Hot Melt Extrusion: A State of the Art and Multifunctional Technique for Oral Film Formulation

By

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

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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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Approval

The thesis/project titled "Hot Melt Extrusion: A State of the Art and Multifunctional Technique for Oral Film Formulation" submitted by Rezwana Tabassum Taheya (14146034) of Spring, 2019 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelors on August 20,2019.

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Ethics Statement

This project involves no human or animal trial.

Abstract

Hot melt extrusion (HME) is one of the most extensively studied techniques for pharmaceutical application. Several researchers have been trying to establish this potential method in oral thin film (OTF) formulation and hundreds research articles have been published on this noble approach. OTF is an emerging dosage form in pharmaceutical field and HME is a promising technology in film formulation. HME is advantageous over other methods since it is a one-step method, does not require solvents; it has showed taste masking capability by solid dispersion and has showed improved bioavailability of drugs. Moreover, the scale up process not being problematic it can be employed on commercial scale production. This review has 3 major objectives. Firstly, it gives an overview on oral thin film and HME technology in formulation of thin film. Secondly, it shows the importance of taste masking and HME in taste masking. Lastly, it discusses multi-functionality of HME in combination of other techniques like 3D printing, co-extrusion and nanotechnology.

Keywords: Oral thin film (OTF); Hot melt extrusion (HME); Taste masking

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Dedication

Dedicated to my parents

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List of Acronyms

OTF	Oral Thin Film
ODF	Oro Dispersible Film
HME	Hot Melt Extrusion
SSE	Single Screw Extruder
TSE	Twin Screw Extruder
MSE	Multiple Screw Extruder
FDM	Fused-Deposition Modeling
IM	Injection Modeling
PAT	Procedure Analytical Technology
5-FU	5-Fluorouracil
EPO	Eudragit
FDSFs	Fast dissolving sublingual films

Chapter 1

Introduction

Oral route is considered most congenial route comparing to other of drug delivery. Maximum pharmaceutical industries have focused their investigation in improving feasible dosage substitutes from oral route for children, aged people and for uncooperative or nauseous patients. Study in oral drug delivery sector has made possible to bring progress from conventional tablets to modified and controlled release tablet to oral disintegrating tablet to modern expansion of fast dissolving oral film (Juluru, 2013).

The inimitable concept of orally disintegrating film in not new. In fact, it was introduced in late 1970s so that patient can receive a more convenient and easier way of drug administration. However, this unique technique has not been utilized appropriately and its biopharmaceutical challenges are yet to overcome (Lai et al., 2018). Time Magazine calls Listerine breath freshening PocketPaks thin strips one of the best inventions which was introduced by Pfizer Inc. in 2001. InnoZen introduced first over-the-counter (OTC) ODF in 2003, which contained an active pharmaceutical agent. Numerous others OTC films has been introduced to the US market ever since (Hoffmann & Breitenbach, 2011).

It is advised that the drugs straight enter the systemic system after its been administered via buccal or sublingual route. This consequence in faster drug absorption and greater bioavailability escaping the first pass effects. Additionally, oral thin films doesn't require water and gives immediate action from rapid disintegration and release of API from dosage form (Lai et al., 2018).

1.1 Film Drug Delivery System

In general, oral thin film is defined as a flexible thin layer of polymer, which may or may not comprise plasticizer. As for this nature, it seems to be less obstructive and more convenient to patients. Basically, thin films are great options for focusing sensitive locations which would be impossible with tablet or liquid preparations. Thin films have presented proficiencies in advancement of the onset of drug action, reduction of dice frequencies and to enhance drug efficacy. Likewise, these may be useful in removing unwanted drug effects and reducing intensive metabolism resulted from proteolytic enzymes activity on drugs (Karki et al., 2016).

Relating to different membrane sites (i.e. nasal, intestinal and rectal); the oral mucosa holds greater vascularity, not as much of activity of protein and shows less status to irritation and injury. The membrane of oral route can be utilized for not only local but also systemic administration of drugs (Uddin, Sultana, Nipa, Chowdhury, & Douroumis, 2017).

The administration of ODFs has numerous advantages. It is convenient, easy to transport, dosage is accurate and ideal for pediatric, geriatric, unsupportive and dysphasic patients (Karki et al., 2016) as it does not require water nor cause any choking hazards (Bala, Khanna, Pawar, & Arora, 2013). It is more stable, the onset of action is rapid and bioavailability is increased hepatic first pass metabolism can be bypassed (Karki et al., 2016). Moreover, the manufacturing is easy and inexpensive (Bassi & Kaur, 2017). From promoting viewpoint, oral films give new commercial prospect like product diversification, promotion (Bilal et al., 2016). These are non-invasive in nature (Siddiqui, Garg, & Sharma, 2011).

Almost drug of all class is incorporated in film. Drugs with low dose and high action are sometimes initial alternative for oral first dissolving film (Zhu, Chuah, & Wang, 2018). Moreover, oral film allows the patient to eat, drink or speak without major discomfort unlike the marketed conventional tablets (Bhagurkar et al., 2018).

There are some drawbacks of thin film. Use of thin films is usually restricted for the most part thanks to limited drug loading competency for a less potent drug given at high dose. Gas-x thin strip introduced by Novartis Customer Health has loaded 62.5mg of simethicone per strip however there stay range of restrictions with the preparation of film strips (Bilal et al., 2016). Some superlative characteristics of appropriate drug candidate includes tiny to moderate mass, solubility and functional stability in water likewise as saliva, permeation capability through oral membrane tissue and capacity of being part unionized at the pH of oral cavity (Bala et al., 2013). Addition of two or more drugs alongside could be an actual difficult task in oral film preparation as not only the rate of dissolution but also co administration of a drug affects the disintegration time in the films. The problem to get a high grade of precision with regard to the quantity of drug in specific unit dose of the film may result in therapeutic disaster, non-reproducible effects and may also cause poisonous effects to the patient. These thin films are sometimes absorptive in character. Thus, in order to preserve it for extended period, special precautions are required (Karki et al., 2016) (Thakur, Bansal, & Sharma, 2013).

1.2. Required characteristics of ODFs

An ideal ODF ought to be thin and versatile, however stable to guarantee a strong manufacturing and packaging method and ease of handling and administration. The films have to be portable, not sticky and keep a plane type while not rolling up. They must offer a suitable style and a satisfying mouth-feel. Disintegration time ought to be as short as possible. It's difficult to suits of these necessities, because of the opposite relationship between mechanical properties and disintegration time (Hoffmann & Breitenbach, 2011).

Ideal thin films must unveil desirable features like adequate drug filling capacity, rapid dissolution rate or extended staying time where drug has been administrated and acceptable stability of the formulation. They should be non-toxic as well as biocompatible and decomposable (Irfan et al., 2016).

Table 1: A typical composition contain following (Thakur et al., 2013)

INGREDIENTS	QUANTITY (W/W)
Drug	1-30%
Film forming polymer	40-50%
Saliva stimulating agent	2-6%
Sweetening agent	3-6%
Plasticizer	0-20%
Surfactant	quantity specification
Flavoring agent	quantity specification

1.3 Suitable drugs for oral film formulation

There are some ideal features for drug candidates of oral thin film (OTF) (B. P. Panda, Dey, & Rao, 2012) has mentioned some characteristic that a drug should possess to be incorporated in oral thin film formulation.

Drugs that have low molecular weight are preferable to incorporate into OTFs. Drugs should have lower loading dose, which should not exceed 40mg. The drugs should be easily soluble and should show stability in saliva as well as in water it should have the permeability through mucosal tissue membrane. The drug should be moderately ionized at the pH of buccal cavity. Should retain a pleasant taste (B. Panda, 2016)

Table 2: Below List of few drug that can be incorporated in fast dissolving film (Bilal et al., 2016)

Drug	Therapeutic Class	Dose (mg)
Azatidine maleate	Antihistaminic	1
Acrivastine	Antihistaminic	8
Chlorpheniramine maleate	Anti-allergic	4
Cetrizine	Antihistaminic	5-10
Diphenhydramine HCI	Antihistaminic	25
Famotidine	Antacid	10
Dicyclomine	Muscle relaxant	25
Dextromethorphan HCI	Cough suppressan	10-20
Desloratidine	Antihistaminic	5
Flurazepam	Anxiolytic, Anticom	15-30
Ketoprofen	Anti-inflammatory	12.5-25
Loratidine	Antihistaminic	5-10
Lopramide	Anti-diarrheal	2
Nitroglycerine derivatives	Vasodilators	0.3-0.6
Nicotine	Smoking cessation	1-15
Oxycodone	Opioid analgesic	2.5-10
Omeprazole	Proton pump inhibitor	10-20
Sumatriptane succinate	Ant migraine	35-70
Tripalodine HCI	Antihistaminic	2.5
Zolmitriptan	Anti-migraine	2.5

1.4 Types of film

Numerous names of thin films has been presented, which includes oral film, oral soluble film, oral strip, wafer, orodispersible film (ODF), bioadhesive and mucoadhesive film, transmucosal film, buccal film and ophthalmic film . Many films are designed such a way that they dissolve rapidly within the mouth so that the drug can be absorbed in the gastrointestinal cavity (oral and oral soluble, or orodispersible films). On the other hand, some films are designed so that the drug can be transported to the site of administration (e.g., buccal, gingival and ophthalmic thin films). Drugs that can be rapidly absorbed through mucosa are considered to be appropriate for sublingual and buccal delivery with films. Similarly, ophthalmic films can be used to treat eye disease like chronic dry eye syndrome,glaucome and inflammation (Karki et al., 2016).

