2015).

4. Oral strip technology gives a substitute route for drugs which eliminates first pass metabolism (Caliceti & Matricardi, 2019).
5. This dosage form is ideal for patients experiencing dysphagia, recurrent emesis, mental disorders and motion sickness as they can't swallow expansive amount of water (Sheoran, 2018).
6. ODFs are distinctively similar to a postage stamp by appearance and dissolve on the patient's tongue for fast release of at least one or more APIs in a matter of seconds. The detailing of dissolvable film is generally encouraged through water based polymeric materials that comprises a wide range of molecular weight (MW), which gives adaptability to accomplish specific physical properties (Khames, 2019)
7. From the point of view of business, thin film drug delivery innovation offers an open door to new business opportunities like differentiating products, product advancement, patent expansions and life cycle controlling (Abdulraheman Z.S., Patel, 2015).
8. Loss due to friability is less. (Sheoran, 2018).
9. These require more affordable packaging and processing materials (Liew et al., 2013).
10. No scope of distress due to choking (Panda, Dey, & Rao, 2012).
11. Less amount of excipients is needed (Sheoran, 2018).
12. Can be utilized as oral (local) anesthetic as the replacement the of syringes in dental activities (Pallavi & Pallavi, 2017).
13. Great mouth feel (Patil, More, & Tour, 2015).
14. Fast absorption, quicker action and enhanced bioavailability (Pallavi & Pallavi, 2017).
15. Increased patient compliance (Panda et al., 2012).
16. Upgraded product life cycle (Chaudhary, Gauri, Rathee, & Kumar, 2013).
17. Improved stability (Panda et al., 2012).

18. Lyophilization is a typical procedure for assembling ODTs, the assembling of ODFs depends on the same procedure as transdermal patch technology, which is more affordable than lyophilization (Hoaffmnn et al., 2011).

1.7 Challenges of ODF

This dosage form has some special challenges such as,

1. Drugs which get degraded at buccal pH cannot be used (Panda et al., 2012).
2. Drugs which cause inflammation or discomfort to the buccal mucosa cannot be administered through this route (Bala et al., 2013).
3. A medicine which is needed in a small amount can be administered only in orodispersible film form. Large dose cannot be formulated into the strip. According to a research, the level of concentration of the active can be increased up to 50% per dose weight. ODFs are constricted to highly potent low-dose drugs (De Caro et al., 2019).
4. A significant disadvantage of orodispersible dosage forms is taste. Taste masking may decrease greatest medication load. For tremendously bitter APIs, taste masking may even be incomprehensible (Journals et al., 2018).
5. ODFs are fragile and needs special packaging so that these are protected from water (Mady, Donia, & Al-Madboly, 2018).
6. The manufacturing process requires solvents and high temperature for drying. These elements possibly influence stability of the medicine or the different excipients, like sweeteners and flavors (Tian et al., 2017).

Table 1 Examples of global marketed orodispersible films (Hoaffmnn et al., 2011)

Brand Name	**Manufacturer**	**Drug(generic) Name**
Benadryl[R] Allergy Quick dissolve strip	Mc Neil-PPC	Diphenhydramine HCL
GAS-X[R] Thin strips	Novartis consumer health	Simethicone
Risperidon HEXAL[R] SF Schmelzfilm	Hexal AG	Risperidone
Sudafed[R] Quick dissolve strips	Mc Neil-PPC	Phenylephrine HCL
Theraflu[R] Thin strips long acting cough	Novartis consumer health	Dextromethorphan HBr
Triaminic Thin strips	Novartis consumer health	Dextromethorphan Phenylephrine HCL

1.8 Limitations of 3D Printing

Despite the fact that 3D printing is exceedingly encouraging for manufacturing customized dosage form, there are various regulatory and technical difficulties that should be solved before it is generally used for pharmaceutical applications (Horst, 2018).

Various 3D printing technologies depend on nozzle system to construct sequenced layers while the printed item is formed. This makes it challenging to keep up a reproducible and

consistent flow on demand as the print head stops and re-begins in the middle of printing a solitary or multiple objects (Jamróz et al., 2018). In powder based 3D printing for instance, obstructing of the nozzles in the 3D printer head, binder migration and unsuitable powder feeding, bleeding and scratching are issues that should be tended to (Hernandez, 2015).

Another restriction of 3D printing is appearance of the final product, where defects on the surface might be obvious. Moreover, post-treatment procedures for example, drying time, rate and technique can influence the properties and appearance of the finished product. This is of critical significance in powder based; inkjet and expulsion based 3D printing techniques which all require post-operative drying (Alhnan et al., 2016).

Steam lines generally appear between layers, when FDM 3D printing is being used. Whereas in case of FDM, it is reckless to incorporate thermoplastic polymers to form the product through extrusion from a hot nozzle (Alhnan et al., 2016). There are a few restrictions: high temperature procedure may degrade the primary material(s), requires planning of fibers ahead of time and it is restricted to thermoplastic polymers (Lim, Kathuria, Tan, & Kang, 2018).

So far, the choices of material, colors, and surface finishes right now accessible for 3D printing are moderately restricted when contrasted with traditional drug dosage forms (Lim et al., 2018).

Regarding regulatory issue, eighty-five 3D printed medical devices and implantables have got clearance from FDA (Adams-Hess, Anne Hanna, Partner, & Sonia Weiss, 2018). A few pathways exist to acquire FDA endorsement; among them one is: PMA. To date, all endorsed medical devices and implantables created utilizing this methodology got clearance by the “Premarket Notification” (PMN) demonstrating that "3D printed item is significantly equivalent to a lawfully marketed gadget" (Lennox, 2014). Such a regulatory approach can be actualized by affirming a 3D printed dosage form as a bioequivalent item to endorsed ones.

Besides the traditional routes, FDA may grant approval of 3D medical devices through constricted pathways. Regardless of whether 3D printing of measurement structures could go through these truncated courses isn't clear. Despite of every single regulatory obstacle related with 3D printing prescription, FDA endorsed the primary 3D printed pill, Spritam® (levetiracetam) in August of 2015 (Lennox, 2014).

The specifications of FDA approved ODFs are given in Table 2.

Table 2 FDA approved orodispersible film products

SL No	Approval Date, NDA Number	Product Name & Manufacturer	Active Ingredient	Strengths	Size
1	July 16, 2009 NDA 022266	Onsolis® Buccal Soluble Film, BioDelivery Sciences International	Fentanyl Citrate	200 µg, 400 µg, 600 µg, 800 µg, 1200 µg	Thickness: 50-150 µm
2	Nov 25, 2009 NDA 022470	Nexcede® Oral Film, Novartis Consumer Health	Ketoprofen	12.5 mg	22 mm x 32 mm
3	July 2, 2010 NDA 022524	Zuplenz® Oral Soluble Film, Midatech Pharma US	Ondansetron base	4 mg, 8 mg	8 mg is 32 mm x 32 mm and the 4 mg is 32 mm x 25 mm Thickness: 0.1 mm
4	Aug 30, 2010 NDA 022410	Suboxone® Sublingual film, Indivior Inc	Buprenorphine HCl/Naloxone HCl	2 mg/0.5 mg 4 mg/1 mg 8 mg/2 mg 12 mg/3 mg	22.0 mm x 12.8 mm, 22.0 mm x 25.6 mm, 22.0 mm x 12.8 mm, 22.0 mm x 19.2 mm
5	June 6, 2014 NDA 205637	Bunavail® Buccal Film, BioDelivery Sciences International	Buprenorphine HCl/Naloxone HCl	2.1 mg/0.3 mg, 4.2 mg/0.7 mg, 6.3 mg/1 mg	2.1 mg in a 2.2 cm^2 = 22 mm2 film; 4.2 mg in a 4.4 cm^2 = 44 mm^2 film; 6.3 mg in a 6.5 cm^2 = 65 mm^2 film
6	Oct 23, 2015 NDA 207932	Belbuca® Buccal Film, BioDelivery Sciences International	Buprenorphine HCl	75 µg; 150 µg; 300 µg; 450 µg; 600 µg; 750 µg; 900 µg	1.215 cm^2 = 12.15 mm^2; 2.431 cm^2 = 24.31 mm^2; 0.934 cm^2 = 9.34 mm^2; 1.400 cm^2 = 14 mm^2; 1.867 cm^2 = 18.67 mm^2; 2.334 cm^2 = 23.34 mm^2; 2.801 cm^2 = 28.01 mm^2

1.10 Literature Review

Said et al. discussed about the treatment process of Oral Lichen Planus, which consists of application of steroids that is incorporated into mouthwashes and creams as well as ointments. As only a little amount of drug gets in contact with the affected area, the treatment can be unsuccessful. In this study, the mucoadhesive patches were assessed based on their ability to facilitate targeted delivery of drugs. Mucoadhesive patches produced using Electrospun polymers were constructed and their physical properties as well as cytotoxicity was characterized and this was done prior to the residence time assessment. Into the patches a steroidal component, Clobetasol-17-propionate was included and prepared to released drug to the oral mucosa in sustained manner. Moreover, these patches were tested for release and duration time of the drug in in-vivo animal models which exhibited not only prolonged adhesion but also desired drug release in required doses. This study mainly demonstrates the ability of electrospun patches to adhere to oral mucosa with causing no damage to mucosal tissue and that these patches can be loaded with active drugs without failing. These patches are very promising in treating oral mucosal diseases (Said et al., 2018).

Recently in the improvement of customized medicines with special properties and release behavior, Fused Deposition Modeling has been utilized. In this study, Gioumouxouzis et al. discussed about two anti-diabetic drugs in a bilayer dosage form which contained different dosage regimen, for example metformin and glimepiride, were produced through FDM 3D printing. It was examined utilizing a different procedures and in vitro characterization was done as well. Metformin and glimepiride were both incorporated into Eudragit® RL and it continued to release layer and polyvinyl alcohol (PVA) layer individually. Consolidation of multiple API's in formulation is alluring which lowers the treatment cost and also enhances patient compliance and decreases cost of treatment, particularly when different doses of APIs

can be incorporated in accurate amount which fulfills every patient's particular needs. Various distinctive formulation techniques, including the diverse plasticizers and extruders, were tried on the prepared Eudragit® RL for printing the layer which will facilitate release of drug in sustained manner. The filament properties were evaluated by methods for mechanical and physicochemical characterization systems and the filaments with the ideal properties were utilized for printing. Disintegration tests demonstrated that adequate amount of drug was released for the two drugs in wanted time periods (75 min for glimepiride and 480 min for metformin). The outcomes from the present study highlighted the use of 3D printing innovation for customized dosage forms for combination drug therapy; even at the situations when API's with different release profiles are used (Gioumouxouzis et al., 2018).

