A 3D Printed Quick Response Encoded Orodispersible Film for Personalized Medicine

By

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

The Department of Pharmacy
Brac University
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Declaration

It is hereby declared that

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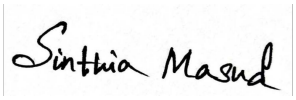

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Approval

The project titled "A 3D Printed Quick Response Encoded Orodispersible Film for Personalized Medicine" submitted by Sinthia Masud (17346049) of Spring, 2017 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on July, 2021.

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Ethics Statement

This study does not involve any human or animal trial.

Abstract

Personalization is the future of medicine for patient adherence and safety. A 3D printed QR encoded orodispersible film (3DQRODF) is an efficient alternative to usual dosage form of capsule and tablet with the potential of tailored treatment. Orodispersible Film (ODF) is compliant to patient for ease of administration without water, particularly patients with swallowing problems e.g. pediatrics and geriatrics. 3D printing is utilized for precise shape and size of ODF. Quick Response (QR) code was printed in one step process by directly feeding nozzle of hot melt extrusion (HME). QR code is designed with drug loaded encoded information and can be accessed by QR scanner with the aid of smart device. Patient specific QRODF with uniform dosing allows personalized treatment, as well as tracking of QR code can turn aside counterfeit of medicine. 3DQRODF is promising to shift the paradigm from 'one size fits all' to personalization.

Keywords: 3D Printing; Orodispersible Film; QR Code; Personalized Medicine, Hot Melt Pneumatic Extrusion

Dedication

Dedicated to my parents

Acknowledgement

This is a collaborative project under the joint supervision of Professor Dr. Md Jasim Uddin, Associate Professor and Namara Mariam Chowdhury, Lecturer, Department of Pharmacy, Brac University.

I would like to convey my earnest respect to my supervisor, Namara Mariam Chowdhury (Lecturer, Department of Pharmacy, Brac University) for her valuable guidelines and recommendations which helped my project work to be more presentable. I am truly thankful for the support; she has provided me, with her valuable time, assistance and significant suggestions.

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List of Acronyms

ODF	Orodispersible Film
3D	Three Dimensional
2D	Two Dimensional
QR	Quick Response
HMPE	Hot Melt Pneumatic Extrusion
FDM	Fused Deposition Modeling
CAD	Computer Aided Design
API	Active Pharmaceutical Ingredient
PEO	Polyethylene Oxide
POX	Poloxamer
RH	Relative Humidity

Chapter 1

Introduction

Pharmaceutics has recently grown interests in three-dimensional (3D) printing technology for its prominent advantages of drug design and cost efficacy. Due to the flexible nature of this innovative technology, 3D printing can be modified for personalization of medicine (Musazzi et al., 2018) with the potential of manufacturing precise and adjustable doses (Raijada et al., 2013) along with the possibility of personalized release features (Scoutaris et al., 2011; Daly et al., 2015).

Contemporary medicines and treatment approach generally focus on "one size fits all" principle, where available drug dose is same for all patients, with limited variation in dosage strength (Litman, 2019). Drugs with broad therapeutic window are suitable for this paradigm; however challenges arise for drugs with narrow therapeutic window. Besides, this approach does not fit medicines showing high alteration of pharmacokinetic or pharmacodynamics profiles. Each patient requires accurate dose and under dosing or overdosing might lead to compromised therapeutic effect or adverse effects (Edinger et al., 2018).

Personalization of dosage form is required as the solution of current approach, where medicines can be tailored considering age, gender, physiology and genetic profile for precise indication of each patient, at the correct time (Litman, 2019; Florence and Lee, 2011). In order to shift from "one size fits all" to personalized medicine, 3D printing technology can be utilized for manufacturing dosage forms in various size, shape, and combination of drugs (Vaz & Kumar, 2021).

1.1 3D Printing

3D printing technology is the manufacturing process to develop 3D object by deposition of materials in layers (Schubert, Van Langeveld, & Donoso, 2014). 3D printing or additive manufacturing produces a three-dimensional solid object of any virtual shape from a digital model. 3D printing enables to produce complex shapes using less material than traditional manufacturing methods. Traditional manufacturing techniques rely on the removal of material by cutting or drilling whereas in 3D printing multiple layers are added consecutively (Shahrubudin et al., 2019). 3D printers were first used in the 1980s where a pattern submerged in a liquid polymer was traced by a computer (Shahrubudin et al., 2019). Currently, 3D printing is offering medical equipments, pharmaceuticals and emerging research fields including tissue and organ printing (Fan et al., 2020).

3D printing method gradually constructs a solid model by deposition of material. Computer aided design (CAD) software is applied for transferring the necessary signals to a 3D printer. Product manufacturers and engineers upload a digital CAD file to a 3D printer, which later converts the computerized digital model into two-dimensional (2D) sections to generate solid layers of the desired 3D objects (Vaz & Kumar, 2021). 3D printing precisely forms sequential layers, which aids to design unique shape of the object for controlled drug release (Joo et al., 2020; Kilicarslan et al., 2018; Park et al., 2019).

3D printing enables to print on-demand solutions for a wide range of pharmaceutical dosage form (Choong et al., 2020). In 3D printing, thermoplastics are the most frequently used materials. However, the printing technology also includes metal, photopolymer, resin and epoxy. A mixture of human cells and gelatin used for cutting-edge bioinks has also been supported to 3D print complex tissue models (Cho et al., 2020).

3D printing has been employed in the development of complex oral dosage forms and at commercial scale for the production of fast dissolving tablet. Amongst the multiple technologies applicable to 3D printing, material extrusion based fused deposition modeling (FDM) is the most frequently used in pharmaceuticals. FDM has been employed to develop various oral drug delivery systems. FDM printing technique is usually two steps process. Initially, mixing and heating materials along with the use of hot melt extrusion (HME) screws for filaments. Finally, manufacturing objects by melting filaments (Musazzi et al., 2018).