1.4.1 Classification based on site of administration

OTF can be classified as buccal, sublingual, gingival and soft palatal and transmembrane film based on its site of administration.

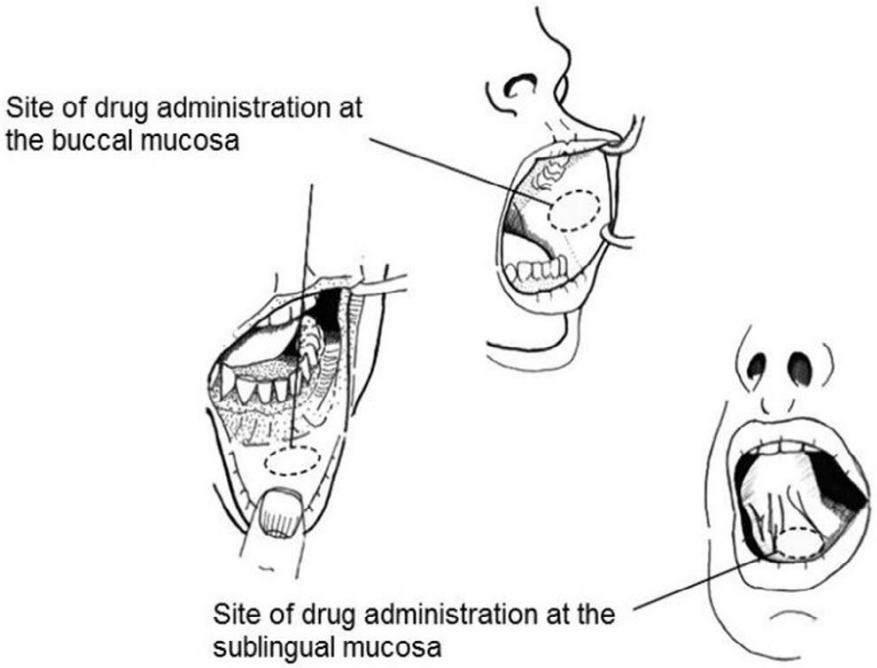

Figure 1: Common site for application of film in buccal and sublingual mucosa (Karki, 2016)

i. Buccal Film

Buccal tissue layer has wonderful accessibility and is appropriate for retentive dosage forms since it comprises of immobile mucosa and an area of smooth muscle tissue. It can successfully enhance bioavailability as first pass metabolism can be efficiently avoided and the blood supply in this region being rich, contributes to the systemic circulation (Palem, Gannu, Doodipala, & Yamsani, 2011). Moreover there is low enzymatic activity in this route (Hao & Heng, 2003). The formulated can be modified using enzymatic inhibitors, pH scale modifiers or permeation enhancers thus a versatility in formulation and design can be adapted for local or systemic actions (Rossi et al., 2005). Several mucoadhesive preparations have been recommended for buccal delivery including buccal patches, ointments, disc, adhesive gels and tablets. Buccal films are more convenient and flexible thus is chosen over adhesive tablets (Palem, Battu, Maddineni, & Gannu, 2013)

No other technique of drug administration is as safe as this as in case of any sign related to toxicity the dosage form can be eliminated from the buccal cavity. Other routes of drug administration like nasal, sublingual, rectal and vaginal are less patient compliance than buccal drug delivery system and enhanced mucosal permeability with rich blood supply contributes to fast onset of action (Govindswami, Kesavar, & Narasimha, 2013)

ii. Sublingual Film

Sublingual drugs are drugs with increased tissue layer penetrability are well-known to be appropriate for sublingual and buccal delivery with films (Karki et al., 2016). It is a systematic delivery where drug passes through the tissue layers of oral membrane lining the mouth surface (Gawas,2016). Sublingual quick dissolving films contains hydrophillic polymer which is responsible for the disintegration or dissolution of dosage form in the sublingual part of oral cavity. For this, it has to come in contact with saliva without any involvement of drinking or chewing. Fast dissolving sublingual films (FDSFs) may be obtainable for the treatment of a

generalized oral disorder or absorbed through the sublingual tissue layer for systemic medical care. fast delivery to the systemic. It allows fast absorption and increase bioavailability. The high blood flow in the sublingual region also paves the way to rapid onset of action. IV dose can be bypassed by this method (Song et al., 2018)

iii. Gingival and soft palatal Film

Gingival films are administered on the gum space and that they typically give local action (Sanghai, Nandgude, & Poddar, 2016).

Besides, improved patient compliance is anticipated, as a result of this preparation is not required to be swallowed like tablets, and so helpful in patients with dysphagia or problem in swallowing. The employment of bioadhesive polymers within the films can modify them to adhere to the sublingual mucous membrane for improved retention and drug absorption (Koland, Sandeep, & Charyulu, 2010).

Palatal films are typically soft palatal. These preparations are typically mouth freshener that fights against oral microorganism accountable for unhealthy breath. Pfizer introduced a product named Listerine Pocketpaks , a mouth freshener which is thin film product. This bio-film is an example that the company has been putting an attempt in developing oral thin films (Karki et al., 2016)

iv. Trans membrane and transdermal film

The aim of administration of drug through skin is for topical management of skin diseases or for transdermal penetration of drugs within the systemic circulation. The benefit of topical route of drug administration is that it offers a big and diverse surface. Another benefit is easy application and self-administration that provides an alternative to not only oral delivery of medicine as but also hypodermic injection. Skin physiology and physiochemical characteristics of drugs along with delivery system decide thee rate and degree of drug absorption through skin. The available dosage forms, i.e. patches, ointments, creams, etc., are related to many

limitations. Patches come with some disadvantages and skin irritation is the most common one. The reason is their occlusive characteristics imposing barrier of sweat ducts, which successively prevents loss of water vapor from skin surface, problem in applying on the arched surfaces. Other limitations include pain while shedding and poor aesthetic properties (Kathe & Kathpalia, 2017)

1.4.2 Classification based on formulation and functionality

Films can be classified as bioadhesive or mucoadhesive film based on its formulation and functionality. This can further be classified as single layer bioadhesive film and multilayer bioadhesive film.

i. Bioadhesive or mucoadhesive film

Bioadhesion may be defined as the aptitude of a biological or a synthetic substance to adhere to the epidermis or a mucous membrane (M. Chen et al., 2014)

A model bioadhesive film depends on on a biocompatible and nonpoisonous polymer, that should be versatile, flexible, and soft, however should be impervious to breakage because of pressure within the application site. Succeeding the groundbreaking advancements of medicinal technologies in the last thirty years, miscellaneous bio adhesive preparations are developed on the premise of various design principles and conjugation systems. The meaning of bioadhesives can be stretched out from the basic word ‘adhesive’. Adhesive, which is synonym of glue, can be defined antecedently as any substance that can polymerize (or crosslink). Such crosslinking or polymerization can hold the surface of two things together or functions as an obstacle to spillages. Bioadhesives, precisely tissue adhesives, hemostatic agents, and tissue sealing agents, are widely utilized in medical operations and have achieved impressive outcomes in numerous clinical conditions. A tissue adhesive can be defined as a patch or glue that is employed for binding tissues together in order to facilitate wound healing

(e.g., muscle, skin and intestine). The mechanism of a hemostatic agent is by starting creating of blood clots to prevent bleeding directly or indirectly and a sealing agent may be employed to seal the openings so that fluid leakage (e.g., leakage of cerebrospinal fluid) or air leakages (e.g., once lung surgeries) may be prevented (Zhu et al., 2018).