Orodispersible films (ODFs) with loaded protein were prepared in the study. Woerdenbag et al. discussed about the preparation of these ODFs, based on blends of trehalose/pullulan by air and freeze-drying. The two carbohydrates were mainly chosen, depending on the film-forming capacity of pullulan and astounding protein stabilization nature of trehalose. ODFs were prepared incorporating three model proteins. Ovalbumin was utilized to assess the impact of protein addition on the mechanical properties, time of disintegration, thickness and weight uniformity of the ODFs. To assess the protein stability, Lysozyme and β-galactosidase were also utilized. Loading of Ovalbumin did not essentially impact the mechanical properties of freeze dried ODFs, while fuse of ovalbumin in air-dried ODFs prompted a considerable decrease in elasticity. The trehalose: pullulan proportion had no effect on the lysozyme stability, while the dependability of β-galactosidase grew with an increase in trehalose: pullulan proportions (Woerdenbag et al., 2018).

Li et al. (2017) in a research, attempted to investigate fused deposition modeling (FDM) effectiveness with hot melt extrusion (HME) so that a controlled-release drug delivery

product can be manufactured. Glipizide utilized in the treatment of diabetes was chosen as the model drug, and was effectively stacked into polyvinyl alcohol (PVA) filament by using the HME technique. The filaments which had the drug incorporated into them were printed using 3D printer containing double nozzle, lastly a twofold chamber device prepared by a tablet inserted inside a bigger tablet (Duo Tablet), each chamber contains different amounts of glipizide. The 3D printed product with drug loaded, was assessed for drug discharge under in vitro disintegration condition and we found that the release profile fit Korsmeyer– Peppas kinetics. The after-effects of this study recommended the capability of 3D printing technology to manufacture controlled-release delivery system having more than one drug concentrations (Li et al., 2017).

Radicioni et al. discussed about the bioequivalnce sudy of sildenafil ODF in a research. In the study, sildenafil 100 mg orodispersible films pharmacokinetics was compared with the ordinary marketed 100 mg film-covered tablet after the administration of single dose to more than 50 male volunteers who are in good health (matured 18-51 years) in a bioequivalence randomized, two-way and open study. Each subject got a solitary oral portion of 100 mg of sildenafil under fasting conditions. There was a washout interim of more than seven days between the investigations of two administration of the drug product. For pharmacokinetic examination, blood tests were gathered up to 24 h after administration. The essential target was to think about the rate and degree of sildenafil retention after application of single-dose of test and reference. Auxiliary endpoints were seen to depict the plasma pharmacokinetic profiles of sildenafil and N-desmethyl-sildenafil as its metabolite for relative bioavailability and risk profile after administration of single dose. The outcomes recommended that the latest formulation of orodispersible film can be utilized side by side with the traditionally formulated film-coating (Radicioni et al., 2017).

1.11 Purpose of the study

The purpose of this study is discussed as following:

- To design an ideal drug delivery system (single layered or multi layered) where variety of drugs can be incorporated.
- To design a 3D drug delivery system that avoids first pass metabolism.
- To design 3D printed ODF which can be easily administered and thus can improve patient compliance.
- To bring about an effective change in the pharmaceutical sector by introducing multilayered delivery system.

Chapter 2

Methodology

2.1 Methodology

The study was carried out by emphasizing on latest published research articles as well as review articles focusing on orally dispersible film for buccal drug delivery. Moreover, the 3D designs of the orodispersible films were carried out with following the specifications of the FDA approved orodispersible films. This eliminated the scope of designing impractical models. Considerable amount of literature review was conducted followed by the designing of 3D printed orodispersible films. The total of fifteen models containing ten single layered devices and five multilayered devices were proposed for the 3D printing of orodispersible film models to facilitate oral drug delivery for various active pharmaceutical ingredients.

2.2 Software

The software that was used for designing 3D models for drug delivery in this project was Autodesk MAYA 2018. Autodesk Maya is a 3D modeling and animation program that is used for 3D printing and graphics designing. Autodesk Maya 2018 was used as this software provides tools to modify objects which in turn produce professional and quality results. This software is expensive but is free for students doing thesis and research. Countless trial and error models were designed and finally one model was selected to be printed after all the essential measures were confirmed. Some pre-calculated data was also used to design the 3D structures.

2.3 Procedures of designing

The following method was used sequentially for designing the 3D model of orodispersible films,

1. At the beginning, the Autodesk Maya 2018 software was selected from the desktop menu bar.

2. After the opening of Maya software, the software showed a view with large grid, which is mainly the foundation of every 3D model designing. This large grid can also be removed by selecting the 'Display' option of the software and turning the grid option off. But we chose to work with the grids while designing as it ensures precision and any changes in the model can be done with accuracy.

3. Before selecting the structure, the 'Windows' option from the top of software was selected and 'Preferences' option was chosen for putting the specification for the structure.

4. Then the specifications were opened in a new window.

5. Then the 'millimeter' option was selected in the 'Linear' box which ensured all the specifications and modifications to be put in millimeter unit.

6. Then from the upward left corner, the 'Poly Modeling' option was selected which contained various 3D structures and among them a polygon cube was selected.

7. The specifications such as, the size and the shape of the polygon cube was put as required which transformed the 3D structure into the desired one.

8. In case of multilayered films, the cube was then pulled underneath the grid for further placement of more layers. The pulling of the cube was done using the 'Move Tool'.

9. Accurate placement of the base was done by changing the value of ‘Translate X’, ‘Translate Y’ and ‘Translate Z’ from the right side of the window.

10. Layers were designed by changing the ‘Width’, ‘Height’ and ‘Depth’ of the polycube attributes as required using the option named ‘Inputs’.

11. While designing multilayered models, the layers were designed with showing distance between the separate layers. The separation was ensured by selecting the layer which was required to move and moving it using the ‘Move Tool’.

12. The layers of polygon cube were selected individually and the color of the layers was changed to further identify the layers.

13. After selecting one layer, ‘Mesh Display’ was selected which contained the application of color icon. Then from the ‘Color Wheel’, appropriate color was chosen by increasing or decreasing intensity of the selected color for the designed 3D layer.

14. Other layers were colored using the same manner.

15. The uniform distance between the layers, in case of multilayered films was maintained using the ‘Translate X’, ‘Translate Y’ and ‘Translate Z’ option.

16. The whole structure was moved to present the Top, Side, Bottom view of the single layer device designing.

17. In case of multilayered device designing, the whole structure was moved to present five views in total: Top, Side, Layers Merged, Layers Separated and lastly the Bottom view.

Chapter 3

Results and Discussion

3.1 The structural specifications of the orodispersible film models

Fifteen models were proposed in the project, where each one of the models is different from the other due to their different specifications. The specifications and parameters of the models were selected while taking the information from FDA Approved ODF products as well as currently marketed ODFs into account. The ODFs which are approved by FDA lies within a range. The maximum size of the approved ODF is 32 mm x 32 mm (Length x Width) and the minimum size is 4.67 mm x 4.67 mm. We have designed our proposed models with taking these sizes into account so that none of the designs seem impractical. The marketed ODFs and also the ODFs which are approved by FDA are majorly rectangular and square in shape for the better absorption of medication.

For the designing of these models, rectangular and square shaped layers were used. There were different sizes of layers in every models used to select and understand which one would be appropriate for the trial. (Figure 3.1 to Figure 3.15)

The specifications and parameters of all the designed models are included in Table 3.1, Table 3.2 and Table 3.3. In table 3.1, the specifications for square shaped and single layered ODFs are listed. In table 3.2, the specifications for rectangle shaped single layered ODFs are listed and in table 3.3, the specifications are listed for each layer of the multi layered ODFs. The fifteen proposed models were designed using Autodesk MAYA 2018 software.

All the fifteen models had different parameters and specifications. The proposed model 1 consisted of a single square shaped layer and the length and width of the film were 5 mm x 5 mm. The thickness was 2 mm and surface area was 90 mm^2. The amount of drug that can be

incorporated into this film would be very small which is one limitation of this model. On the other hand, the proposed model 2 consisted of a square shaped layer and the length and width were 10 mm x 10 mm and surface area 280 mm^2, which made this model appropriate for the drugs that are required in smaller amounts such as antihistamines. The proposed model 3 was square shaped and the length and width were 15 mm x 15 mm and had the surface area of 540 mm^2. The proposed model 4 had similar parameters but the length and width of the layer were 20 mm x 20 mm, the surface area was 920 mm^2 which made this model appropriate for the delivery of specific drugs that are required in larger amounts such as analgesics. The proposed model 5 had larger surface area of 1425 mm^2 and the length and width were 25 mm x 25 mm, the thickness of the layer was 1.75mm. This model was the best suited for printing using 3D printer as the size of the film was larger than the other square shaped single layered film models. Larger amount of drugs can also be incorporated into the layer (Model 5).

From proposed model 6 to proposed model 10 all consisted of rectangle shaped single layer film designs. Proposed model 6 had the length and width of 5 mm x 7 mm and surface area of 118 mm^2. As this model had lower parameters, the 3D printing would not be flexible. The proposed model 7 had length and width of 7 mm x 9 mm and thickness of the film was 2 mm. Then proposed model 8 had length and width of 9 mm x 11 mm and the surface area was 258 mm^2. But proposed model 9 was suitable for delivery of drugs that are required in smaller amounts. This model had the length and width of 11 mm x 13 mm and the thickness was 1.5 mm. 3D printer can print any structure having thickness more than 1mm, which made the proposed model 10 most suitable for printing. The proposed model 10 had length and width of 13 mm x 15 mm and surface area was 488 mm^2.

Proposed model 11 to proposed model 15 consisted of multiple layered square shaped layer designs which can be accurately printed using 3D printer. Proposed model 11 consisted of three layers where each of the layers had length and width of 6 mm x 6 mm and the thickness

was 2 mm. Proposed model 12 had three layers as well and the length and width of each layers were 10 mm x 10 mm and thickness was 2 mm. Proposed model 13 had three layers where each of the layers had length and width of 14 mm x 14 mm. Proposed model 14 consisted of three layers and the length and width of each layers were 18 mm x 18 mm and the thickness was 1.5mm. Furthermore, proposed model 15 which was the last proposed model had three layers and each of the layers were 22 mm x 22 mm in length and width and the thickness was 1.75 mm. This model was a good choice for 3D printing as the size of the layers was larger than the other models and larger amounts of medicines can also be incorporated as well.