In 3D-printing technology, FDM has recently applied for its potential to precisely fabricate solid formulations. This is an extrusion controlled 3D-printing technique for solid formulations (Joo et al., 2020; Park et al., 2019), which utilize HME and filaments of thermoplastic polymers to develop a melted blend at the nozzle, which is followed with layer by layer formulation (Melocchi et al., 2015).

Nonetheless, a multi-step printing process of FDM has major limitation. In order to prevail over limitation, hot melt pneumatic extrusion (HMPE) is suggested for a one step 3D printing as different type of HME was applied to eliminate the in-between steps, having quicker prospects for the assembly of substances. In HMPE method of 3D printing, powders or pellets are directly fed, which will be a simplified FDM paradigm and customized according to the printing process, the disposal of the drug and dosage form (Musazzi et al., 2018).

Recently hot melt pneumatic extrusion technology has explored to exclude the requirement of filaments in manufacturing. Furthermore, 3D printing can be exploited to accurately print QR code on the film (Oh et al., 2020).

1.2 3D printed QR Code

In 1994, Japan Denso Company invented quick response (QR) code. A QR code is a barcode of two-dimension (Yang et al., 2019) with required encoded data. The encrypted code can be

accessed via a QR code scanner app with the aid of a smartphone to read the coded information. QR codes can function and restore data regardless of partial damage for faults in correction code (Oh et al., 2020; Yang et al., 2019).

In order to prevent counterfeiting of medicine recently QR codes have been utilized (Preis et al., 2015). For instance, at the end stage of dosage form formulation (Logue et al., 2015) fluorescent inks can be applied (You et al., 2016). QR code has been proposed for greater drug adherence and safety for patent friendly access of smart devices (Edinger et al., 2018; Tseng & Wu, 2014; Mira et al., 2015), which has already observed enhanced patient compliance and less number of doctor appointments (Edinger et al., 2018; Rathbone & Prescott, 2017).

QR code received ISO approval with International standard specification issued by ISO, 2006; which has multiple applications such as; storage of information, product tracking website redirection and passenger identification. Moreover, in pharmaceuticals application of QR encoded patient-specific dosage forms utilizing 3D printing has been recently investigated (Oh et al., 2020).

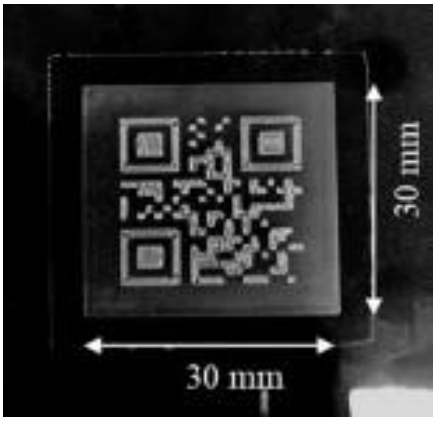


Figure 1: 3D print QR coded oral film (Oh et al., 2020)

3D printed QR code can shift the paradigm from ‘one size fits all’ to personalization by designing QR encoded oral film with coded information and rapid identification with

accurate consistency (Yang et al., 2019; Oh et al., 2020). In a current study, the QR code was not separately printed on the oral film; rather the code was directly designed and developed through a single step method with 3D printing technology (Oh et al., 2020).

1.3 3D QR encoded ODF

Orodispersible film (ODF) is an advanced dosage form with rapid disintegration or dissolution in the oral cavity which results to increased bioavaibility (Stegemann et al., 2012; Karki et al., 2016). Oral thin film is composed of flexible thin layer of polymer which might incorporate plasticizer. ODFs are comparatively more convenient to patients as thin films are flexible for focusing sensitive locations which cannot be attained with tablet or liquid preparations. Thin films demonstrate rapid onset of drug action, with reduced dose frequency to enhance drug efficacy (Karki et al., 2016) along with the constant integrity of drug content remains constant over time (Vishwakarma, 2017).

ODFs are usually introduced to patients as stamp-like strips, either in single-portion sachets or contained in multi-portion packs. ODFs ought to be preferred to seal individually in order to develop stability and reduce the prospect of overdosing due to sticking of multiple films. Potentially, advanced multi-dose dispenser could be utilized where the ideal dose is attained by the caregiver or patient by cutting strips of fitting length from a tape (Lopez, Ernest, Tuleu, & Gul, 2015).

The attributes which determine ODFs acceptability to patient are mechanical properties such as film flexibility and resistance, which can be developed by tensile strength (Krampe et al., 2016). The preference of polymer or polymer blend formulating the film matrix can ensure a flexible robust oral film (Borges et al., 2015; Preis et al., 2013). For instance, molecular weight of polymer decides the polymeric matrix disintegration time after administration. In addition, the existing hydrogen-bonding polymer groups can determine films mucoadhesive

strength (Preis et al., 2013). Also, irritation to the oral mucosa can be prevented by balanced pH level (Tian et al., 2019).

ODF disintegrates and breaks down into soft micro particles, so the patient does not experience discomfort of gritty multiparticulates, which is ideal for patient with dysphagia (Visser et al., 2017). ODFs administration is patient centric as it requires no intake of water and for rapid dissolution (Bala, Khanna, Pawar, & Arora, 2013). Oral film enables improved dosing accuracy relative to liquid formulations as each strip contains a precise amount of the drug. In emergency requirement, oral films can reduce dose with precise content uniformity. Also, the intuitive nature of the dosage form and inherent ease of administration can improve compliance (Vishwakarma, 2017). Taste masking aspect can enhance the palatability of ODFs in patient, significantly in pediatrics (Krampe et al., 2016; Orlu et al., 2017).

Additionally, upon administration due to mucoadhesive properties ODFs instantly stick to the mucosa and facilitate drug release. Also, ODFs can be designed in a layer which exhibits potential for controlled release and fixed-dose combinations. Therefore, layered design of oral film results in lower dosing frequency and hence leads to enhanced patient adherence and compliance (Scarpa et al., 2018). The sublingual and buccal delivery via thin film has the potential to improve the onset of action, lower dosing and enhance the efficacy and safety profile of the medicament (Vishwakarma, 2017).