Bioadhesive films can further be classified as Single layered Bioadhesive Film and Multilayer Bioadhesive Film. Single layer films does not adhere to dry skin. Therefore, it is required to be applied in wet skin to retain there (Preis, Breitkreutz, & Sandler, 2015). A multilayer film usually contains more than one layer of polymer that may be used to serve different purposes. (Cheng et al., 2018)

1.5 Manufacturing processes and film formulation

Various methods for producing oral films are classified as follows:

- Casting and drying: (a) solvent casting (b) semi-solid casting.
- Extrusion: (a) hot melt extrusion (b) solid dispersionextrusion
- Rolling method (Bala,2013)

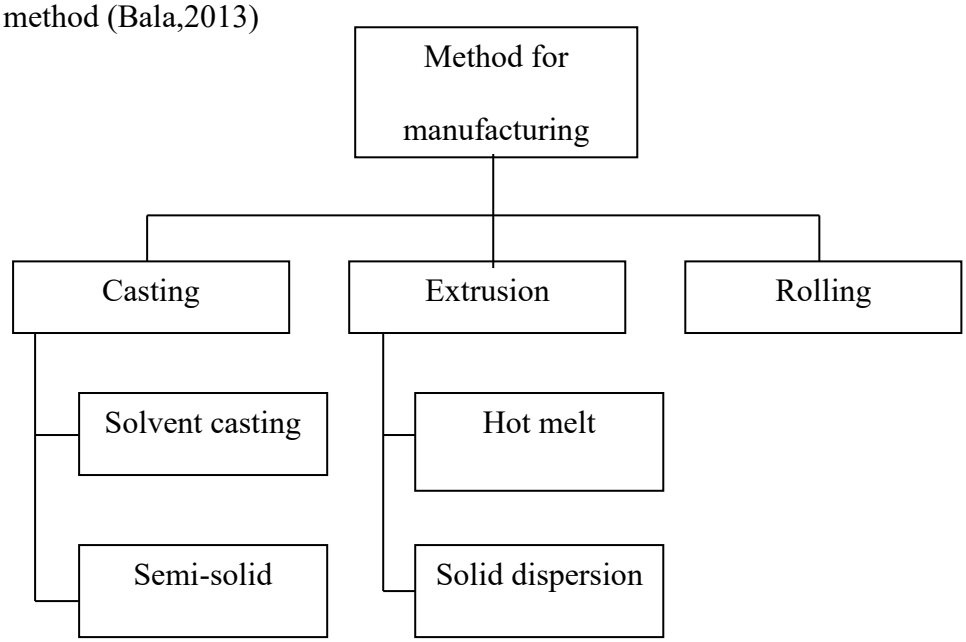

Figure 2: Methods of film formulation (Irfan, 2015)

This is a chart showing the most commonly used techniques for formulating oral thin film (OTF)

1.5.1 Solvent Casting

Solvent casting is most commonly employed in preparation of oral films. This method is associated with dissolving water soluble ingredients into a solution which is clear and viscous. The drug ingredient along with other ingredients are initially mixed and dissolved in small amount of solution and later are combined with bulk which is then introduced to aqueous solution. Finally, the air entrapped are removed and resting solution can be casted as film which is later dried and shaped by cutting into appropriate sizes (Bala et al., 2013)

Following is a flow diagram showing the sequential steps of this whole process.

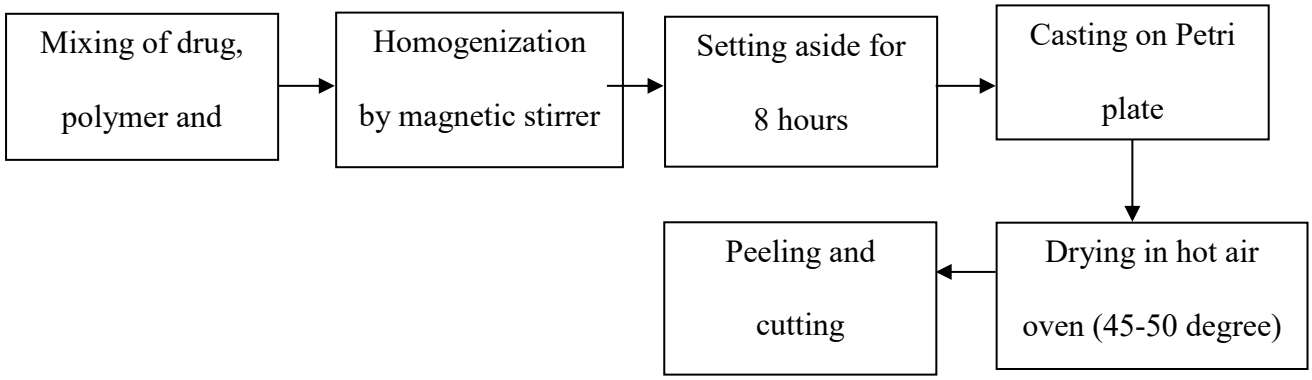

Figure 3: Flow chart of solvent casting process (Irfan, 2015)

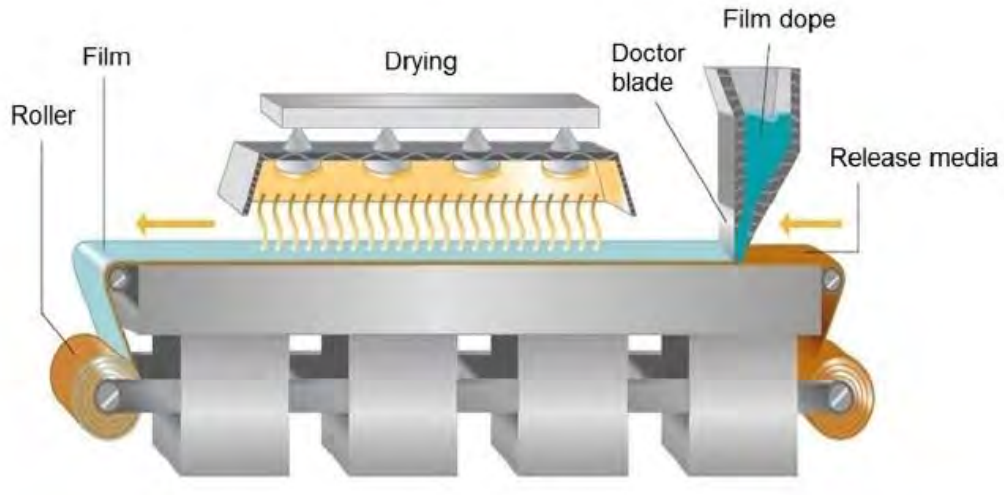

Figure 4: Commercial manufacturing of films based on solvent casting

The figure shows different parts of the equipment that is used to prepare film commercially (Karki, 2016).

The solvent casting method is well established method that comes with many advantages. Firstly, it maintains the uniformity and homogeneity of the preparation and the clarity is better than extrusion. Secondly, the films are more elastic and flexible with better physical characteristics. Lastly the films prepared obtains better aesthetic properties, they are glossy and are not damaged or defected by die lines. However, this method also comes with some drawbacks. The most common one is that the polymers have to be water soluble or should be soluble in volatile solvent. Another problem associated with such method is the formation of stable solution with rational least solid substances and viscosity.

1.5.2 Hot melt extrusion

This process forces the mixture through a die which is set under precise settings which enables to transform a blend of raw ingredients into a product obtaining specific characteristics like precise size, shape and density. HME exploits a liquefied system for this purpose where the viscosity can be adjusted which makes the mix able to flow through the die. Initially the active pharmaceutical agents along with the excipients are added in same apparatus employed for extrusion, or simply in a mixer. The common excipients used may include bulking agents, antioxidants, thermal lubricant, polymer or matrix carrier, plasticizer and additives which can be coloring agent, flavoring agent or taste masking agent or both. Consequently, applying heat one or more ingredients of this mix melt during the time when the plastic mass is being extruded through the apparatus. The extrudate expelled from the machine cools and solidifies which then is subjected to further downstream processes. (Censi & Gigliobianco, 2018).