Table 3: The specifications for square shaped single layered orodispersible film, (model 1 to model 5)

No. of Model	**Film Specifications** **L** x **W** x **T (mm)**	**Surface Area (mm^2)**
Proposed Model 1	5 x 5 x 2	90
Proposed Model 2	10 x 10 x 2	280
Proposed Model 3	15 x 15 x 1.5	540
Proposed Model 4	20 x 20 x 1.5	920
Proposed Model 5	25 x 25 x 1.75	1425

Table 4: The specifications for rectangle shaped single layered orodispersible film, (model 6 to model 10)

No. of Model	**Film Specifications** **L x W x T (mm)**	**Surface Area (mm^2)**
Proposed Model 6	5 x 7 x 2	118
Proposed Model 7	7 x 9 x 2	190
Proposed Model 8	9 x 11 x 1.5	258
Proposed Model 9	11 x 13 x 1.5	358
Proposed Model 10	13 x 15 x 1.75	488

Table 5: The specifications for square shaped multi layered orodispersible film, (model 10 to model 15)

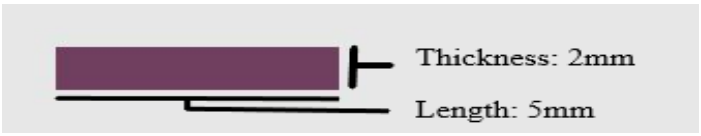
No. of Model	**Film Specifications L x W x T (mm)**	**Number of Layers**	**Surface Area (mm^2)**
Proposed Model 11	6 x 6 x 2	Three	120
Proposed Model 12	10 x 10 x 2	Three	280
Proposed Model 13	14 x 14 x 1.5	Three	476
Proposed Model 14	18 x 18 x 1.5	Three	756
Proposed Model 15	22 x 22 x 1.75	Three	1122

3.2 Proposed Models

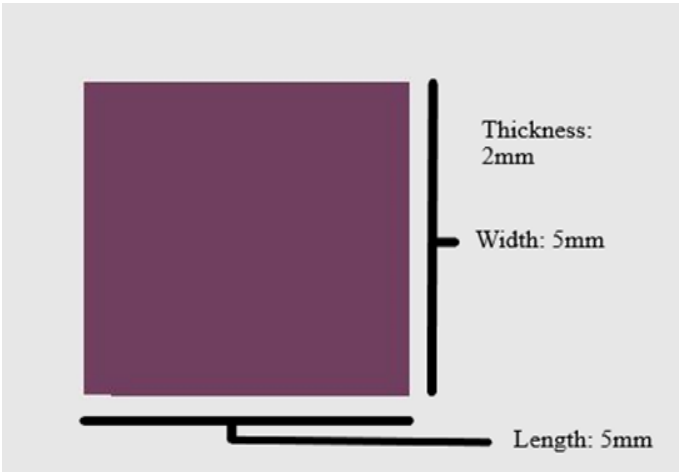
Fifteen models containing ten single layered devices and five multilayered devices were proposed. Figures of fifteen proposed models that were designed using Autodesk MAYA 2018, are represented in Figures 1 to 15.

Proposed Model 1

a)



b)



c)

Figure 1: Proposed model 1: a) side view, b) top view, c) bottom view of the model.

Proposed model 2

a)

b)

c)

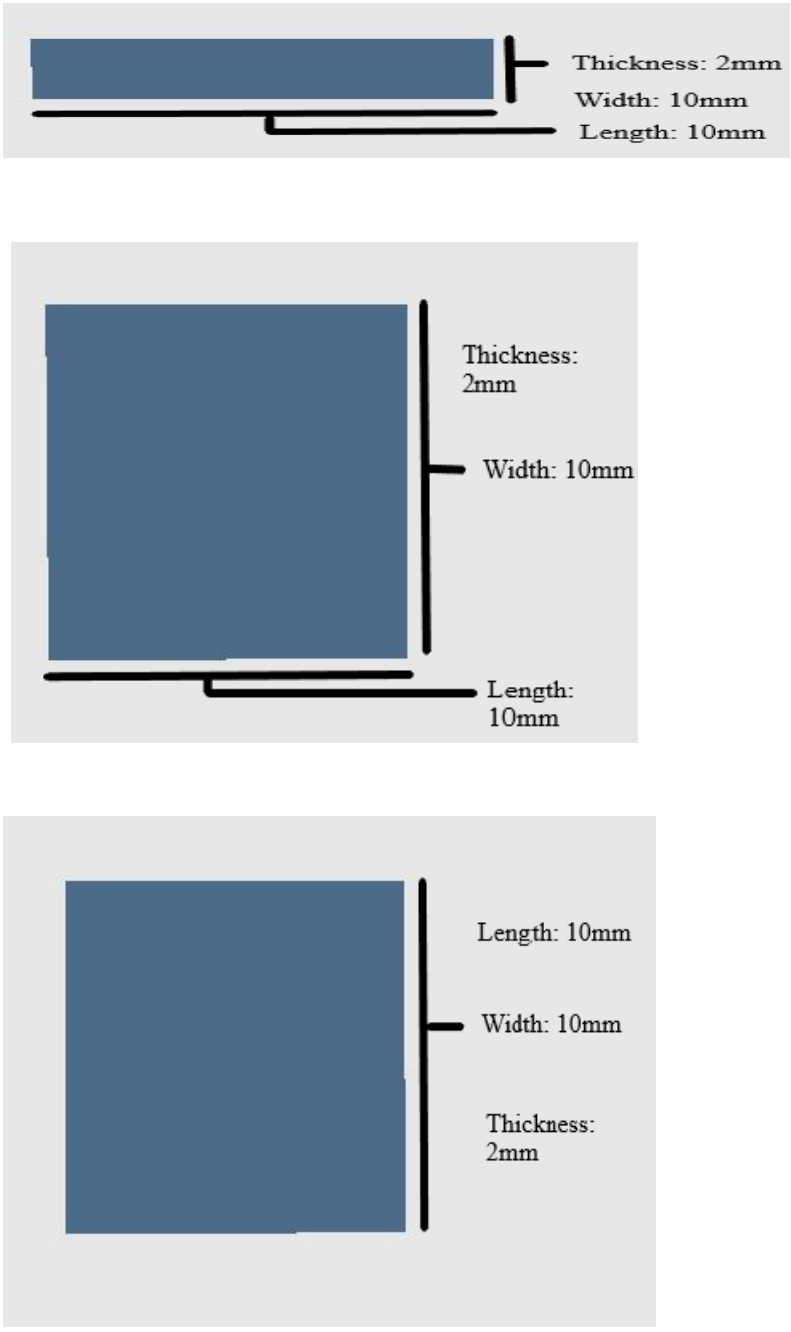


Figure 2: Proposed model 2: a) side view, b) top view, c) bottom view of the model.

Proposed model 3

a)

b)

c)

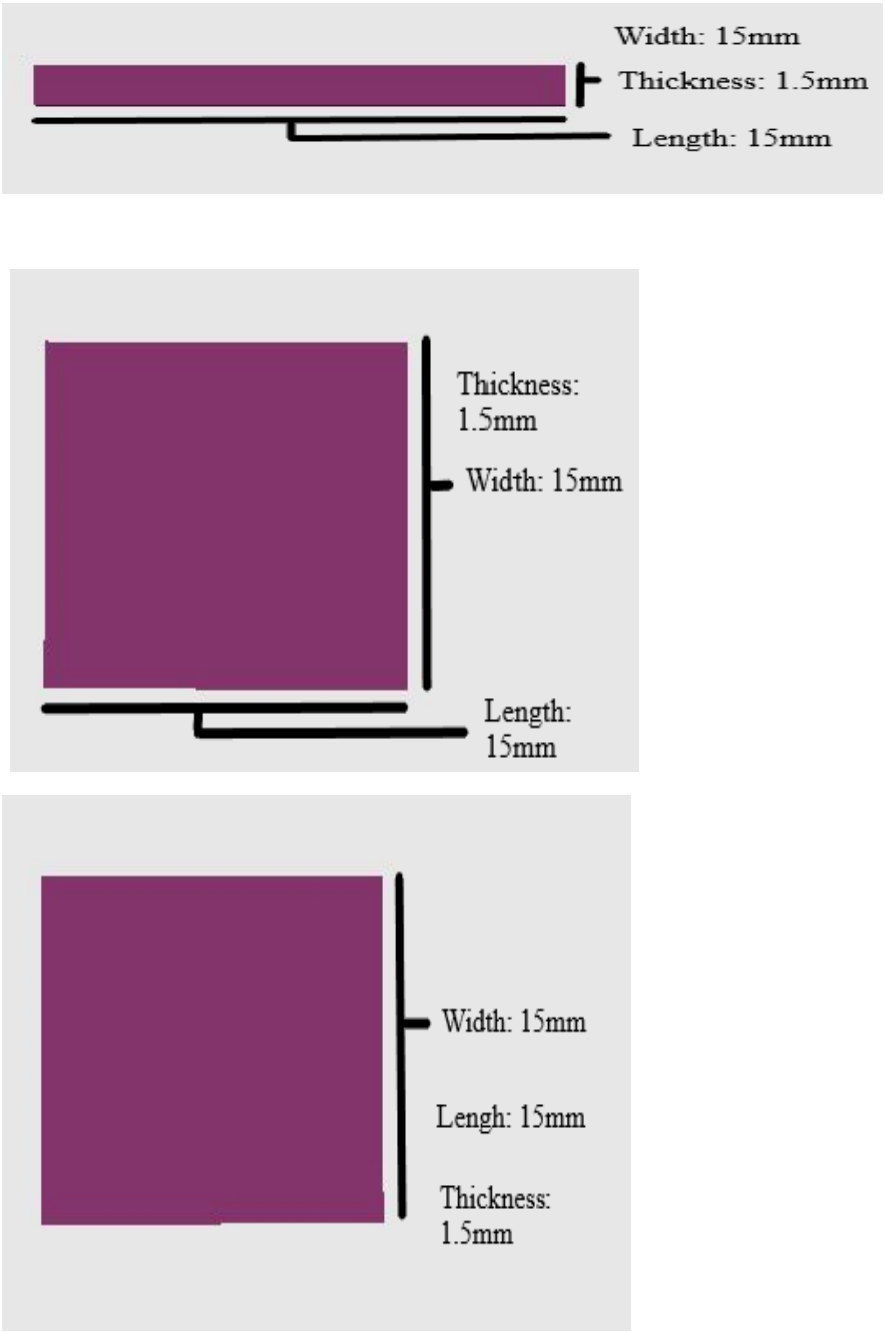
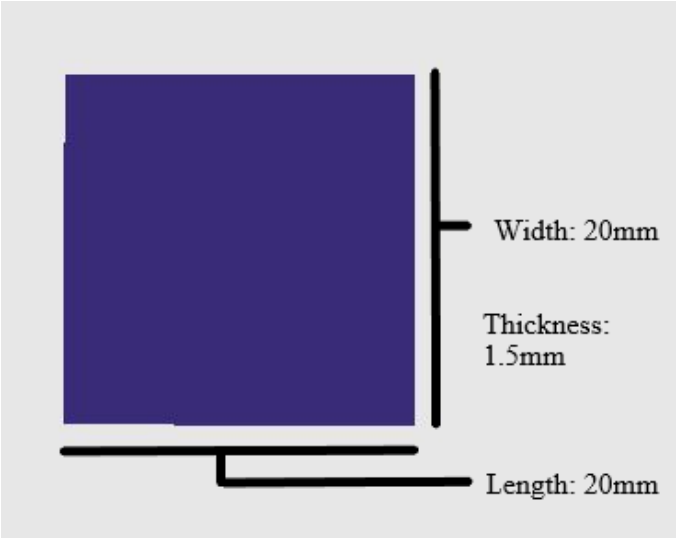


Figure 3: Proposed model 3: a) side view, b) top view, c) bottom view of the model.