ODFs are preferred for both systemic and local treatment as the membrane of oral route is compliant for local as well as systemic administration of drugs (Uddin, Sultana, Nipa, Chowdhury, & Douroumis, 2017). Systemic treatmement can be accomplished mostly by absorbing active pharmaceutical ingredient (API) through the oral mucosa (Hoffmann et al., 2011). The oral mucosa withstands greater vascularity compared to other membrane sites

such as; nasal, intestinal and rectal and with less protein activity and irritation (Uddin, Sultana, Nipa, Chowdhury, & Douroumis, 2017).

Permeability is crucial for systemic administration of ODFs because the buccal mucosa functions as a natural barrier. In multiple studies, animal tissues have been utilized for the purpose of mimicking human buccal mucosa. Most studies have applied esophageal (Abruzzo et al., 2017; Padula et al., 2013) and buccal porcine membranes (Kumria et al., 2016). Also, researches with cell cultures are growing interests, for instance investigations with cell TR146 lines (Castro et al., 2018) and tridimensional human buccal tissue (Morales et al., 2014). The studies of permeation tests showed that Franz diffusion cells are conventionally preferred with specific modification (A. Kumar et al., 2013). The permeation rate is analyzed by flux, where flux is determined through the calculation of slope of the plot. Furthermore, evaluation method of the apparent permeability also requires the flux over the concentration (Castro et al., 2018). The major challenges of permeation tests with animal tissues arise due to high variability of the data. Additionally tissue integrity, viability and storage conditions must be monitored prior to application (Roblegg et al., 2012).

In different studies multiple orodispersible films with prolonged release properties have been developed, where lower dosing frequency extensively improves patient compliance and adherence. Although rapid disintegration is the main aspects of adherence for ODFs, however for patients with swallowing difficulties prolonged drug release from oral film is also potential. A study investigated that prolonged drug release of ODF can be attained by drug-loaded matrix based on Eudragit and silicon dioxide (Speer et al., 2018; Tian et al., 2019), where the matrix particles along with the model drug were fabricated by hot melt extrusion method of 3D printing. However, inhomogeneous distribution of the particles occurred for difference in particle shape and size. In order to overcome this challenge, incorporation of micropellets with microcrystalline cellulose and sodium carboxyl methylcellulose were

suggested (Speer et al., 2019). Therefore, ODFs disintegrate in the oral cavity, where along with saliva incorporated micropellets can be swallowed and later the drug is slowly released in the gastrointestinal tract. Furthermore, drug-ion exchange resin complex is another potential approach for prolonged release of ODFs. For this purpose, a study focused on a drug, which is very hygroscopic along with short half-life and bitter taste. However, drug-ion exchange resin complex efficiently overcome such unfavorable characteristics and ensures prolonged drug release in the gastrointestinal tract from the resin complex (Shang et al., 2018; Tian et al., 2019). In addition, drug loading can be improved with desired sustained release of poorly water-soluble drug. For that, a study proposed a sandwiched film, where the oral film comprised of a drug-loaded hydrophilic layer between to hydrophobic layers. The study exhibited sustained release up to 480 min based on the depth of the inner layer, whereas the films without hydrophobic layers release the drug material within 45 min (Tian et al., 2019; Zhang et al., 2018).

Moreover, in consideration of the dissolution time fast-dissolving and sustained release films, and mucoadhesive films or oral patches can be identified. However, the distinction is not apparent. Mucoadhesives and oral patches are commonly available in the market as sustainable release buccal dosage form (Hoffmann et al., 2011). In order to print formulations on oral film, 3D printers are utilized for accurate and uniform dosing, which aids controlled drug release of oral film (Joo et al., 2020; Park et al., 2019).

3D printing permits the formulation of oral film comprising more than one active substance characterized with different properties and dissolution profiles. Also, 3D printing technology can achieve precise control of dissolution properties with the aid of soluble or insoluble excipients along with the adjustment of required geometry and internal structure of the written dosage form (Jamróz et al., 2018). Nevertheless, this can solely be employed by health care professionals as it requires the data concerning pharmacokinetics of the active

substance and health condition of the patient and it may as well be applied in hospital pharmacies (Jamróz et al., 2018).

In a recent study, QR coded ODF was designed implementing 3D printing method with directly feeding nozzle in one step process for tailored therapy. Drug information encoded in optimal formulation of QRODF could be scanned using a smartphone for personalized treatment approach (Oh et al., 2020).

1.4 Fabrication of 3DQRODF

ODF is frequently manufactured with the conventional solvent casting method (Yang et al., 2019). Currently a study investigated drug-loaded biodegradable labels manufactured by solvent casting the formulation into prepared molds with QR encoded information (Fei and Liu, 2016). A study was conducted applying inkjet printing technique to print QR coded oral film as dosage form (Edinger et al., 2018). Nonetheless, this technology requires rather two-step printing method. Initially the base film was manufactured and later QR code was printed out with drug-loaded ink and the complex process failed to characterize standard drug dissolution and disintegration time (Jamróz et al., 2017).

In order to overcome the complexity of inkjet printing, hot melt extrusion technology was proposed for powdered drug formulation to design QR coded orodispersible film (QRODF). In this method, QR code was printed during film formulation in one step by directly feeding nozzle (Oh et al., 2020).

Nozzle-based deposition system allows direct writing, which relies on computer-controlled manufacturing to deposit ink directly through a nozzle to create a 3D pattern layer-bilayer with controlled composition. This technique may be classified on the process of material melting (Goole & Amighi, 2016).