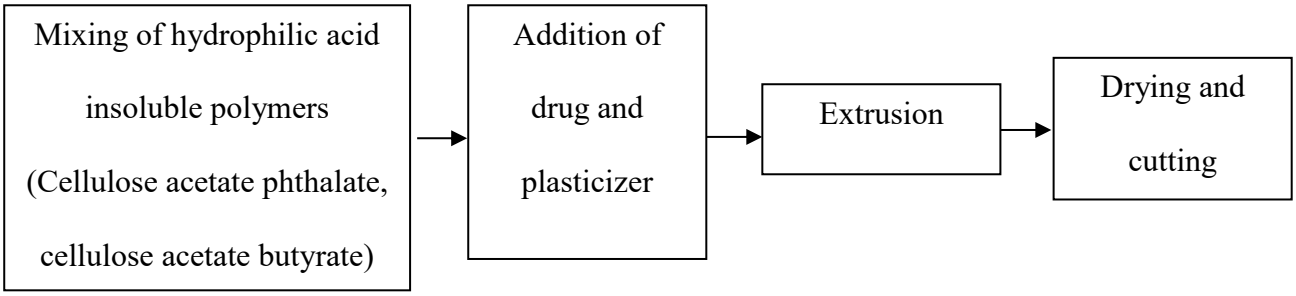

Figure 5: Flow chart of hot melt extrusion Process (Irfan,2015)

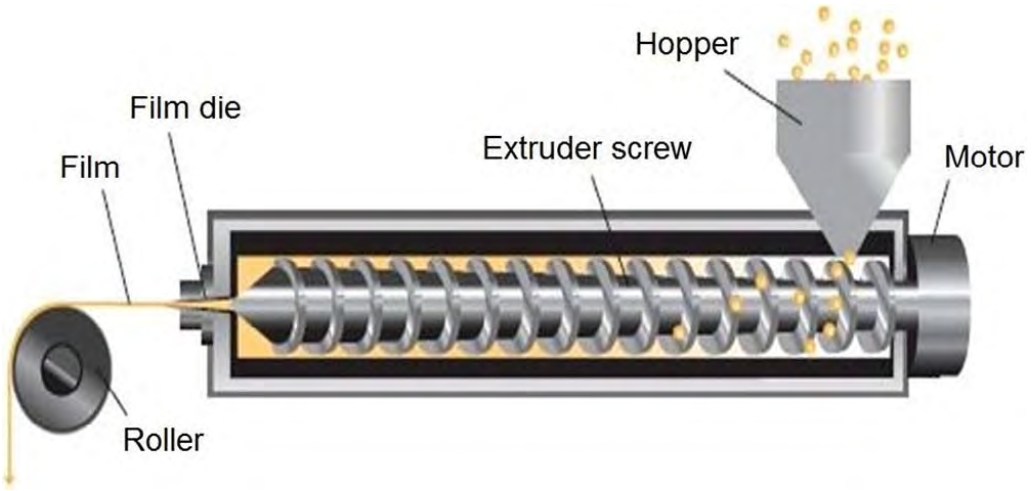

Figure 6: Hot-melt extrusion system for the preparation of films

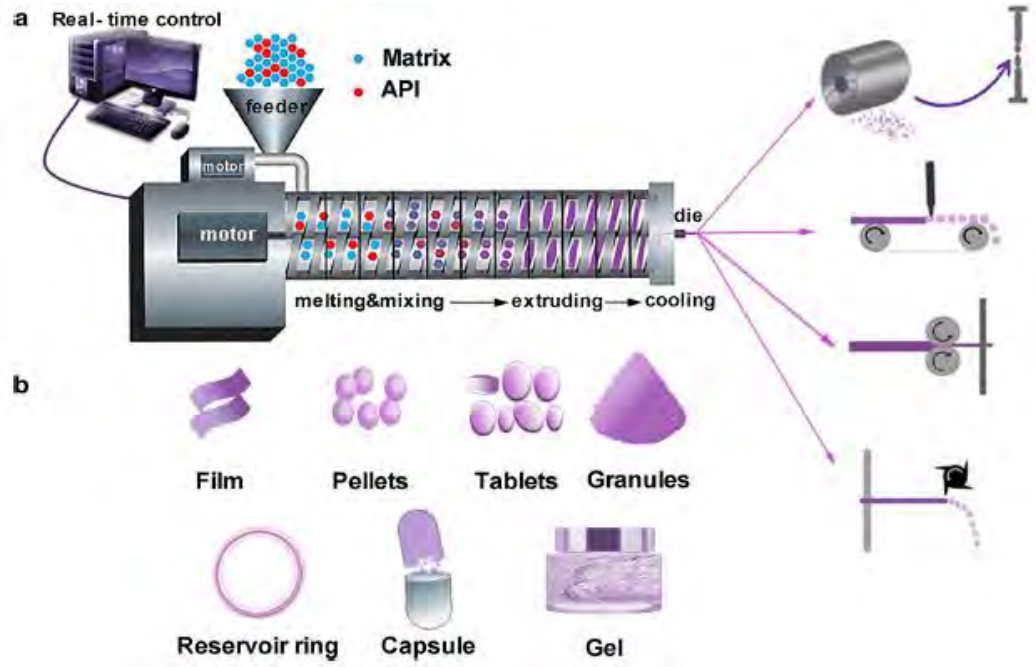

Figure 7: a) equipment used in hot melt extrusion process b) various dosage form formilated in HME technique (Ren, 2018)

HME process comes with some great advantages. To start with, it is a solvent free technique. The manufacturing is easy and continuous and requires a few steps. Therefore, it is time saving and inexpensive. Moreover, the application is multipurpose and it's easy to scale up. And lastly is is undoubtedly maintains the content uniformity as the mixing is of superior quality (Thakur et al., 2013) (Ren,2018).

In spite of having so many advantages, this process comes with many challenges as well. It requires high process temperature and shear force. Therefore, stability of heat labile API's and other ingredients may be compromised. Also the availability of thermal stable polymers is very low. Moreover, it is a highly complex process and requires skill to operate. It requires high energy as well.

This method has some opportunities such as discovery of new polymers with proper characteristics and Development and modification of polymers, optimization of the process and HME design, development of formulation and further development of PAT tools.

Continuous innovations in this technique can result in HME technique to be the ideal and economic technique for manufacturing thin films. Some notable innovations include In-process monitory (PAT), combining other methods such as nanotechniques and 3D printing, coupling with mechanochemistry to carry out multi step chemical reaction (Ren, 2018).

1.5.3 Semisolid casting

A solution is prepared containing water soluble polymer which is then introduced to a water insoluble solution that was made with sodium hydroxide or ammonium hydroxide. An example of such is cellulose acetate phthalate. 1:4 ratio is maintained of acid insoluble polymer to film forming polymer. Plasticizer of appropriate quantity contributes in formation of gel mass. Finally this mass is casted into ribbons or films (Juluru, 2013).

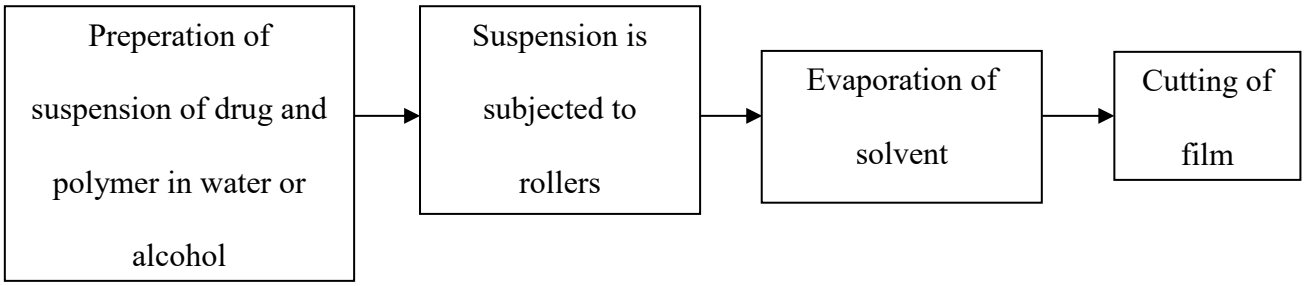

Figure 8: Flow map of semi-solid casting method (Irfan,2015)

1.5.4 Solid dispersion extrusion

In order to load drug this technique includes the solid dispersion of the drug mixed in melted polymer solution. In appropriate liquid solvent the drug agent is introduced in order to dissolve. Then the obtained solution is introduced to the melt appropriate polymer, achievable under 70 degree Celsius where the liquid solvent is not rejected to obtain the solid dispersion. This prepared solid dispersion is finally cut into desirable shape of the dyes. (Bala et al., 2013)