Proposed model 4

a)

b)



c)

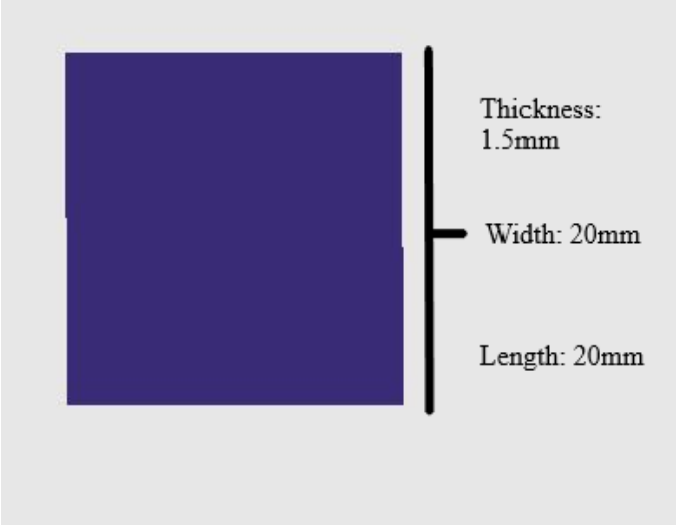
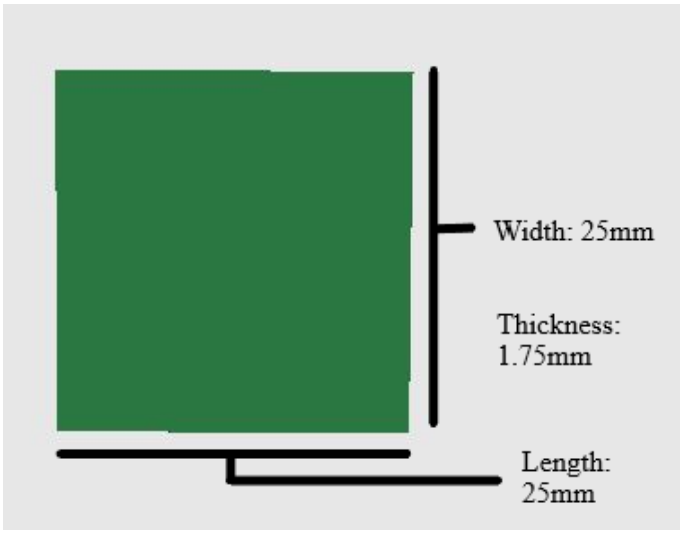


Figure 4: Proposed model 4: a) side view, b) top view, c) bottom view of the model.

Proposed model 5

a)

b)



c)

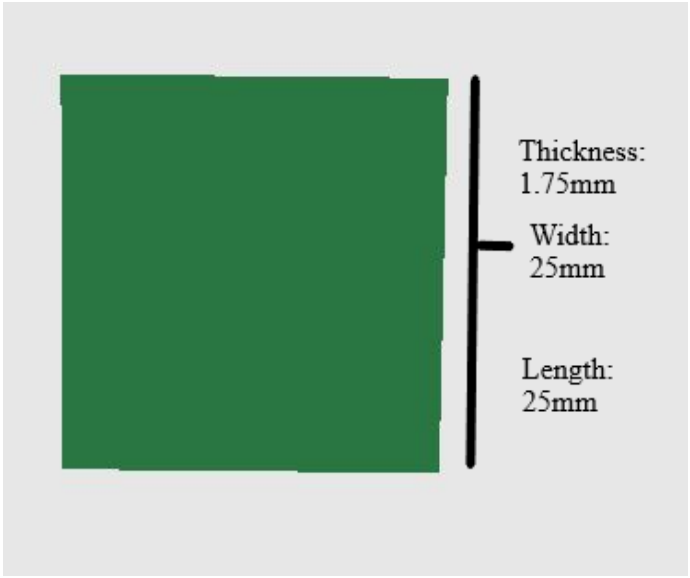
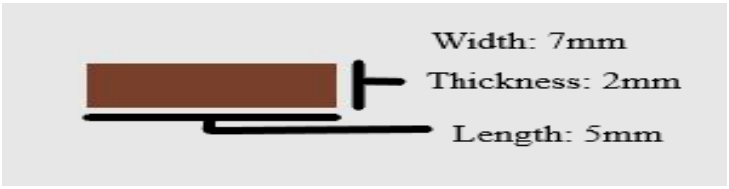


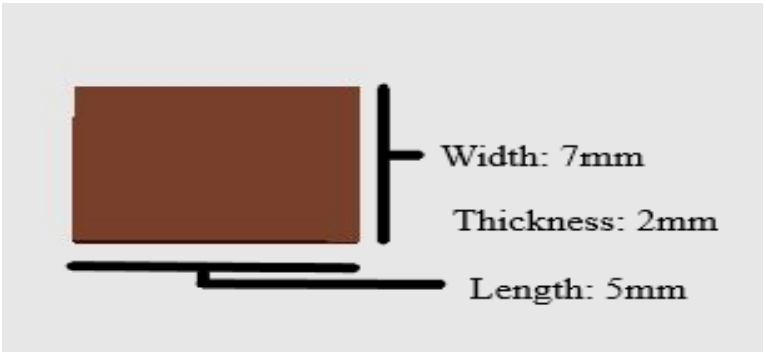
Figure 5: Proposed model 5: a) side view, b) top view), c) bottom view of the model.

Proposed model 6

a)



b)



c)

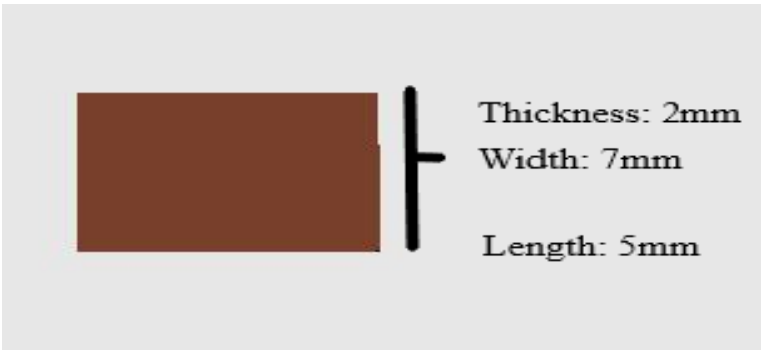
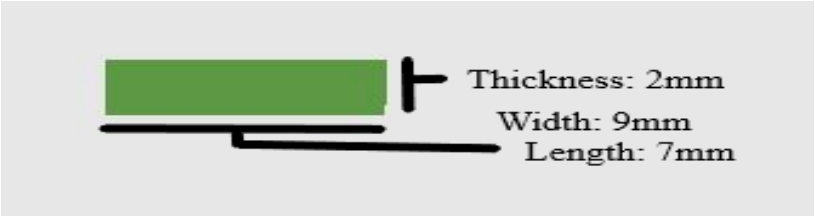


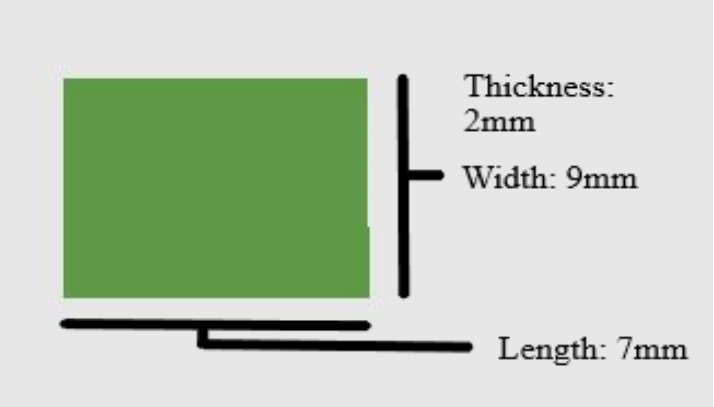
Figure 6: Proposed model 6, a) side view, b) top view, c) bottom view of this model.

Proposed model 7

a)



b)



c)

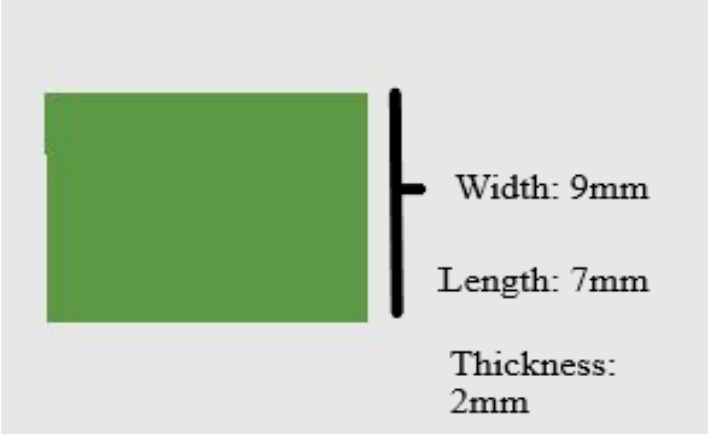


Figure 7: Proposed model 7: a) side view, b) top view, c) bottom view of the model.

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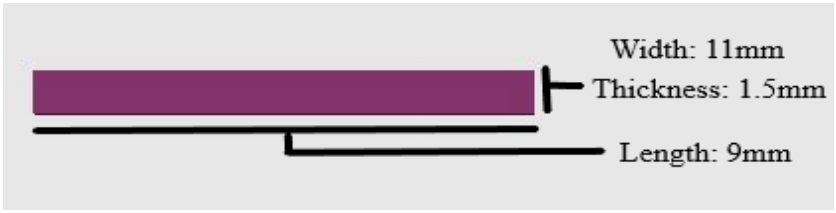
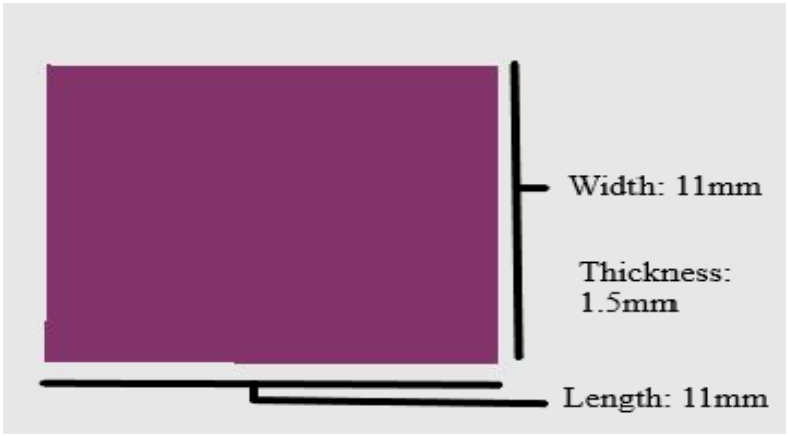
Proposed model 8

a)



b)



c)

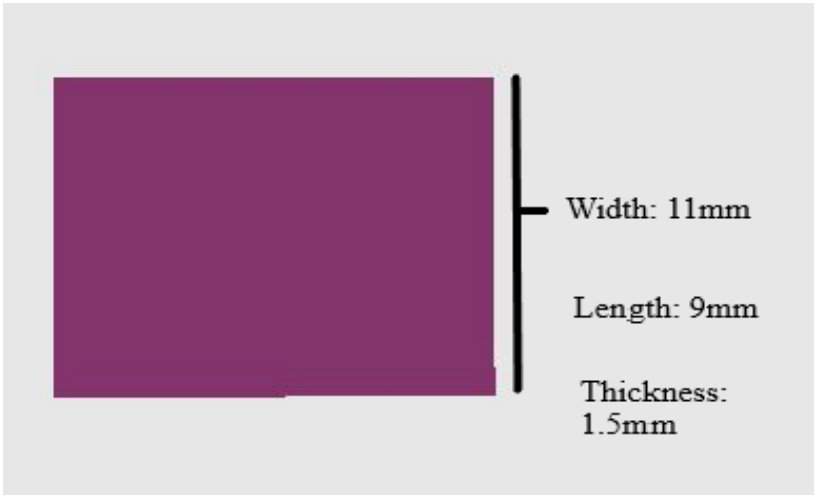


Figure 8: Proposed model 8: a) side view, b) top view, c) bottom view of the model.