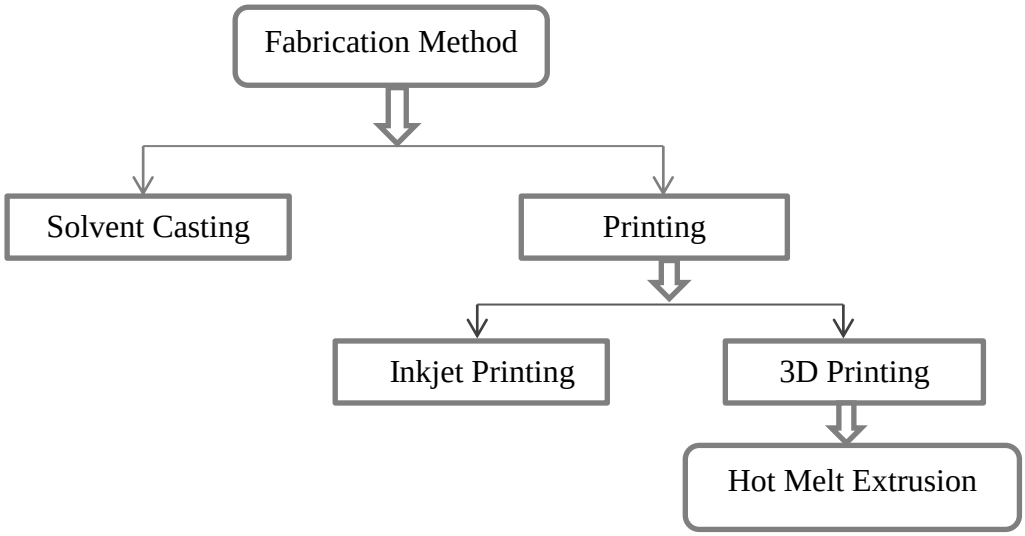


Figure 2: Methods of QR coded Orodispersible Film fabrication (Oh et al., 2020)

1.5 Objective of the study

The objective of this literature review is to explore QR code design on the surface of orodispersible film by hot melt pneumatic extrusion of 3D printing. Also, the study emphasize on patient specific QR encoded information on oral film along with challenges and potential to personalize medication for patient adherence and to prevent counterfeit of medicine.

Chapter 2

Research methodology

Thorough literature review was done to attain all the information used in this review paper. The information was collected from various credible sources, which includes peer reviewed journals, online scholarly database. Following are the list of some of the many databases that were search extensively for the present study.

- Journal Database
- Library Catalogue
- Newspaper Database
- Professional website

On quest to collect as much relevant information regarding 3D Printed QR coded orodispersible film for personalized medicine, thorough search of various journals, research papers and review articles from official sites and research databases was performed. Renowned and reliable databases such as PubMed, SCOPUS and Science Direct helped to gather the information of 3D Printed QR coded orodispersible film for personalized medicine for this review paper. Appropriate key terms, such as; 3D printing, Orodispersible Film, QR code, Personalized Medicine, Hot Melt Pneumatic Extrusion was used to collect relevant articles Since this is a fairly niche topic, the number of articles is minimal to say the least. Depending on the title and key words, almost 150 articles have been screened through. Then, 100 articles were narrowed down after reading abstract. Finally, 75 articles were selected and methodically analyzed to write this review paper. Mendeley software was used for proper and just referencing to as to be respectful with the work or the original authors.

Chapter 3

3DQRODF: Hot Melt Pneumatic Extrusion

In recent times, polymeric-based film-forming agents have developed potential application in 3D printing, where hydrophilic polymers are applied to mediate film-forming in ODF formulation for enhancing dissolution properties (Yang et al., 2019). In order to remove filaments requirement, oral formulations were printed out directly from the powder mixtures of thermoplastic polymers utilizing directly feeding nozzle of hot-melt extruder in presence of high air pressure (Oh et al., 2020). Thus, orodispersible film formulation with hot-melt extrusion method with the aid of polymers demonstrates prospective (Yang et al., 2019).

In hot melt extrusion method a die is precisely set to fabricate mixture of ingredients into desired product attaining precise size, shape and density. Also, viscosity can be adjusted by exploiting a liquefied system to enable the mixture flow through the die. For this purpose, initially the active pharmaceutical agents along with the excipients are mixed in the machine implied for extrusion. The excipients include bulking agents, antioxidants, thermal lubricant, polymer or matrix carrier, plasticizer and additives such as coloring agent, flavoring agent or taste masking agent. Following that, heat is employed to melt the mixture while the plastic mass is being extruded through the machine. The ejected extrudate from the machine cools and solidifies which is further intended for downstream processes (Censi & Gigliobianco, 2018).

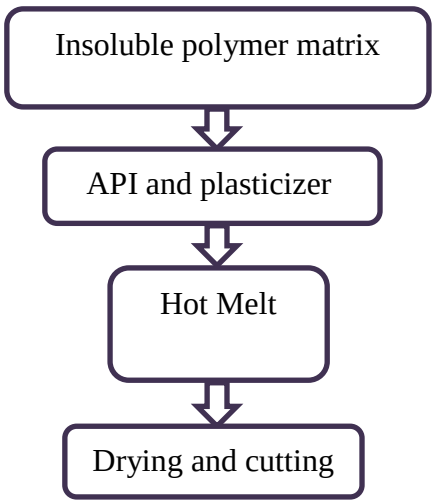


Figure 3: Hot Melt Extrusion method (Irfan et al., 2016)

HME technology is solvent free and gives multiple advantages. The manufacturing process is continuous and hence requires few steps, which makes the formulation less time consuming and inexpensive. Also, this technology ensures multipurpose implication and scaling up. Moreover, hot melt extrusion technique upholds the drug content uniformity due to vigorous mixing procedure (Thakur et al., 2013; Ren, 2018).

However, the extrusion process raises many challenges as it requires high process temperature and shear force. Therefore, it might compromise with stability of heat labile API's and other ingredients. Also, challenges occur due to low availability of thermal stable polymers and required high energy. The extrusion based manufacturing process is extremely complex process and requires efficient skills to operate. It is apparent that HME comes with opportunities such as modification of polymers, optimization of the process and HME design in 3D printing (Ren, 2018).