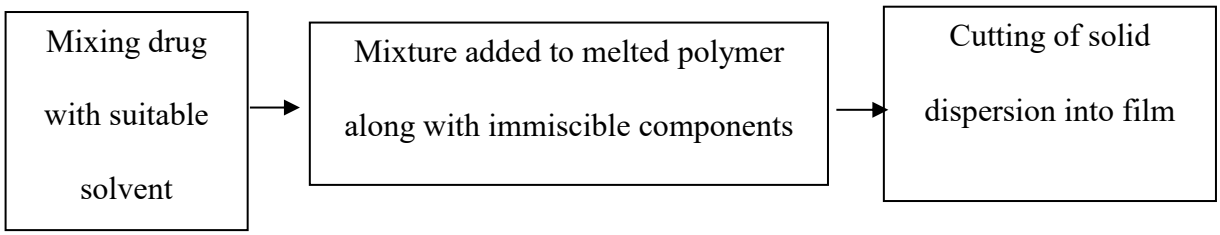

Figure 9: Flow map of solid dispersion extrusion (Irfan, 2015)

1.5.5 Rolling

At first, a pre-mix preparation is required by introducing drug and following the film formulation. (Rathi, 2011). The pre-mix batch contains polar solvent, film forming polymer and other components but the active pharmaceutical agent which is incorporated to the feed tank of main batch. A previously measured quantity of drug is loaded into the mixer and mixed to obtain a homogenized mix for a required amount of time. A second metering pump is used

to transfer a fixed quantity of matrix fed into a pan. The film thickness is managed by the metering roller. The film is then prepared on a substrate and dried

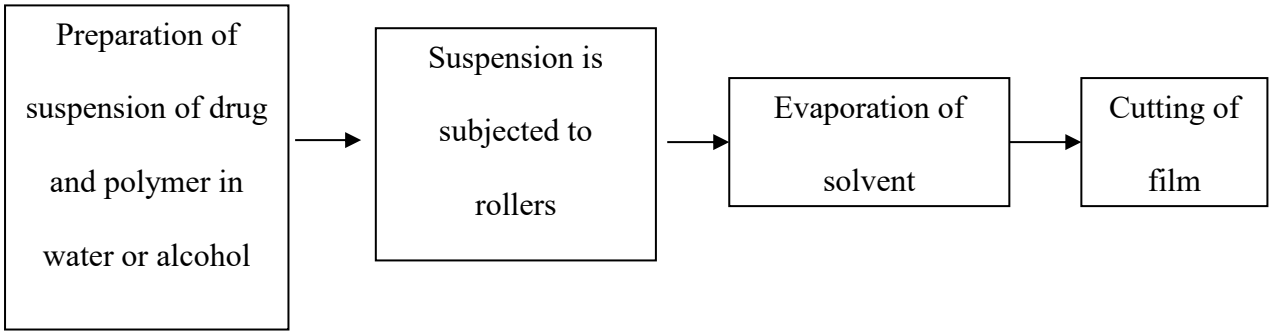

Figure 10: Flow Map of rolling method (Irfan,2015)

1.6 Role of taste of drugs

Drugs that have unpleasant taste needs to be masked which have the evidence of increasing acceptability among geriatric and pediatric patients. The unpleasant or bitter taste is critically associated with patient's compliance since oral administration can sometimes become very difficult due to the taste of the drug which consequences non-compliant patients and can further exaggerate the condition. Refusal toward solid dosage form as tablets or capsules is observed in people of all age due to difficulty in swallowing and fear of chocking. Most common age group would be young children and elderly patients as their physiology becomes different as they grow. It was found that forty-five out of hundred stroke survivors, thirty-three out of hundred nursing home citizens and sixty-three out of hundred cancer patients experiencing palliative care in the hospital or clinics report dysphagia. In order to reducing of unpleasant taste of drugs and to improve palatability of oral pharmaceuticals several conventional methods can be employed (Wadhwa & Puri, 2015).

Taste receptors, also known as taste buds are located primarily on tongue surface. These organelles look like onion and has open pore on the surface. These cells contains G protein couple receptors. At the basal membrane they are connected to nerve endings that can

generate electric impulses that gives perception of taste (Joshi & Petereit, 2013). Human tongue can sense 5 basic tastes like sour, salty, sweet, bitter and umami (Vummaneni & Nagpal, 2015)

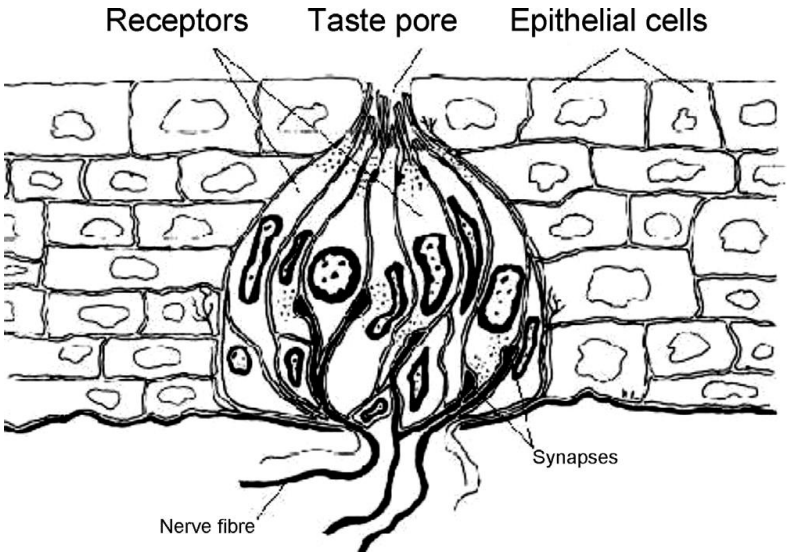

Figure 11Taste buds on human tongue (Joshi & Petereit, 2013)

1.7 Need and concept of taste masking

In present-day situation not only private but also government, institutions accentuate on pediatric medication. Pediatric drugs are different from normal drugs as the dose differs from adult dose. Huge quantity of money is being financed each year to improve the formulation however, it is very challenging work. A great challenge is observed in case of poor bioavailability which occurs when the active drug agent is low water soluble or is absorbed poorly or both and unpleasant bitter taste of drugs (Lou et al., 2013).

Many oral dosage forms such as tablet, capsule, syrup, suspension, chewable tablets and wafer and many more which are commercially available. Adding to the list orally dissolving films and mini tablets are gaining popularity. However, taste masking is still an issue when it comes to formulation for effective pediatric dosage forms because a good number of drugs having therapeutic action tastes bitter. Bitter taste is an obstruction in formulation of successful dosage form for children as well as elderly people since compliance rate is poor due to

flexibility, palatability and swallowability concerns that can hamper the biologic effectiveness.

1.8 Taste masking measures

Numerous techniques have been introduced by the researchers in formulation of effective dosage form to alleviate unpleasant taste. These technologies can be divided into three large classes-

1. Physical obstruction
2. Change of solubility of drug
3. Change of taste sensitivity (Felton, 2018)

Masking the bitter taste of prescription drugs can be accomplished by adding flavors, sweeteners, or effervescent agents. This is the most common method of masking a drugs bitter taste. Split-tongue taste stimulation studies have further demonstrated that bitter taste is suppressed by sweet taste stimuli. In addition, sweet taste stimuli have the added benefit of reducing pain in infants, children, and adults. (Cherian, Lee, Tucker, Lee, & Smutzer, 2018).

There are many other approaches masking the bitter taste of drug. One approach to minimize the bitter taste of a drug is to chemically block a specific bitter taste receptor. In humans, a family of twenty-five G-protein-coupled taste receptors that are encoded by theTAS2R gene family activates bitter taste. A number of bitter taste antagonists have recently been identified and include compounds such as probenecid, GIV3727, and γ-aminobutyric acid (Cherian et al., 2018).Molecular concepts includechemical modifications, such as the prodrug approach or saltformation using either anions or cations such as magnesium or inter-action with ionogenic polymers, such as (meth)acrylates (Joshi & Petereit, 2013).