Proposed model 9

a)

b)

c)

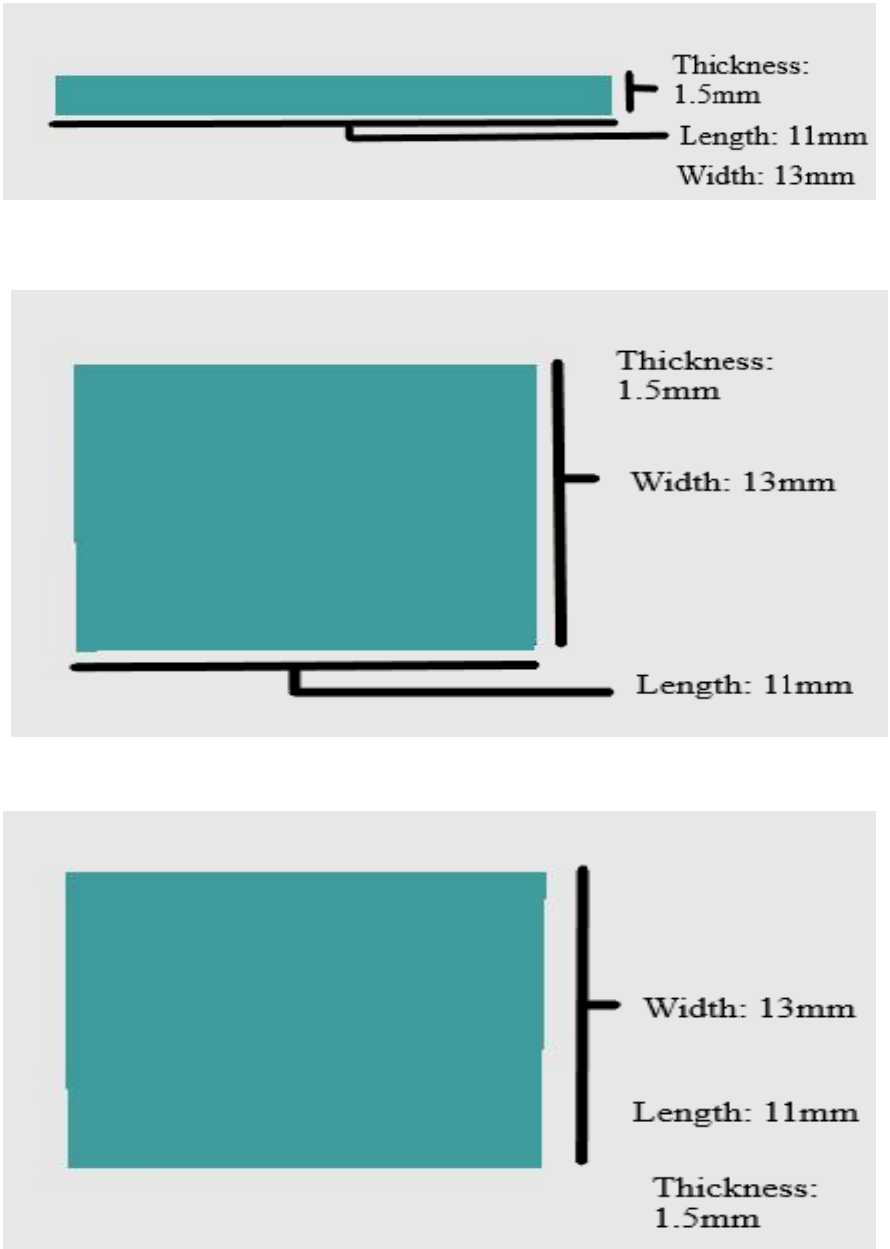


Figure 9: Proposed model 9: a) side view, b) top view, c) bottom view of the model.

Proposed model 10

a)

b)

c)

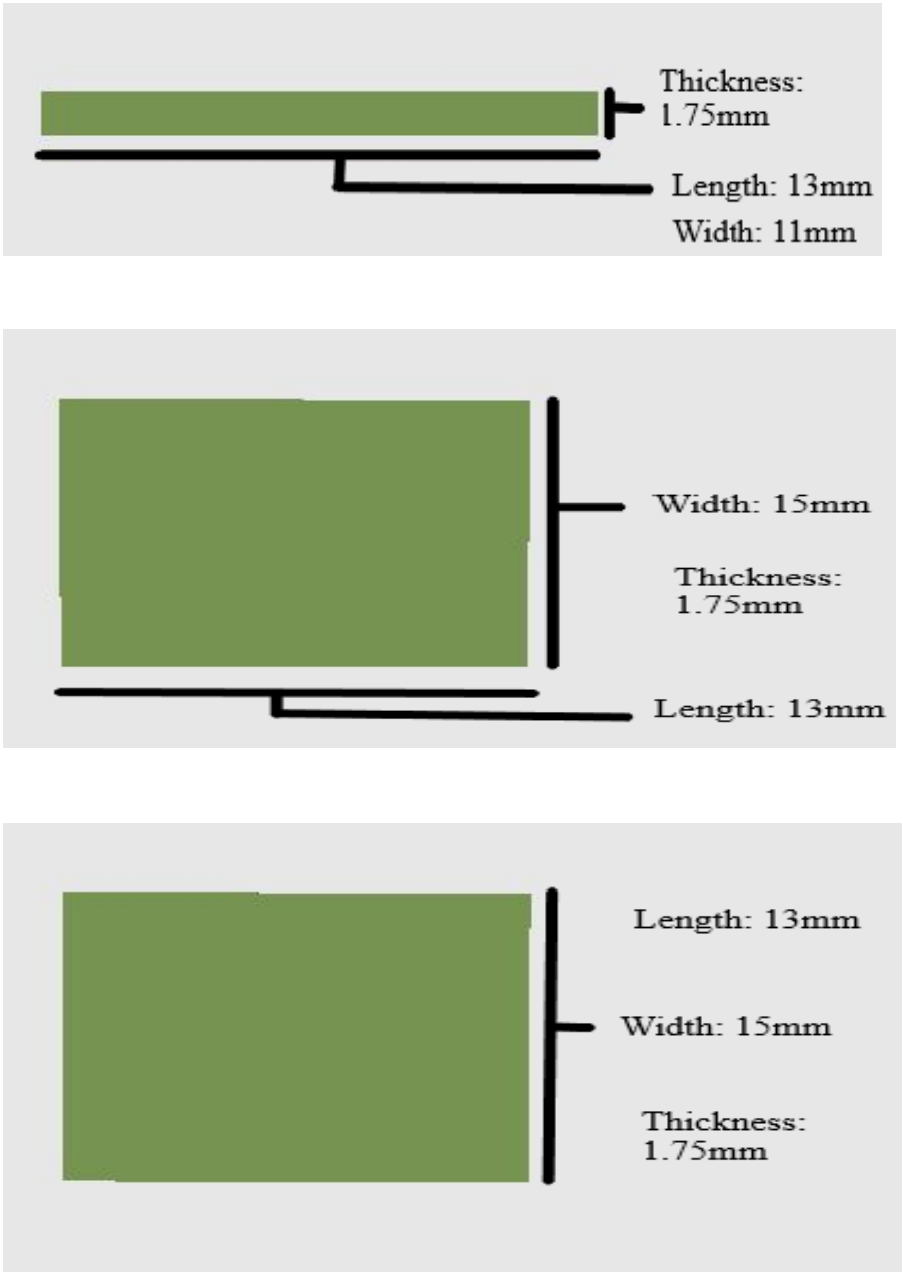


Figure 10: Proposed model 10, a) side view, b) top view, c) bottom view of this model.