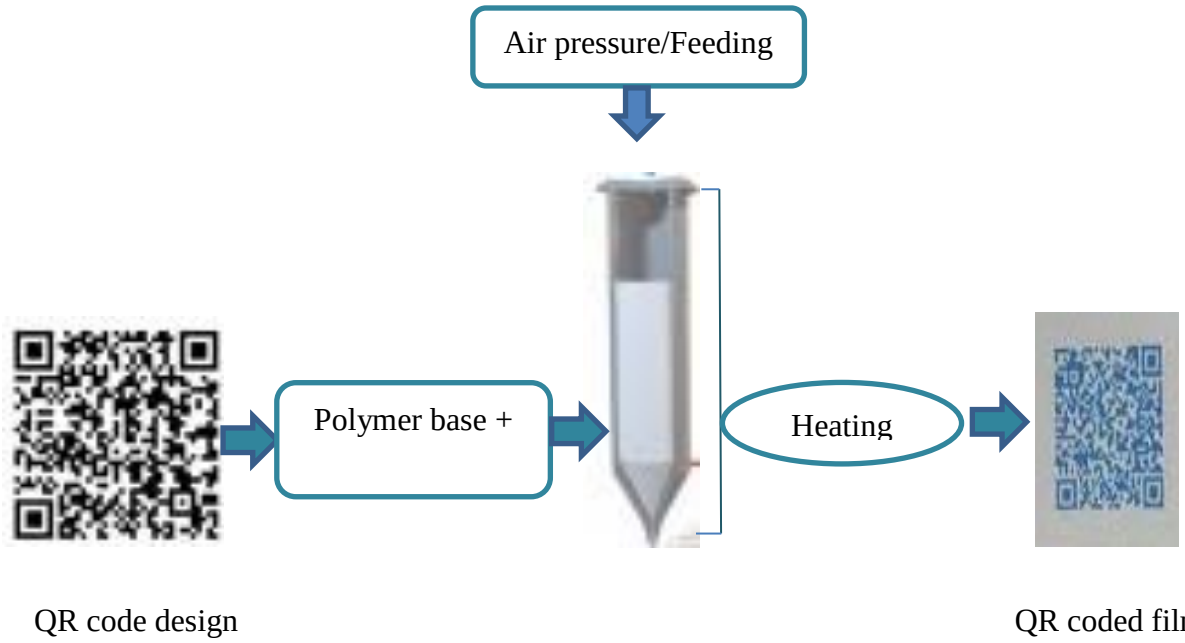


Figure 4: HMPE 3D printing for QRODF design (Oh et al., 2020)

In current study, QR code was not separately printed on the surface of ODF rather throughout formulation in one step process with directly feeding nozzle (Oh et al., 2020).

3.1 Optimization of 3D Printing

In HMPE 3D printing technique wettability, flowability, and viscosity are the most important conditions to be maintained. In the recent study, 3D printer employed a tip made of steel at the bottom of a pneumatic dispenser to dispense the polymer ink through a small split at the tip of the nozzle.

Table 1: *3D printing Optimization (Oh et al., 2020)*

3D printing factors	Optimum value
Melting point (PEO)	(65–67)°C
Melting point (POX)	52°C
Temperature	140 °C
Pressure	350 kPa
Printing time	30 mins

PEO was considered suitable as the film-forming agent for its compliance of hot melt extrusion and optimal melting point range within (65–67)°C. In addition, PEO enhances dissolution of poor water-soluble drugs as solubilizer. However, PEO could make the film less flexible if added alone. Thus, to modify the flexibility of oral films POX was induced as plasticizer, with the melting point of 52°C. The study developed that in low temperature extrusion fails and the polymers burn in high temperature. The optimal temperature was observed at 140 °C and the pressure of the printer was optimum at 350 kPa. QR coded oral film was printed with 3D printer and the printing time was 30mins, considering the melting point of the drug content applied in the study no thermal degradation was observed within 30 mins (Oh et al., 2020).

3.2 QR design of 3D printer

A study explored QR design and the model of QRODF was designed by Autodesk in the Fusion 360 software. The QR code was designed to be compatible with a HMPE 3D printer with directly feeding nozzle, while extruder speed and infill were being in control and later transformed to 3DODF (Oh et al., 2020).

The film dimension, infill, extrusion conditions of nozzle speed, nozzle size and layer size of film (Table2) is specified (Oh et al., 2020).

Table 2: *QR code design in extrusion conditions of 3D printer (Oh et al., 2020)*

QR design	**Extrusion condition**
Film dimension	3 × 3 × 0.3 cm
Layer height	0.1 mm
Nozzle speed	5 mm/s
Nozzle size	0.4 mm
Infill	100%

To design QR code, smaller nozzle is preferred but a nozzle of 0.2 mm often induced nozzle blockage, hence 0.4 mm nozzle was optimized. In addition, the qualitative evaluation demonstrate that the printed mix could be extended on the printing mark less than 5 mm/s nozzle speed, however nozzle speed above 5 mm/s could break the printing line. Thus, the encoded film was optimized with the nozzle size of 0.4 mm and 5 mm/s nozzle speed for good resolution of QR code.

In this study, The QR code was 3D printed in one step during the film formulation, not separately over the film (Oh et al., 2020).

3.3 Physicochemical characterization of 3DQRODF

Patient friendly administration of QRODF can be ensured by maintaining physical properties such as flexibility, thickness, content uniformity, disintegration time and pH values of drug formulation. 150 to 250 μm (Musazzi et al., 2018) is considered as the suitable range of film formulations for patient management (Oh et al., 2020).