Table 3: Summary of quick-dissolving chewable tablets and thin films (Douroumis,2010)

Technology	Marketer	Active	Indication	Products
Medichew (Fertin Pharma)	Novartis	Nicotine	Nicotine replacement	Nicotinell
	Glaxosmithkline	Nicotine	Nicotine replacement	NiQuitin
Mcneil Consumer Healthcare	Mcneil Consumer Healthcare	Acetaminophen	Cold/Flu	Tylenol Meltaways
OraVescent (CIMA)	Pfizer	Acetaminophen/ Dextromethorphan HBr/Pseudoephedrine HCI	Cough/sore throat	Triaminic Softchews
	Bristol-Myers Squibb	Acetaminophen	Fever	Tempra Quicklets
Casting (Zengen)	Prestige Brands	Benzocaine	Sore throat/pain	Chloraseptic Relief Strips
Casting	McNell Consumer Healthcare	Diphenhydramine HCI	Allergy	Benadryl quick dissolve strips
	Novartis	Diphenhydramine HCI/Phenylephrine HCI	Cold and cough	Triaminic thin strips

1.8.1 Hot melt extrusion in masking bitter taste of drug

HME was first developed and used in plastic industry and later was introduced in pharmaceutical industries as it is a as a simple, reproducible, and robust method for producing many solid dosage forms of drugs for different delivery routes, such as the oral route (granules, pellets, and tablets), the transdermal and transmucosal route, and the subcutaneous route (implants), some of the most widely developed applications are for:

1. Taste masking

2. Improved dissolution of poorly soluble drugs

3. Sustained release formulations

4. Preparation of Nano systems (Censi & Gigliobianco, 2018)

Hot melt extrusion (HME) approach has become prevalent for taste masking of bitter drugs, besides its solubility enhancement capabilities, by producing solid dispersion that prevent drugs from coming into direct contact with the patient's taste buds. Eudragit EPO is a cationic copolymer based on dimethyl aminoethyl methacrylate and is soluble at a pH below 5.5. This polymer can thus prevent the release of the drug in the saliva (pH 6.8-7.4) while readily dissolving in the gastric fluids (pH 1.0-1.5). Hence, Eudragit EPO is a appropriate matrix for taste masking poorly soluble solid dosage forms. In this study, a co-rotating twin screw extruder with a screw diameter of 16 mm and a barrel length of 640 mm was used. The length of the screws in the extruder is given in terms of length of the screw to the screw diameter (L/D) ratio, which in this case is 40:1. The extruder consists of two screws, which are assembled with the standardized screw elements, conveying and kneading elements. The conveying elements are installed at the beginning and end of the extruder working jointly to transport the melted material to the die plate. The kneading elements have various angles and produce higher mixing and shearing. The twin screw variables, for example screw design, barrel layout, screw speed directly affect the process parameters like shear rate, residence time, dispersion of drug in polymeric matrix and color of extrudates.

1.9 Aim of the project

The goal of the present study was to establish HME technique as a noble method in development of stable, taste masked and personalized oral film formulations of a bitter tasting drug, which would be economical and can be introduced to industrial production.

Chapter 2

Material and method

2.1 Equipment used in HME

Extrusion refers to a process where a substance is forced under controlled environment through a die or an orifice to change is physical properties. The equipment that are used in extrusion process can be categorized into three main types: screw, ram and radial screen (Kleinebudde & Lindner, 1993). Screw extruder is most important and most commonly used in pharmaceutical industries.

Types of screw extruders

Screw extruders are of three types:

1) Single-screw extruders (SSE)
2) Twin-screw extruders (TSE)
3) Multi screw extruders (MSE)

All these extruders comes with unique structure and particular advantages. As the names suggest, SSE contains one screw where TSE is composed of two and MSE incorporates more than two. SSE is easy and simple thus is most widely used extruders (Luker, 2003). However, TSE offers numerous advantages like higher kneading capacity, greater productivity and flexibility, reduced tendency of overheating and better process parameter control. Therefore it is becoming more popular in industries (Crowley et al., 2007).

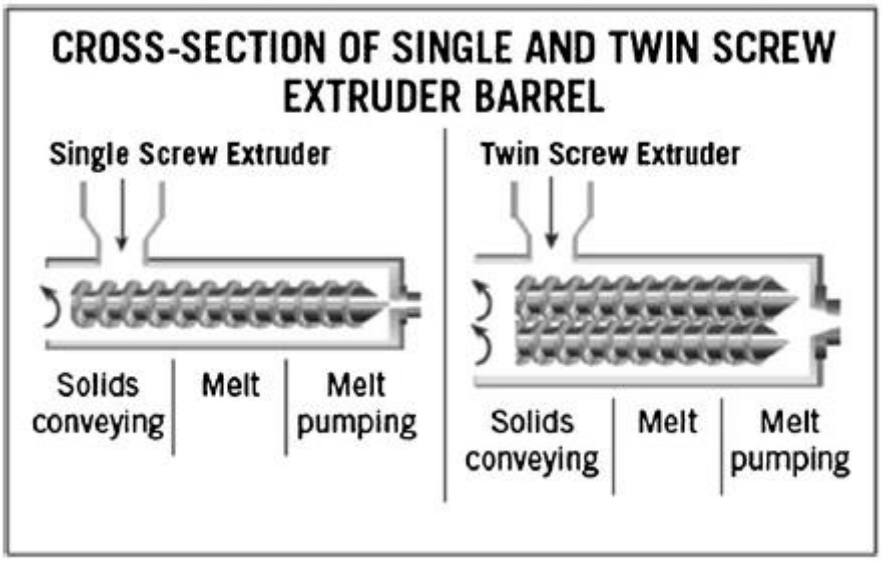

Figure 12: Structural differences between SSE and TSE . (Patil, Tiwari, & Repka, 2016)

This figure shows the cross section of SSE and TSE

2.2 Process

Hot melt extrusion is a technology in which API enters matrix as a whole and melted under the preset temperature, then forced forward the die into products. The extrusion process can be divided into dry or wet extrusion according to the characteristics of feedstock. In wet extrusion, the process can be done at or near room temperature, which allows the thermal-sensitive drugs to be loaded into matrices for pharmaceutical applications. However, the use of solvents and the ultimate solvent removal method make wet extrusion a complicated, costly, and less environmentally friendly process. The drying temperature can affect the final properties of the extruded pellets according to Schrank et al., (2015), different with wet extrusion, dry extrusion is a solvent-free technique; thus, many process steps are reduced and results in HME, a singlestep operation. The feedstock in dry extrusion is generally in solid form and heated, softened by the elevate temperature in the barrel, the friction and the shear stress during transit, and finally shaped into the desired shape (Ren, Mei, Zhou, & Guo, 2019).

Chapter 3

Discussion

Hot melt extrusion (HME) process has been well recognized in early 1930s and soon enough it suited the most extensively used as food processing method in the food industries as well as rubber and plastic industries (Patil, Tiwari, & Repka, 2016). At present as the high throughput screening has arrived, HME technology have been used to manufacture greater than fifty percent of plastic products comprising bags, sheets and pipes (Kaufman et. al, 1977). These are synthetic materials where numerous polymers had been used consequently to melt and to form distinct structures and shapes for both commercial and household applications (Maniruzzaman, Boateng, Snowden, & Douroumis, 2012). At present, greater than 1/2 of all plastic merchandise, for instance plastic baggage, pipes and sheets are synthetic using this technique (Crowley et al., 2007). In 1966, Spesier et al, . Started to use HME to the pharmaceutical field. After that, due to the shortage of enough interest, associated research papers are published intermittently, and the development of HME within the pharmaceutical field become gradual. In the early Nineteen Seventies, HME changed into first utilized in pharmaceutical formulation, which means that HME has come to be a familiar approach for preparing solid pharmaceutical forms (Ren et al., 2019). Nowadays, researchers are trying to develop this technology to use in pharmaceutical field and over hundreds of articles published in the medical literature since last decade. The quantity of patented issue on this technology for pharmaceutical field has progressively multiplied since the beginning of 1980's with worldwide opportunities (Crowley et al., 2007) (Repka, Prodduturi, & Stodghill, 2003).

HME technology is strategic over conventional solvent casting methods for preparing thin film and patches since it is a continuous process and it does not require solvent. The transdermal route of drug delivery offers many potential benefits of enhanced drug pharmacokinetics,

elimination of problems such as low absorption and first pass metabolism. Besides, it reduces dose frequency and improves patient compliance (Qi & Craig, 2016)

According to biopharmaceutical classification system (BCS), the percentage of drugs with high water solubility and permeability is only 5 (Loftsson & Brewster, 2010). Researchers estimated that about 40% of the molecules obtain poor bioavailability and low aqueous solubility. This percent is in all likelihood growing because of the arrival of combinatorial chemistry and the significance of lipophilic receptors (Kerns, 2001). Formulation scientists are facing bold challenges to formulate these compounds for oral route (Crowley et al., 2007).