Proposed model 11

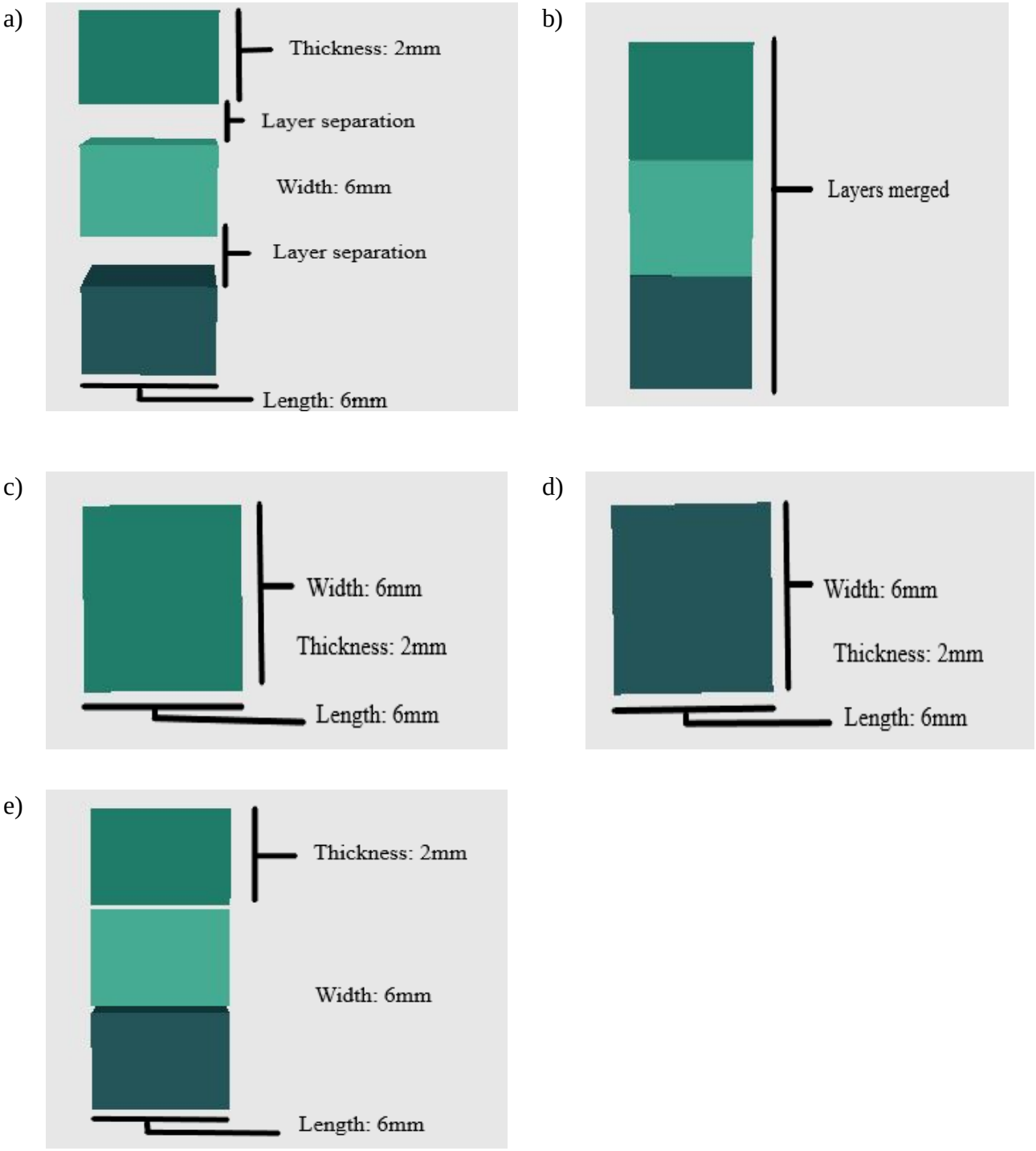


Figure 11: Proposed model 11: a) layers separated, b) layers merged, c) top view, d) bottom view, e) side view of the model.

Proposed model 12

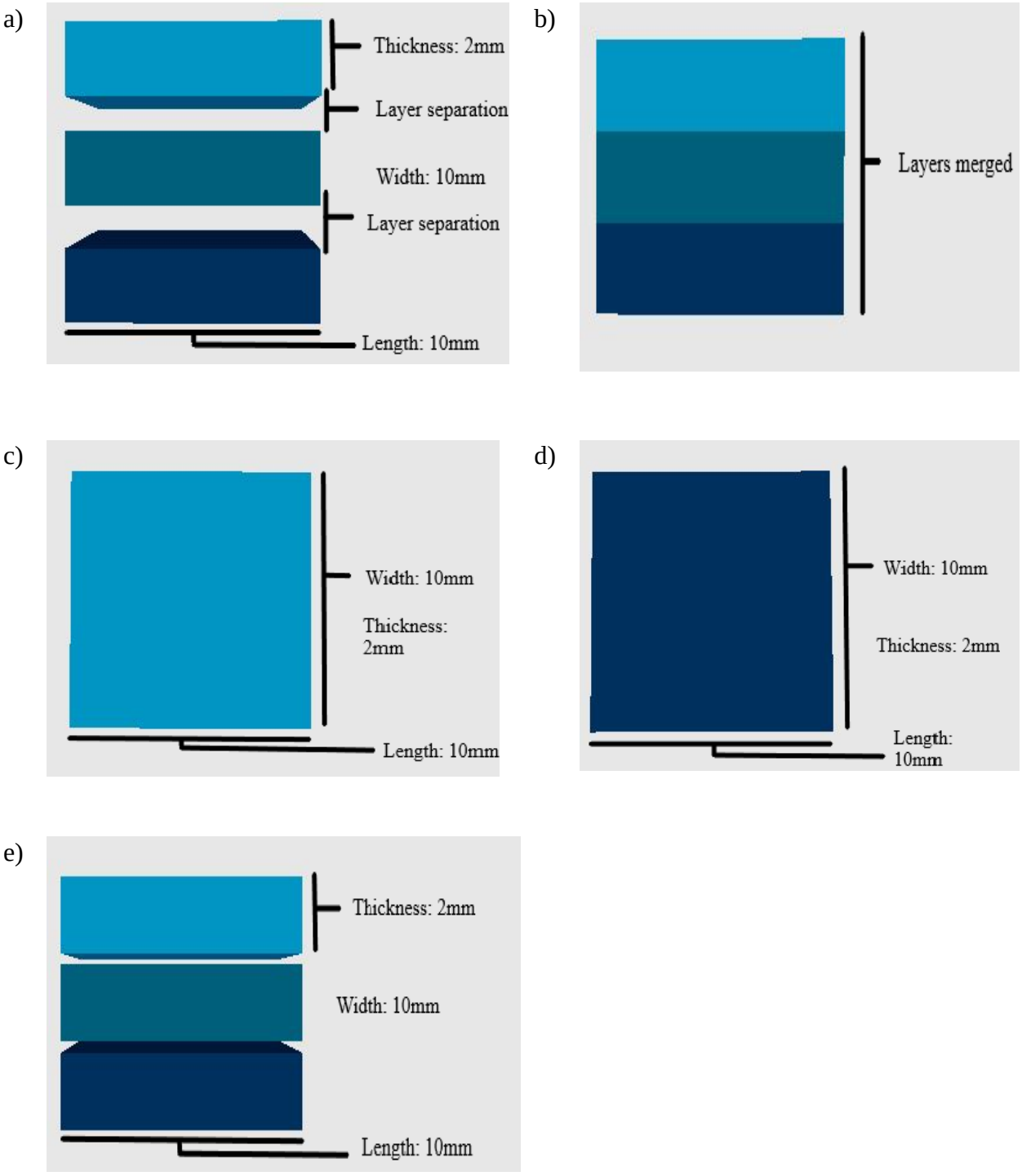


Figure 12: Proposed model 12: a) layers separated, b) layers merged, c) top view, d) bottom view, e) side view of the model.

Proposed model 13

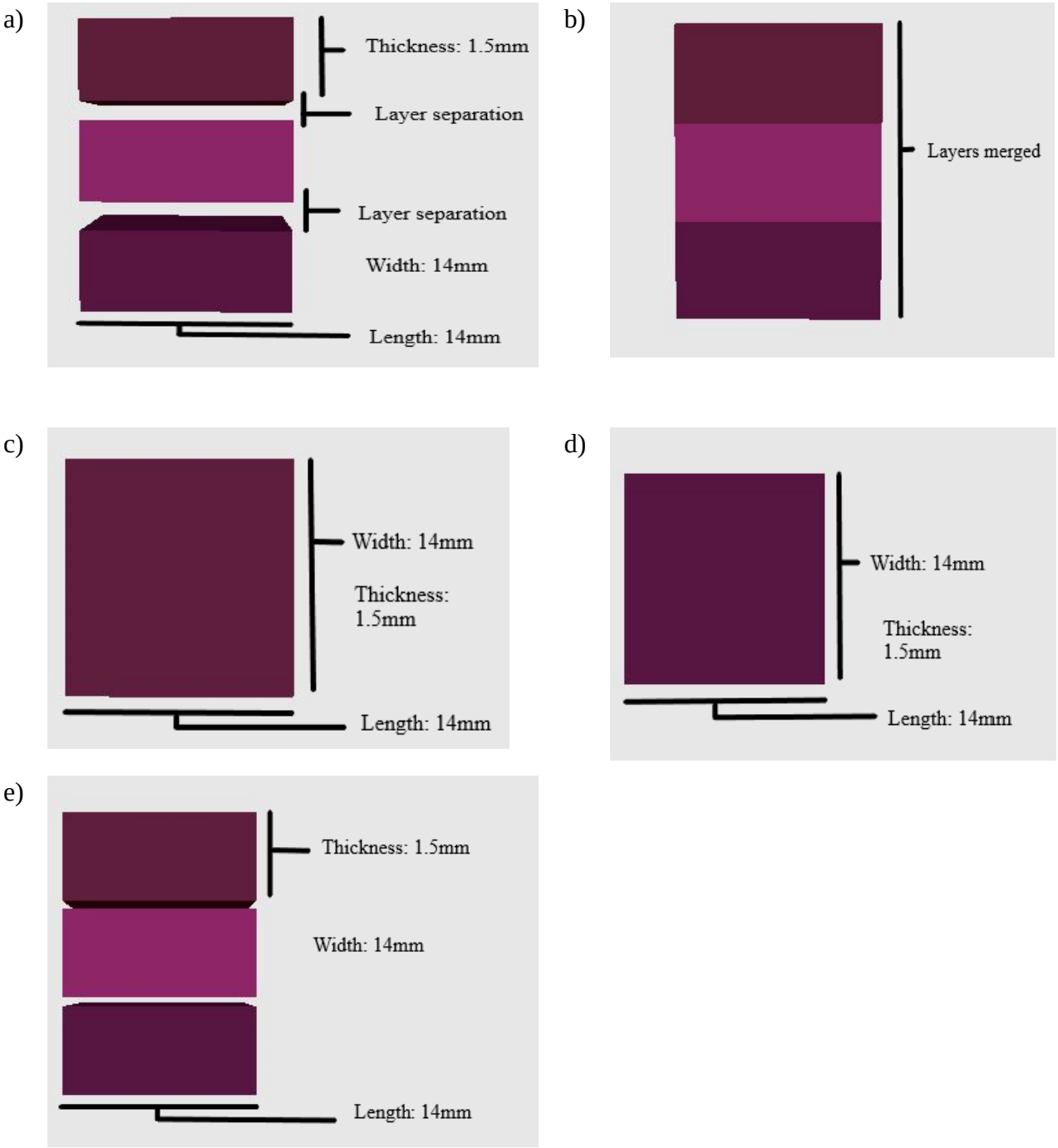


Figure 13: Proposed model 13: a) layers separated, b) layers merged, c) top view, d) bottom view, e) side view of the model.