A recent study explored that the thickness of the printed films ranged within 158 μm to 366 μm and finally formulation was of 219 μm, compatible for patient. However, the study investigated that POX concentration evidently enhance the thickness of the QRODF. Improved flow ability of the polymer mixture resulted with high printed mass and variation in POX concentration controlled the thickness. Also, flexibility of films was decided with the indication of tensile strength. It has observed that during storage films with high tensile strength had the advantage of avoiding breakage (Oh et al., 2020).

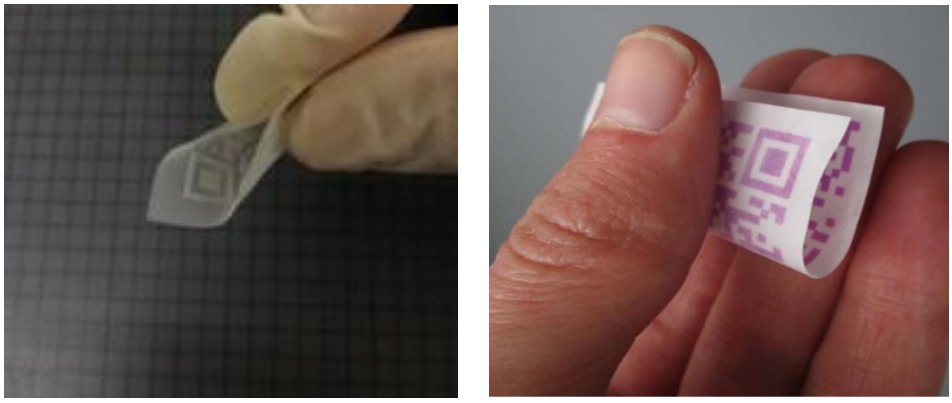


Figure 5: Flexibility of QR coded oral film (Edinger et al., 2018; Oh et al., 2020)

The study observed that highest tensile strength was 5 ± 0.8 MPa, whereas the lowest value was 1.22 MPa for F4. It was also mentioned that citric acid addition did not alter tensile strength. Also, the amount of POX in the formulation decides the strength of the film. The film formulation could be fragile, if POX was greater than 10% of PEO (Oh et al., 2020).

In purpose of avoiding irritation of the oral cavity and also to intensify the drug dissolution, the surface pH of the oral film was adjusted (Joshua et al., 2016; Oh et al., 2020). Thus, the pH of the film was observed to decrease proportionally in addition of citric acid. Also, the study demonstrated free acid-based film pH range within 8.79 to 8.14 and citric acid-based films within 5.24 to 6.41, which specified that the pH level in range and appropriate for the oral cavity (Oh et al., 2020).

According to the CDER guidelines, the standard disintegration time of ODF must be within 30s for orally disintegrating tablets (Loveleen Arora, 2017). In the conducted study all film formulations disintegrate within 19.7s-22.2s, which ensured rapid disintegration of QR coded ODF in the oral cavity (Oh et al., 2020).

Table 3: Physicochemical characteristics of 3DQRODF (Oh et al., 2020)

Physicochemical properties	**Characterization**
Film thickness	219 μm
Tensile strength	1.22 - 5 ± 0.8 MPa
PH (free acid-based film)	8.79 - 8.14
PH (citric acid-based film)	5.24 - 6.41
Disintegration time	19.7s - 22.2s

Chapter 4

QR encoded ODF

4.1 QR code generation

A free online QR code generator is utilized to generate QR code loaded with required information (QR code generator, 2017). The format which was preferred in study to download QR code is png-format and later uploaded with the help of customized script. In each code a low level of error corrections, such as within 7% unreadable data was permitted (Kato et al., 2010). Furthermore, the script cut off the white edges from QR code and black pixels number was counted, which is followed by including required information. Then, required black pixels to attain the precise dose were calculated and the image was resized and saved accordingly to be uploaded manually as the printing template (Edinger et al., 2018).

4.2 3D QR code

In the current study the extruded film was 30 mm × 30 mm, where QR code was printed on 22.3 mm × 22.3 mm of the film. In addition, the QR code was printed precisely on the edge of the film for ease of scanning via smartphone. To design QR encoded ODF, the incorporated information could include details of drug content, dose, efficacy and volume. However, the QR code becomes complicated with the more detailed information. It is suggested that uniform resource locator (URL) could be preferred to access a huge volume of data contained in a homepage, thus a small URL could be alternatively applied to store information in a QR code (Oh et al., 2020).

4.3 Drug content of QRODF

In the research conducted to analyze drug content of QRODF, QR encoded films were observed in altered dimensions due to the variation of black pixels, related with the loaded information within QRODF. Thus, pixel images of QR code were accustomed based on droplet volume and API concentration of the ink. In order to adjust the image, semi-automatic software was designed to resize the printing configuration to hold the accurate amount of colored pixels and therefore to attain precise dosing of the API in the oral film. For instance, the study evidently presents that a film comprised of 1 mg API was 3 × 3 cm^2 , whereas, a film containing 2.5 mg API was 4.5 × 4.5 cm^2. Here, it was also mentioned that API content can be determined by HPLC analysis and the doses ranged within 3% of the indicated strength (Edinger et al., 2018).

In addition, another recent study evaluated dose consistency of ODF and it was evaluated through the drug content of each specific film. The study developed that drug content range of all films was within 96.42% to 104.89% (Oh et al., 2020), where in all films L1 ± 15% (Sharma et al., 2007) was set to maintain dose uniformity within limits (Oh et al., 2020).

Therefore, drug content analysis enables precise printing of API with high resolution images and ensures feasibility of 3D printed QRODF, where dose uniformity is preserved along with encoded patient specific encoded information (Edinger et al., 2018; Oh et al., 2020).

4.4 Readability of QR code

In QRODF, information is encoded and can be accessed via android and iOS smartphones with QR scanners. However, correct alignment of substrate prior to printing is crucial because if the substrates were not on flat surface or precisely aligned then the readability of QR code gets altered. Hence, deforming and twisting the QR code is not encouraged as it becomes difficult to decode the encoded information. Also, the research observed that the

application of Barcode Scanner required a great deal of time for scanning, whereas Best QR Barcode Scanner scanned the data in within a second. It is noted that the application could have an impact on scanning time and feasibility, such as; color identification and contrast improvement from background (Edinger et al., 2018).