HME is an alternative approach that can enhance the dissolution rate of drugs that show poor water solubility (HuÈlsmann, 2000). The HME approach can not only enhance the dissolution of API but also enhance bioavailability of drug (Xue et al., 2019). An active ingredient's bioavailability is managed with the aid of aqueous solubility the compound. Consequently, increasing the solubility of water insoluble drugs continues to be an actual challenge within the formulation development method. Since drug discovery procedure has already been introduced to high throughput screening, the subsequent compounds showcase poor solubility as they are of quite lipophilic character and are of high molecular weight. Numerous pharmaceutical interventions have been done by researchers to overcome the issue with solubility (Maniruzzaman et al., 2012). Solubility development procedures may be divided into physical strategies, chemical strategies, or a few different techniques (Savjani, Gajjar, & Savjani, 2012). Physical strategies encompass reduction of particle size, modification of the crystal properties, solid dispersion, and cryogenic techniques. Chemical methods consist of salt formation, complexion, derivatization, altering of pH, and many others. Further to physical and chemical modifications of drugs, different strategies also can be adapted to increase solubility of water-insoluble drugs, such as supercritical fluid method, addition of surfactant, solvency, hydrotrophy, solubilizer, and some modern excipients (Ren et al., 2019). Many techniques exist

to enhance dissolution rate and solubility, preparation of solid solutions and dispersions has gained great interest. For this reason, HME has been effectively implemented to put together solid molecular dispersion of APIs into unique hydrophilic polymer matrices. Bioavailability of drugs, particularly having low water solubility, can be improved by formation of molecular dispersion using HME technology (Maniruzzaman et al., 2012).

Many methods were observed to enhance the solubility of poorly water soluble compound. is one of the most effective approaches to enhance the solubility is reduction of the particle size. Hot melt extrusion is a unique processing technology in developing nano-size particles through the pinnacle-down technique. on this method, the coarse particle is to turn out to be nano sized with the aid of excessive shear forces. The discovery and improvement of the floating dosage form supplied ability blessings for drugs with terrible bioavailability because of their absorption being confined to upper GIT, due to the fact this dosage form maximizes absorption and improves the absolute bioavailability of drugs. Over the previous few years, formulation scientists have used numerous methods to produce effervescent and non-effervescent floating drug delivery system (FDDS) to increase the residence time of medication in the stomach (Patil et al., 2016).

Other than enhancement of solubility and bioavailability, HME also can prepare targeted, sustained, and shaped drug delivery systems (Miller, Dinunzio, Yang, Mcginity, & Iii, 2008) (Vo et al., 2017) (Khor, Ng, Kanaujia, & Chan, 2017). The matrices-loaded pills can be sorted into chemical drugs, natural extracts, organic agents, and multiple drugs. Appropriate drug delivery systems are required for better therapeutic impact. targeted drug delivery systems can offer some advantages, for instance decreasing drug dosage and avoiding first pass metabolism, thereby minimizing or preventing side outcomes resulting from high drug doses (Balogh, Farkas, Domokos, Farkas, & Démuth, 2017). In addition, HME can be applied to develop sustained drug delivery system, which means that the drug is released in a period with a

controlled manner (R. Chen, Li, Han, Wu, & Guo, 2016). A study by Zhang,(2015) using HME showed that the controlled release of diclofenac sodium for intestinal delivery was better than the one used by traditional method. Form of the final product performs a vital function in the route of administration, wherein the certain form is required (Ren et al., 2019).

A variety of natural or synthesized substances may be used in HME process; diverse substances carry specific properties to the final product. kinds of material not only determine the characteristic of extrudates, but also may additionally alter some physical properties of the active pharmaceutical ingredient (API). Moreover, the temperature during the HME process needs to be greater than the melting temperature and glass transition temperature of substances to attain combination of APIs, polymers, and aids in molecular level, hence thermal stability is the pivotal consideration factor in the selection of materials (Liu, Zhang, & Mcginity, 2001). Materials choice is crucial when designing polymeric formulations for various drug delivery systems. however, thermal instability of drugs and polymers constantly limits the spectrum of selectable polymers so it's far crucial to design new appropriate polymers (Ren et al., 2019).

HME technology has been well documented to be an efficient processing technique to reduce particle size. The nanotechnology based drug delivery system has many advantages. To start with, both lipophilic and hydrophilic API's can be incorporated. Moreover, it improves the aqueous solubility, which contributes to enhanced bioavailability. Furthermore, drug can be delivered in the body to a particular region. Also drug is present within the frame for a prolong period which increases the half-life of clearance. Lastly, the carrier potential is high. Formerly drug delivery system that is based on nanotechnology, such as; nano-crystals, nano suspensions and nano emulsions been prepared using numerous batch based conventional methods. Recently, nanotechnology based product have been produced using HME technology. It not only saves time of processing but also reduces the price of the product and variability of the final product performance. Many literature reports supports this technology to produce nano

based drug delivery system because itt is not only advantageous but also feasible (Patil et al., 2016). Particle size is reduced from micro to nano by the the twin screw extruder that generates high sheer force. Particle size is reduced by state a high energy process that brings about transition to an amorphous state from crystalline state. Drug compound in its nanoparticle form is commonly obtained by a high shear which improves its bioavailability and bio accessibility. An increase in rate of dissolution through and increase in the particular region can be observed as the particle size is reduced (Azad, Kim, Jin, & Kang, 2019).

Many active pharmaceutical ingredients are of bitter taste. These drug particles gets dissolved in saliva and have and interaction with taste receptors located at the tongue which causes signal transduction from taste buds, the taste receptors that can produce taste sensation like sweet, sour, bitter or other. There are sensitive nerve endings present at these taste buds. Electric impulses are produce and transmitted through 7th, 9^{th} and 10^{th} cranial nerves by these nerve ending. These cranial nerves are located at the brain and are responsible to give perception of taste. Therefore, it is of prime concern to mask the bitter taste so that palatability can be enhanced. Two approaches are usually adapted to overcome this problem. The primary approach is conversion of drug form into crystalline form from amorphous form, which would reduce drug solubility. The second one is alteration of interaction between the taste receptor and drug. HME technology uses a taste-masking polymer in formulation of solid dispersion which can mask the unpleasant taste of a drug. Solid dispersion inhibits the interaction between taste bud and drug molecules by inhibiting the drug release in the saliva. Formation of hydrogen bond between the polymer matrixes with drug component to achieve taste masked product (Patil et al., 2016)

Orally disintegration tablet development faces primary challenge, which is to mask the unpleasant taste of bitter drugs. HME technology uses taste-masking polymers and creates a solid dispersion, which creates an obstacle for the bitter drug to come in contact with taste bud

of the patient. For this reason many researchers has reported this technique to be an effective method. It is reported more recently that HME technology has been used in taste masked formulation of paracetamol and ibuprofen. In these reports, the intermolecular forces(i.e. hydrogen bond) between the polymer matrix and the active substance is processed by oppositely charged compounds by HME which helps achieving the taste masked product. In a study by Gryczke et al has processed only eudragit EPO (50%) and talc (10%0 with 40% of ibuprofen IBU during extrusion which showed enough taste masking of the compound. It was found that since IBU has plasticizing effect compared to other conventional plasticizers and so increased IBU concentration contributed increased drug polymer interaction (Censi & Gigliobianco, 2018).

Implantable clinical equipment are extensively used within the pharmaceutical manufacturing. Lately, several studies has reported the advantages and versatility of HME technology as it can be applied as a new feasible method in preparation of implantable devices. Moreover, critical parameters and factors ensuring effective HME process in preparation of implantable devices have been highlighted by other studies.

Rothen-Weinhold et al. prepared, a somatostatin analogue named vepreotide containing long acting poly lactic acid (PLA) implants using HME technology. The authors observed that the formation of peptide impurity in the PLA is expressively influenced by the presence of a residual lactide. Ghalanbor et al. found that in preparation of protein/PLGA (poly lactic co-glycolic acid) based implant, HME can be feasible where much given importance was stability of protein, complete release profile and burst release profile. They chose lysozyme from egg white of hen as model protein. Determination of biological activity, high performance liquid chromatography (HPLC), Differential scanning chromatography (DSC) and Fourier transform infrared chromatography (FTIR) confirmed the stability of the lysozyme. The biological activity of lysozyme was confirmed by the results after the HME process. It persisted 60-80

days for in vitro release of the enzyme. The protein integrity was not modified by the HME method which was confirmed by the restoration of active lysozyme. This study concluded that protein theraputics delivery can be efficiently done by HME since this promising approach is simple, it is a single step process for formulation and it maintains protein stability in a good manner (Patil et al., 2016).

Commercially existing oral pharmaceutical products do not fulfill all desires of unique populations, which includes dysphasic (Cilurzo, Musazzi, Franzé, Selmin, & Minghetti, 2017), pediatrics (Visser, Woerdenbag, Hanff, & Frijlink, 2016), geriatrics and patients who may have nutritional restrictions or hypersensitive reactions (Minghetti, Pantano, Grazia, Gennari, & Casiraghi, 2014) . In those cases, either re-formulated drug must be used or a drug made from exceptional inactive substances that would comply the specific medical needs.