Proposed model 14

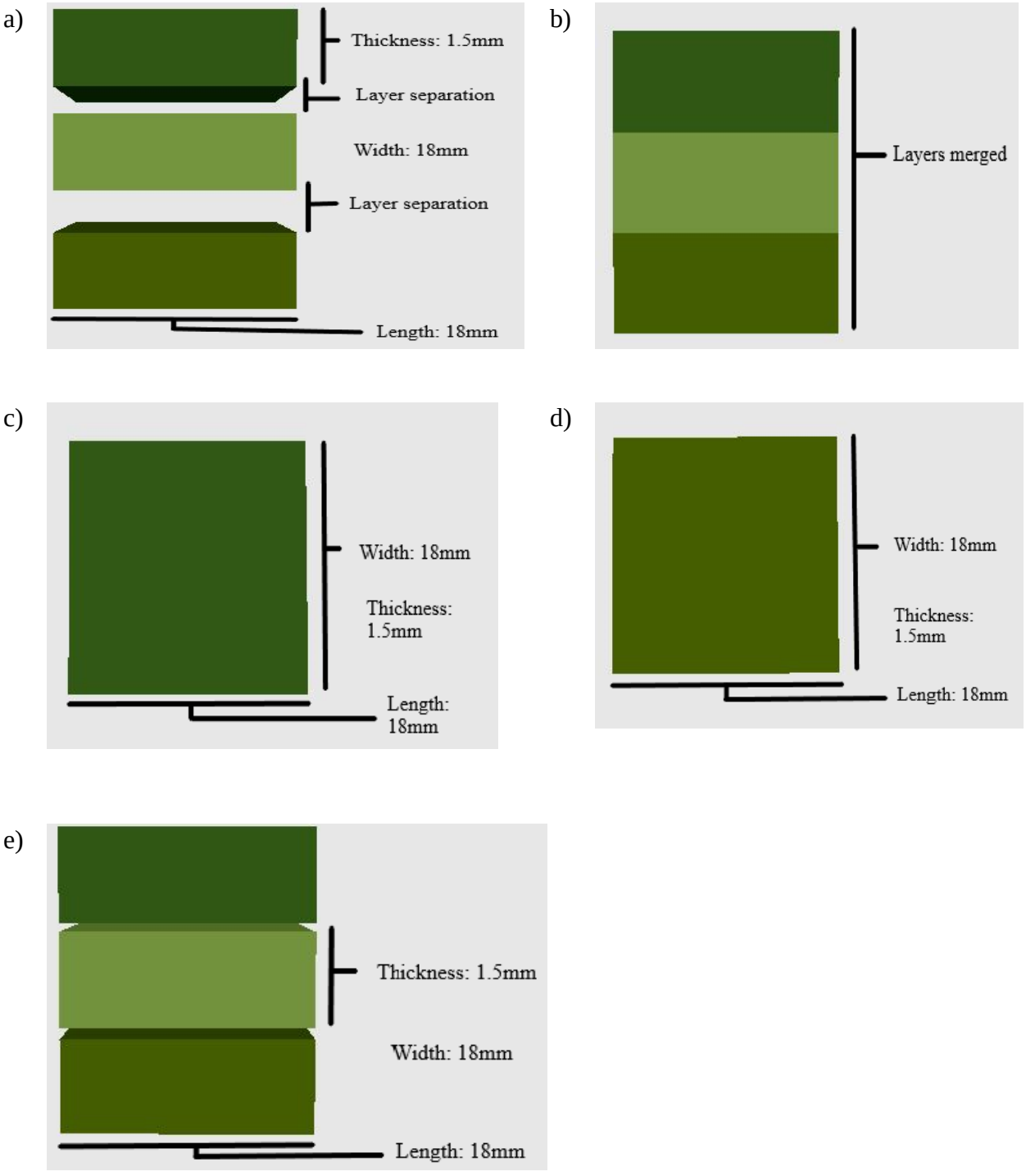


Figure 14: Proposed model 14: a) layers separated, b) layers merged, c) top view, d) bottom view, e) side view of the model.

Proposed model 15

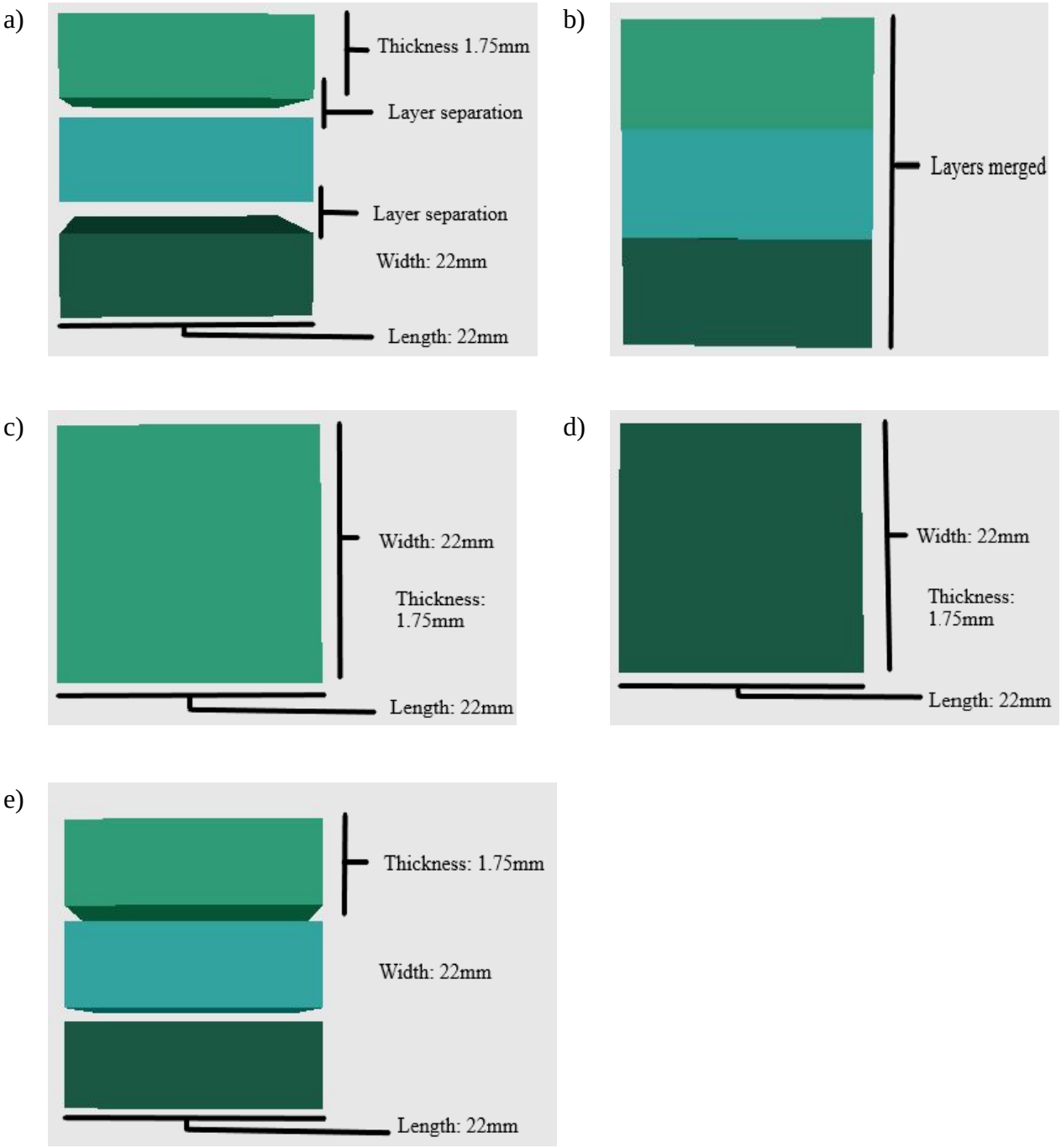


Figure 15: Proposed model 15: a) layers separated, b) layers merged, c) top view, d) bottom view, e) side view of the model.

3.3 Discussion

In the past decade, the usage of 3D printing technology has considerably increased not only in pharmaceutical sectors but also in industries. The 3D printing technology is assumed as one of the major contrivances in realizing the notion of personalized medicine from a realistic point of view. Also, using 3D printer complex structure and dosage forms can be formulated in less amount of time, making it better than the conventional manufacturing process, also it can be constructed pretty fast than conventional process (Ehtezazi et al., 2018). In pharmaceutical sector, 3D printing technology is a combinative technology which consists of designing, pharmaceutics and material engineering. This all sectors attempt to produce and develop the final product by working together. This technology might be beneficial from early drug development to personalized therapy (Lamichhane et al., 2019).

The use of these films has reasonably expanded over the past few years. FDA has also approved some ODFs and so there are many ODFs marketed currently. The ODFs are gaining popularity due to their ease of administration especially with children and geriatric patients. Oral cavity is considered as an effective route for drug administration, especially for those drugs that get degraded in the gastric pH. The mean total surface area of human mouth is 214.7 +/- 12.9 cm^2 (Batista et al., 2019). The large area facilitates incorporation of drug in larger amount. Drugs that are degraded in oral cavity or drugs that affect the oral mucosa such as aspirin cannot be administered in a high dose using oral film as drug delivery system (Arafa, Ghalwash, El-Kersh, & Elmazar, 2018). But medicines which is required in a less amount can be easily incorporated (Karki et al., 2016) .

Medicines of antihistamine, antidepressant, antiemetic and opioid origin can be formulated into orodispersible films. The general shelf life of ODFs is two to three years but it mainly depends on the shelf life of the active ingredient. Drugs that undergo first pass effect and

drugs that are degraded in gastro intestinal tract can be administered using orodispersible film as it facilitates direct absorption into the systemic circulation. The conventional dosage forms such as disintegrating tablets can be replaced by ODFs as these are most convenient to all age groups (Bala et al., 2013).

The only drawback of this delivery system is that large amount of drug cannot be formulated into ODFs (Zaman, Hanif, & Shaheryar, 2018). They also require individual packaging as putting two or more films together can cause the films to stick together. Drugs that are required in smaller amounts can be incorporated into the separate layers, drugs that are incompatible can also be incorporated into different layers and the middle layer can be made placebo to separate the two layers, also drugs can be incorporated into the layers to facilitate controlled release. Also, more than two drugs can be combined and they can be incorporated into different layers with different or same dissolution rate. These films can be formulated to provide not only local but also systemic action. For their various advantages, ODFs can be the most promising approach in formulating different kinds of drugs.

Chapter 4

Conclusion

4.1 Conclusion

The present study shows that all models can be successfully printed using 3D printing technology. Multiple resources are used to design the 3D models of orally dispersible films. The method that has been used to design orodispersible films in this study is flexible and it influences invention of new practical and easier method in order to achieve better patient compliance. 3D printer is used for printing as it provides accuracy in dosing, appropriate for layer by layer fabrication and the resolution is good.

Using 3D printing technology to prepare ODFs may provide a better alternative to injections. ODFs can increase bioavailability of drugs. Further in vitro studies should be carried out using the orodispersible film for determining dose accuracy, film strength, moisture content, and surface pH for effective oral drug delivery.