In addition, high relative humidity () can result to edge bleeding and inclusion of the adjacent printing squares which eventually affects the QR code pattern and readability of the film. For instance, analysis showed that if the damage occurred at the bends of the QR code and three adjacent squares then the substrate absorbs a great extent of water at 95% relative humidity (> 40% w/w), but later at lower relative humidity release water. Thus, storage of the QRODF could be altered due to exposure at high RH for stability and readability of the QR code. A study explored readability of the films using smartphone while it was stored. After exposed to high RH of 75%, QR codes could be accessed with smartphone and the appearance was not compromised as well. However, storage at 95% RH caused the shift of water-soluble dye in the film due to water absorption and lead to localized edge bleeding of the QRODF (Edinger et al., 2018).

(A) QR code after printing (B) QR code at 75% RH storage (C) QR code at 95% RH storage

Figure 6: Altered readability of QR coded film in relative humidity (Edinger et al., 2018)

Although the shape of QR coded films was preserved while handling, encoded films were unusually softer. As a result, the QR coded films must be stored in sealed containers and a

dehydrating agent is required for prolonged shelf life in high RH storage conditions (Edinger et al., 2018).

Chapter 5

Personalization of 3DQRODF

5.1 Dose personalization

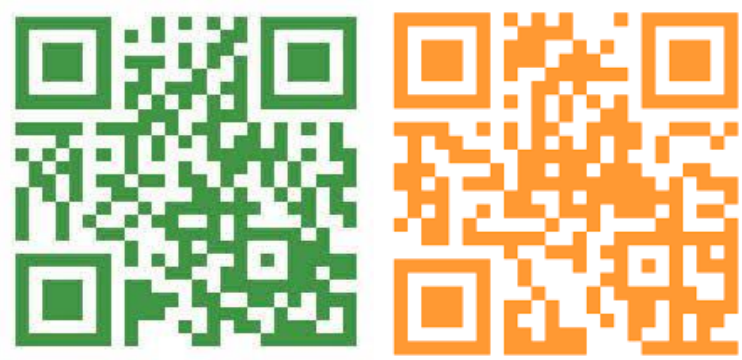
In pharmaceuticals, 3D printing indicates extensive potential to tailor the dosage forms for individuals by precisely adjusting the doses, dose combination or altering the drug release profiles according to the requirement of each patient (Vaz & Kumar, 2021).

For instance, to attain flexibility of doses for children according to the age and body weight, 3D printing offers dose personalization. In 3D printed ODF formulation, dosage forms can be adapted with 3D printers with precise control of liquid formulation dispensed on the oral film. Also, ODF formulation can be altered in shape and dimension to personalize medication (Musazzi et al., 2020). In addition, to modify dosage forms of multiple release profiles of individual requirements, 3D printing fabricates alternative shapes and geometries of film (Gültekin et al., 2019).

Also, QR code printed on the surface of oral film encodes patient centric information in the purpose of personalized medication and can be optimized for individualized diagnosis and treatment approach.

In recent study, a framework was proposed with symptom centric QR codes for disease (COVID-19) containment. In this framework, public health authorities distributed two distinct colors of QR healthcare codes to determine the health status of individual patient, where QR codes do not recover user’s location data. The healthcare QR codes are authorized

as healthcare e-certificates of individuals, which can optimize patient tracing, medical appointments, self-update of medication, healthcare and self-triage (Nakamoto et al., 2020).



(A) Green QR code for non-infected patient (B) Orange QR code for high risk for infection

Figure 7: QR code approach for disease containment (Nakamoto et al., 2020)

In this study, with the aid of a diagnosis of test, a green QR code indicates that patient is not disease infected, whereas an orange QR code determines infected patients or patient with high risks. Hence, QR coded health verification test determines infected patients to contain disease and also for efficient public health and regulatory policies to improve public health surveillance (Nakamoto et al., 2020).

5.2 Anti-counterfeiting medicine

Drug safety is an issue of concern in the counterfeit medicine supply chain, which is correlated to initial drug manufacturing process. In order to trace drugs from manufacturing process to patient, blockchain with encrypted QR code is proposed (R. Kumar & Tripathi, 2019). Thus, ondose identification for the dosage forms; e.g. oral film is the preferred approach for verification of drug rather than on packaging materials. In the purpose of preventing counterfeit medicines in the supply chain, a startup proposed micro QR codes, which can be directly printed during the formulation of dosage forms, such as; inkjet printing, 3D printing (Vruddhula, 2018).

The printed micro QR codes contain details about medicine and can include cryptographical signature of the manufacturer, which can access by smartphone for verification purpose and patient can determine authenticity of the medicine (Kumar & Tripathi, 2019; Vruddhula, 2018).