If the required dose of a solid dosage form is not available, the common solution that is taken is to split it into half which often leads to inaccurate dosing. The feasible alternative is to compound a customized drug product or personalized medicine, e.g. syrup, solutions, capsules and pills, in pharmacy settings. Though personalizing dose is a noble approach, problems associated with dose inaccuracy is partly solved. For instance, using syringes or spoon does not ensure an appropriate withdraw of the precise quantity of liquids. On the other side, though the solid dosage forms overcome this downside, the therapeutic adherence is questionable for patients who are noncompliant, or those who has difficulty in swallowing or has fear of chocking (Cilurzo, Cupone, Minghetti, Selmin, & Montanari, 2008) (Musazzi et al., 2018).

There are only 5% of drugs which might be noticeably permeable and water soluble, and plenty of others are insoluble in water, which restrict their usage in medical applications, despite the fact that they have got the ability to deal with usual medical issues, along with cardiovascular disease, most cancers, inflammation, and infection. Maximum of the marketed products

prepared by HME are small-molecular drugs. In this section, different chemical drug loaded formulations prepared by means of HME may be discussed. Cancer is taken into consideration as a disease that cannot be absolutely cured. As a usually used method in most cancers therapy, chemotherapeutic drugs commonly cause normal cell damage and side effects because of loss of tumor-targeting and the specified high-dose administration. Therefore, a sustained-release formulation of drug with local anticancer activity is an advantage for delivery of chemotherapy drug, which can be realized via HME (Nattawut Leelakanok, Sean M Geary, 2019). 5-Fluorouracil (5-FU) is a chemotherapy agent that serves for the remedy of numerous cancers, however it's far removed swiftly and has a short biological half of-life, that is a drawback in clinical applications (Fang et al., 2016). In a latest research, 5-FU was loaded into PLGA-based injectable pellet through HME; sustained 5-FU release was observed in both in vivo and in vitro. in the meantime, the end result discovered that the 5- FU-loaded implant showed more advantageous anticancer activity in colon cancer model whilst compared to a soluble 5-FU formulation with equal dose (Nattawut Leelakanok, Sean M Geary, 2019). However, reports on the use of anticancer drugs in HME formulations are not rich sufficient in recent times (Ren et al., 2019).

Biological agents, including peptides and proteins, were broadly used due to their ideal therapeutic outcomes. But, the shortcomings exist concurrently, which include short half of-life duration and easy degradation under physiological environment. HME is a typical approach for encapsulating small molecule drugs (Khor et al., 2017), and it's been mentioned that biological agents also may be encapsulated with remaining activation and discount degradation even on the high temperature. PLGA-primarily based implants with the bovine serum albumin (BSA) embedded was managed for the purpose of protein sustained release (Cossé, König, Lamprecht, & Wagner, 2016). In addition, PLGA was also implemented to encapsulate lysozyme within the technique of HME, activity of enzyme retained and the stability of

lysozyme improved with the usage of solid-state ball milling (Lee & Pokorski, 2017) (Ren et al., 2019)

The probability to combine a polymer and a drug with precise solubility permits alteration of the drug release (sustained, modulated, retarded). 3d printing (3DP) and injection molding (IM) can utilize similar extrusion procedures. Therefore, these two technologies are often correlated to the more conventional Hot Melt technique.

IM is a versatile and fast manufacturing which is when applied in the pharmaceutical industry, pharmaceutical dosage forms with distinctive size and shape can be produced. In a closed mold that has a specific size and shape, the molten mas under high temperature and pressure is injected. The finished product is removed from at the end of manufacturing that has cooled down and/or solidifies inside the mold.

In recent times, 3D printing has got more attention in pharmaceutical field. It is a layer by layer manufacturing of 3D items. In August 2015, FDA has approved its first 3D printed drug (Censi & Gigliobianco, 2018).

For preparation of complex dosage form 3D printing has been used. It has also been employed for Spritam® fast dissolving tablet production at industrial scale. Therefore, 3D printing may be the solution to overcome the drawbacks of on-going fast dissolving thin film (FDF) manufacturing methods and to develop and produce FDM with desired characteristic. Particularly, fused-deposition modeling 3D printing (FDM 3-D) is closer to the hot-melt extrusion process. FDM 3-D has been hired to expand various oral drug delivery systems. Filaments are used by traditional 3D printers to provide the preferred object. In this tool, there are rotating pulleys/gears and narrow tubing system inside the head of 3D printers through which a filament is passed. Here, a nozzle of narrow diameter (.4 mm usually) is used to extrude the filament after its heated FDM 3D printers can produce objects with reproducible

dimensions, particularly whilst filaments are used with uniform diameters (low diameter tolerance). If there is an inconsistency in diameter of the filament (being too wide or too thin), either the printed object would have abnormal dimensions and weight or the extruder might fail to print. Therefore, FDM 3-D ought to potentially permit producing FDFs with reproducible dimensions and physicochemical properties. Furthermore, FDM 3D presents the possibility of laminating multiple layer in a film. Then, those hypotheses were tested in. within the present work, FDM 3D changed into employed to produce 3-d FDFs with taste-masking layers being printed on the drug containing layer and also to create mesh design of FDFs to reduce disintegration time. This property of 3-d FDFS was as compared to a commercially available FDF (Ehtezazi et al., 2018).

Regulatory bodies maintain to encourage the funding in the use of fine with the aid of design (QbD) and procedure analytical technology (PAT), which are already crucial equipment within the HME technique, to beautify product and procedure know-how. As a continuous method, HME suits flawlessly within this framework. PAT tools which includes Raman and near-infrared (NIR) spectroscopy play a critical function in real-time quality assessment and understanding of the extrusion procedure in the manufacturing pharmaceutical dosage forms (Patil et al., 2016)

In addition to the improvements mentioned above, there are a few different developing applications of HME. Co-amorphous drug-amino acid system is a substitute to usual amorphous formulations, and is infrequently realized through HME due to the fact amino acids may degrade at temperatures above 200°C. Lenz et al. evaluated HME as a new technique for the preparation of stable co-amorphous indomethacin-arginine, however phase separation also occurred relying on the practice process. moreover, as a new method for preparing gel formulations, no scraping or blending is needed within the HME system. Co-extrusion is a novel extrusion technique that extrudes multiple layers of different formulations through a

single die. This simultaneous technique shows excellent potential in constant dose mixtures and provides a manner to properly integrate various substances and exceptional formulations. presently, there are most effective two commercially to be had coextruded pharmaceutical products, which include NuvaRing® and Implanon®. Mofidfar and his colleagues prepared PCL-based fibers containing the antifungal compound clotrimazole by coextrusion, and confirmed its superior overall performance within the field of wound dressing over electro spun fibers of the same formula. The idea of co-extrusion is ability for lots dosage forms, which includes oral, transdermal, and implant applications

Chapter 4

Conclusion

Even though solvent casting is widely established approach via formulation scientist to cast Orodispersible film, hot melt extrusion has colossal capability for the same. Common issues observed throughout the scale up and their remedies are very well mentioned which will be useful for voyage of film formulation from lab scale instruments to heavy duty production scale continuous manner machines (Jani & Patel, 2015). This technology is appropriate for each high dose and potent compounds. The mixing that takes place in the barrel of the extruder during processing ensures accurate content uniformity of the active material in the final product. Moreover, the availability of a huge variety of thermo analytical and microscopic techniques permits for the characterization of physical and chemical stability of actives and/or excipients used in the melt extrudate with proper predictability. (Crowly,2007). Furthermore, HME is amplifying its advantages by using combining with a few other techniques which includes HPH and 3D-printing for patient-focused issues. Besides the attainment of solvent-free, one-step technique, HME provides shorter processing time and is extra environmentally friendly in comparison with traditional processing approach. (Ren, 2018).

Chapter 5

Current status and future recommendation

Due to the fact, HME has many advantages over conventional methods, the enormous applicability of HME in pharmaceutical field has been continuously observed in recent years. HME presents many advantages for commercial production as a continuous method. At the same time, the practicability of combining HME with different technology has also tested beneficial for further formulation development. This technique may be incorporated with 3D printing technology to prepare personalized medicine. Jamróz et al., (2017) has observed promising result formulating aripiprazole the usage of HME and 3D printing method. As this technique requires much less step and no solvent which makes it environment friendly, this technique may be employed in commercial manufacturing of medication formulation techniques. 3D printing, a natural evolution of HME, as it shares with HME the extrusion technique, is now attracting accelerated interest. Growth in the quantity of authorized drug products produced using 3D printing must be anticipated within the coming years (Censi,2018)

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