Chapter 5

References

Adams-Hess, L., Anne Hanna, B., Partner, M., & Sonia Weiss, B. (2018). *3D Printed Pharmaceuticals and Devices Article Series: Assessing, Managing, and Insuring Against Risk in the Next Era of Drugs and Medical Devices – Part 1*. 2014–2017. Retrieved from http://www.bowmanandbrooke.com/~/media/Documents/Insights/Articles/2016/3D Printing Article Series BerkleyLS.pdf

Alhnan, M. A., Okwuosa, T. C., Sadia, M., Wan, K. W., Ahmed, W., & Arafat, B. (2016). Emergence of 3D Printed Dosage Forms: Opportunities and Challenges. *Pharmaceutical Research*, *33*(8), 1817–1832. https://doi.org/10.1007/s11095-016-1933-1

Arafa, M. G., Ghalwash, D., El-Kersh, D. M., & Elmazar, M. M. (2018). Propolis-based niosomes as oromuco-adhesive films: A randomized clinical trial of a therapeutic drug delivery platform for the treatment of oral recurrent aphthous ulcers. *Scientific Reports*, *8*(1), 1–14. https://doi.org/10.1038/s41598-018-37157-7

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

Batista, P., Castro, P., Madureira, A., Sarmento, B., Pintado, M., Batista, P., … Pintado, M. (2019). Development and Characterization of Chitosan Microparticles-in-Films for Buccal Delivery of Bioactive Peptides. *Pharmaceuticals*, *12*(1), 32. https://doi.org/10.3390/ph12010032

Bilal, M., Mahboob, H., Riaz, T., Jamshaid, M., Bashir, I., & Zulfiqar, S. (2016). Oral Films:

A Comprehensive Review. *International Current Pharmaceutical Journal*, *5*(12), 111–117. Retrieved from http://www.icpjonline.com/documents/Vol5Issue12/03.pdf

Caliceti, P., & Matricardi, P. (2019). Advances in Drug Delivery and Biomaterials: Facts and Vision. *Pharmaceutics*, *11*(1), 48. https://doi.org/10.3390/pharmaceutics11010048

Chaudhary, H., Gauri, S., Rathee, P., & Kumar, V. (2013). Development and optimization of fast dissolving oro-dispersible films of granisetron HCl using Box–Behnken statistical design. *Bulletin of Faculty of Pharmacy, Cairo University*, *51*(2), 193–201. https://doi.org/10.1016/j.bfopcu.2013.05.002

Chougule, P. C., Bhat, M. R., & Chimkode, R. M. (2017). Design and Evaluation of Formulated Mouth Dissolving Film of Domperidone and Study the Effect of Concentration of Polymers on Drug Release. *Asian Journal of Pharmaceutics*, *11*(4), 846–853.

De Caro, V., Murgia, D., Seidita, F., Bologna, E., Alotta, G., Zingales, M., & Campisi, G. (2019). Enhanced In Situ Availability of Aphanizomenon Flos-Aquae Constituents Entrapped in Buccal Films for the Treatment of Oxidative Stress-Related Oral Diseases: Biomechanical Characterization and In Vitro/Ex Vivo Evaluation. *Pharmaceutics*, *11*(1), 35. https://doi.org/10.3390/pharmaceutics11010035

Ehtezazi, T., Algellay, M., Islam, Y., Roberts, M., Dempster, N. M., & Sarker, S. D. (2018). The Application of 3D Printing in the Formulation of Multilayered Fast Dissolving Oral Films. *Journal of Pharmaceutical Sciences*, *107*(4), 1076–1085. https://doi.org/10.1016/j.xphs.2017.11.019

Gioumouxouzis, C. I., Baklavaridis, A., Katsamenis, O. L., Markopoulou, C. K., Bouropoulos, N., Tzetzis, D., & Fatouros, D. G. (2018). A 3D printed bilayer oral solid dosage form combining metformin for prolonged and glimepiride for immediate drug

delivery. *European Journal of Pharmaceutical Sciences*, *120*, 40–52. https://doi.org/10.1016/j.ejps.2018.04.020

Hanif, M., Zaman, M., & Chaurasiya, V. (2015). Polymers used in buccal film: A review. *Designed Monomers and Polymers*, *18*(2), 105–111. https://doi.org/10.1080/15685551.2014.971389

Hernandez, D. (2015). Factors Affecting Dimensional Precision of Consumer 3D Printing. *International Journal of Aviation, Aeronautics, and Aerospace*, *2*(4). https://doi.org/10.15394/ijaaa.2015.1085

Hoaffmnn, E. M., Breitenbach, A., & Breitkreutz, J. (2011). Advances in orodispersible films for drug delivery. *Expert Opinion on Drug Delivery*. https://doi.org/10.1517/17425247.2011.553217

Horst, D. J. (2018). 3D Printing of Pharmaceutical Drug Delivery Systems. *Archives of Organic and Inorganic Chemical Sciences*, *1*(2), 3–8. https://doi.org/10.32474/aoics.2018.01.000109

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*, *24*(5), 537–546. https://doi.org/10.1016/j.jsps.2015.02.024

Jamróz, W., Szafraniec, J., Kurek, M., & Jachowicz, R. (2018). 3D Printing in Pharmaceutical and Medical Applications – Recent Achievements and Challenges. *Pharmaceutical Research*, *35*(9). https://doi.org/10.1007/s11095-018-2454-x

Journals, H., Article, R., Dose, L., & Permeability, H. (2018). *Fast Dissolving Oral Films: A Review with Future Prospects*. (2), 1–18.

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

Khames, A. (2019). Hexyl alginate derivative, an amphiphilic innovative buccal film-forming material of promising mechanical and release characteristics for the improvement of repaglinide bioavailability . *Drug Design, Development and Therapy*, *Volume 13*, 925–940. https://doi.org/10.2147/DDDT.S196425

Lamichhane, S., Bashyal, S., Keum, T., Noh, G., Seo, J. E., Bastola, R., … Lee, S. (2019). Complex formulations, simple techniques: Can 3D printing technology be the Midas touch in pharmaceutical industry? *Asian Journal of Pharmaceutical Sciences*, (2019). https://doi.org/10.1016/j.ajps.2018.11.008

Lennox, K. (2014). Substantially Unequivalent: Reforming Fda Regulation of Medical Devices. *University of Illinois Law Review*, (4), 1363–1400.

Li, Q., Wen, H., Jia, D., Guan, X., Pan, H., Yang, Y., … Pan, W. (2017). Preparation and investigation of controlled-release glipizide novel oral device with three-dimensional printing. *International Journal of Pharmaceutics*, *525*(1), 5–11. https://doi.org/10.1016/j.ijpharm.2017.03.066

Liew, K. Bin, Peh, K. K., & Fung Tan, Y. T. (2013). Orally disintegrating dosage forms: Breakthrough solution for non-compliance. *International Journal of Pharmacy and Pharmaceutical Sciences*, *5*(4), 4–8.

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. https://doi.org/10.1016/j.addr.2018.05.006

Lopez, F. L., Ernest, T. B., Tuleu, C., & Gul, M. O. (2015). Formulation approaches to

pediatric oral drug delivery: benefits and limitations of current platforms. *Expert Opinion on Drug Delivery*, *12*(11), 1727–1740. https://doi.org/10.1517/17425247.2015.1060218

Mady, O. Y., Donia, A. M., & Al-Madboly, L. A. (2018). Miconazole-urea in a buccal film as a new trend for treatment of resistant mouth fungal white patches. *Frontiers in Microbiology*, *9*(MAY), 1–13. https://doi.org/10.3389/fmicb.2018.00837

Oyewumi, (2015). 3D Printing Technology in Pharmaceutical Drug Delivery: Prospects and Challenges. *Journal of Biomolecular Research & Therapeutics*, *4*(4). https://doi.org/10.4172/2167-7956.1000e141

Pallavi, K., & Pallavi, T. (2017). Formulation and Evaluation of Fast Dissolving Films of Eletriptan Hydrobromide. *International Journal of Current Pharmaceutical Research*, *9*(2), 59. https://doi.org/10.22159/ijcpr.2017v9i2.17386

Panda, B., Dey, N. ., & Rao, M. E. . (2012). Development of Innovative Orally Fast Disintegrating Film Dosage Forms : A Review. *International Journal of Pharmaceutical Sciences and Nanotechnology*, *5*(2), 1666–1674.

Patil, P. B., More, V. N., & Tour, N. S. (2015). Recent Trends in Orodispersible Tablets – An Overview of Formulation Technology and Future Prospects. *International Journal of Pharma Sciences and Research (IJPSR)*, *6*(7), 1056–1066.

Radicioni, M., Castiglioni, C., Giori, A., Cupone, I., Frangione, V., & Rovati, S. (2017). Bioequivalence study of a new sildenafil 100 mg orodispersible film compared to the conventional film-coated 100 mg tablet administered to healthy male volunteers. *Drug Design, Development and Therapy*, *11*(April), 1183–1192. https://doi.org/10.2147/DDDT.S124034

Said, Z., Baker, S. R., Hansen, J., D'Apice, K., Thornhill, M. H., Madsen, L. S., … Santocildes-Romero, M. E. (2018). Pre-clinical evaluation of novel mucoadhesive bilayer patches for local delivery of clobetasol-17-propionate to the oral mucosa. *Biomaterials*, *178*, 134–146. https://doi.org/10.1016/j.biomaterials.2018.06.009

Tian, Y., Teekamp, N., Hinrichs, W. L. J., Woerdenbag, H. J., Visser, J. C., Frijlink, H. W., & Olinga, P. (2017). Addition of Pullulan to Trehalose Glasses Improves the Stability of β-Galactosidase at High Moisture Conditions. *Carbohydrate Polymers*, *176*(August), 374–380. https://doi.org/10.1016/j.carbpol.2017.08.084

Trenfield, S. J., Goyanes, A., Telford, R., Wilsdon, D., Rowland, M., Gaisford, S., & Basit, A. W. (2018). 3D printed drug products: Non-destructive dose verification using a rapid point-and-shoot approach. *International Journal of Pharmaceutics*, *549*(1–2), 283–292. https://doi.org/10.1016/j.ijpharm.2018.08.002

Ventola, C. L. (2013). WHO | The WHO Recommended Classification of Pesticides by Hazard. *Who*, *39*(10), 704–711. https://doi.org/10.1016/j.infsof.2008.09.005

Webster, L., Camilleri, M., & Finn, A. (2016). Opioid-induced constipation: rationale for the role of norbuprenorphine in buprenorphine-treated individuals. *Substance Abuse and Rehabilitation*, 81. https://doi.org/10.2147/sar.s100998

Woerdenbag, H. J., Frijlink, H. W., Hinrichs, W. L. J., Tian, Y., Visser, J. C., & Klever, J. S. (2018). Orodispersible films based on blends of trehalose and pullulan for protein delivery. *European Journal of Pharmaceutics and Biopharmaceutics*, *133*(August), 104–111. https://doi.org/10.1016/j.ejpb.2018.09.016

Zaman, M., Hanif, M., & Shaheryar, Z. A. (2018). Development of Tizanidine HCl-Meloxicam loaded mucoadhesive buccal films: In-vitro and in-vivo evaluation. *PLoS ONE*, *13*(3), 1–14. https://doi.org/10.1371/journal.pone.019441

Abdulraheman, Z.S., Patel. (2015). International Journal of Universal. *International Journal of Universal Pharmacy and Bio Sciences*, *3*(4), 93–113.