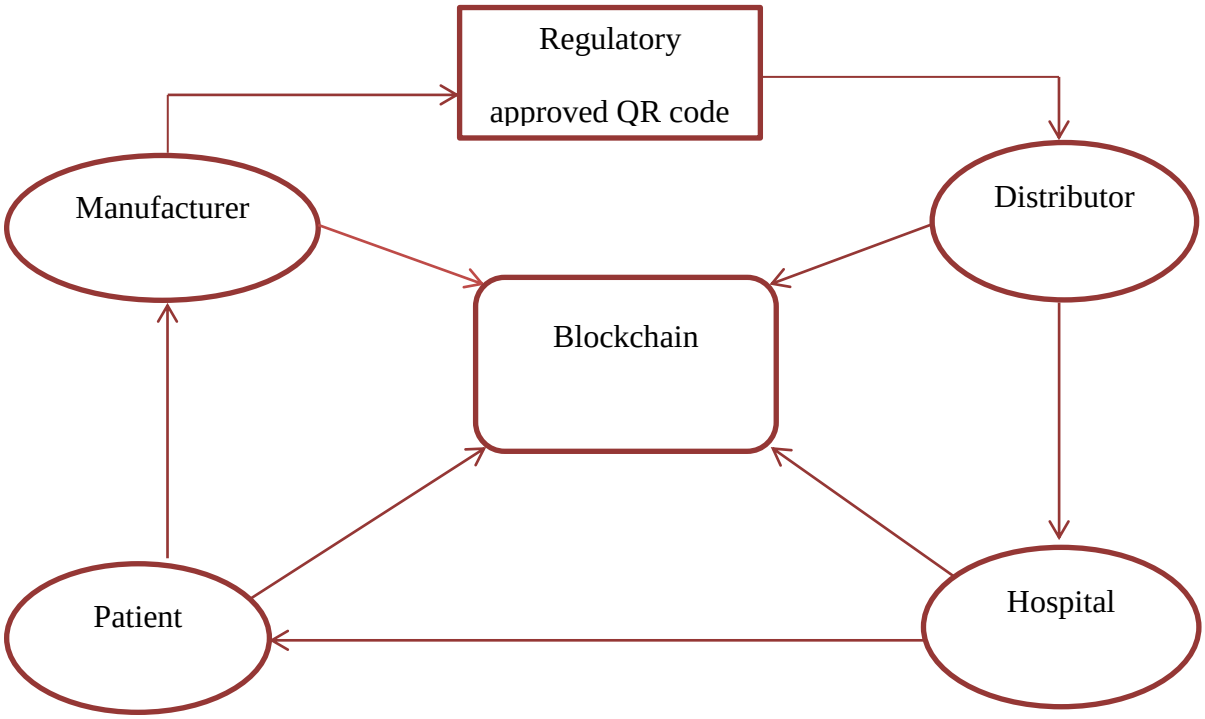


Figure 8: Counterfeit medicine supply chain tracing through blockchain (R. Kumar & Tripathi, 2019)

The study demonstrates that software based printed micro QR codes would be unique for different manufacturing batch. In addition, each transaction of drug in the blockchain would be automatically recorded, which would ensure secure, decentralized and tamperproof supply chain. It is apparent that the blockchain framework efficiently traces counterfeiting as each supplier must scan and sign the encoded message in QR code, while the drug passes through the supply chain. Therefore, digital tracing of drug with printed QR code can be the future potential to prevent counterfeit medicine (Kumar & Tripathi, 2019; Vruddhula, 2018).

5.3 Limitations of QR coded film

3D printed QRODF can be challenged with various limitations to implement as personalized dosage form. Firstly, aid of smart device, i.e. smartphone is a must for personalizing the treatment approach. It must be expected that any disturbance might occur while smart phone is used by patients to scan the QR coded information, for instance; low battery of smartphone, inaccessible network, particularly if the QR code is designed with URL holding with all required information. In addition, if QRODF is crumpled or wrinkled throughout storage, then readability of QR code might be compromised. Also, storage conditions can fade the QR code or color can migrate from the surface of the film. Therefore, humidity, light, and temperature resistant edible dye is suggested along with proper packaging for 3D printed oral films. In spite of all the limitations optimization of digital printing indicates potential for personalized QRODFs to improve patient adherence (Edinger et al., 2018).

5.4 Future prospects of QRODF

To fabricate personalized medicine based on patient's demand pharmacoprinting is utilized at the pharmacy also at the nursing home with the possibility of individualized dosing for each specific patient (Lind et al., 2017). It is apparent that dosage forms consisting of the drug and encoded information would be more patient friendly to confirm that the precise dose is administered by the patient at the exact time. National authorities could design a format to insert required information in QR code, which can include the precise time of administration in the patient's calendar to generate an alarm.

However, it is doubted that counterfeit of the QR printed dosage form could be easily achieved, for example, printing out the QR code without the presence of API on a regular printer. Thus, additional anti-counterfeiting features must be included for optimization of the QR coded approach (Fei & Liu, 2016), for example; holograms could inhibit counterfeiting

of QR encoded oral films in the market. Also, developing particular smartphone application for medication management could be implied (Sarzynski et al., 2017), with the use of QRODF. For instance, the application which patients could exhibit relevant information in order to confirm accurate treatment, whereas the application designed for manufacturer would reveal the information related to supply chain, raw materials and as well as the manufacturing tools. Additionally, particular mobile phone applications could be utilized to keep records of administration the medicine, thus growing patient adherence (Nor et al., 2017).

In this study, another possibility is highlighted that QR code could exceed the capacity limit with detailed information by encoding a URL of the web-page. Hence, the limitations related to the dimensions of QR code and readability can be avoided. Furthermore, encoded URL can enhance data redundancy by decreasing the data stored in the QR code. For this reason, QR code would be less affected by error due to mechanical damage or imperfect printing process. (Vakili et al., 2016) Furthermore, multiple drugs can be printed on QR encoded film surface by inks of different colors. If printed in non-adjacent dots each drugs could be visually recognized, also drug-drug interactions could be avoided. In addition, printed dose of the drug on oral film could vary in intensity of color, e.g. higher strength dose can be printed in brighter color (Wickström et al., 2017).

Chapter 6

Conclusion

3D printed QR coded orodispersible film is flexible and patient friendly for ease of access to encoded information. The printed QR codes contain details data of dosage form which can be scanned by QR scanner of smart device. 3D printing is optimized with hot melt extrusion to directly print the QR code along with the film in one single step. QR encoded ODF loaded with formulation of drug efficiently indicate higher drug solubility and also physicochemical characteristics such as, disintegration, dissolution rate and morphology of drug were evaluated, which assures patient compliant treatment. 3D print QR code could be a favorable method for personalizing medication as patients can scan the QR code of QRODF to access details of drug formulation and also could individualize dose as per patient conditions.

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