Oral Thin Film: A review on orodispersible thin films for effective drug delivery of antiemetic drugs.

By

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

Department of Pharmacy
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April 2021

Declaration

It is hereby declared that

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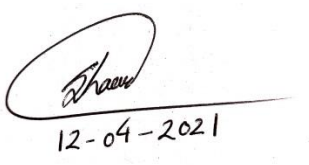

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Approval

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Ethics Statement

This project does not involve any human or animal trials.

Abstract

The oral route is the most preferable route for drug administration because it is the simplest, most convenient and safest means of drug administration that is pain free and can be self-administered by the patients. Most of the medicines available in the market are oral solid dose. Most of the drugs delivered through oral route have comparatively slow onset of action, cannot avoid the fast pass effect, low bioavailability and shorter therapeutic window. There are many people like children, elderly people, dysphagia and cancer patients who have difficulties in swallowing. On the other hand, approximately 28% of people have swallowing problems and they are prone to choking during taking the oral solid dose. That's why oral thin film or orodispersible thin film (OTF) is being introduced as a novel drug delivery system. The antiemetic OTFs are more patient-friendly as there is no need of water to swallow it and it dissolves in the oral cavity within seconds. Being absorbed by oral mucosa, OTFs can avoid the fast pass effect and give quick onset of action.

Keywords: Oral; Swallowing; OTF; Dose; Drugs; Bioavailability

I want to dedicate this work to my beloved parents who were always beside me during the hard times.

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Table of Contents

List of Tables

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List of Figures

List of Acronyms

OTF	Orodispersible Thin Film
Etc.	Et cetera
EMA	European Medicine Agency
FDA	Food and Drug Administration
API	Active Pharmaceutical Ingredients
BCS	Biopharmaceutics Classification System
CTZ	Chemoreceptor Trigger Zone
OTC	Over The Counter

Chapter 1

Introduction

1.1 Background

For ages, people are using drugs to cure disease. There are many routes of administration like oral, parenteral, rectal, transdermal etc. Among them, the oral route is the most common route of drug administration because it is the easiest way than the other routes. Most of the time, the patient does not need any assistance from others to take medicine through the oral route where parenteral, rectal or other routes need assistance from the others to administer drugs properly. We have learned from several studies that almost 60% of total dosage forms which are available in the market are the solid oral dosage form (e.g. Tablet, capsule etc.). The lower bioavailability, slow onset of action time and dysphagia patients have forced the pharmaceutical companies to think about parenteral and liquid oral dosage forms. Yet, the liquid oral dosage (e.g. syrup, solution, emulsion, suspension etc.) mostly have the problem of precise dosing, they are proven effective in patients such as newborn & children (pediatrics), elderly patients (geriatrics), bed rest patients (bedridden) and in cancer patients. Moreover, parenteral dosages are painful to deliver drugs to such vulnerable patients. Despite the limitations, the patients go for these drug delivery systems (Bhusnure et al., 2017). The oral route has its own limitations, like one vital drawback of conventional and traditional dosage forms (tablets or capsules) is difficulty in swallowing for patients having dysphagia (who have difficulty in swallowing), Parkinson's disease, mucositis and vomiting tendency. They are also problematic for self-administration by pediatrics, the geriatric population and particularly to those ill-fated people who have a scarcity of clean drinking water at their places (Gupta et al., 2020). Study shows that there are approximately 28 % of the people for

whom it seems difficult to swallow solid dosage forms, which shows its poor acceptance to the patients (Gupta et al., 2020).

To avoid these complications scientists have developed a novel drug delivery system which is named as Orodiapersible Thin Film (OTF) or Oral Thin Film or Fast Dissolving Oral Thin Film. A film that readily dissolves in the oral cavity is generally termed as an orodispersible film according to European Medicines Agency (EMA) or simply soluble film according to FDA. Usually, these films are ultra-thin (50–150 μm) having the size of a postage stamp, which dissolves in the oral cavity within seconds after being in contact with saliva, resulting in quick absorption and instant bioavailability of drug avoiding the fast pass effect (Chauhan et al., 2012)

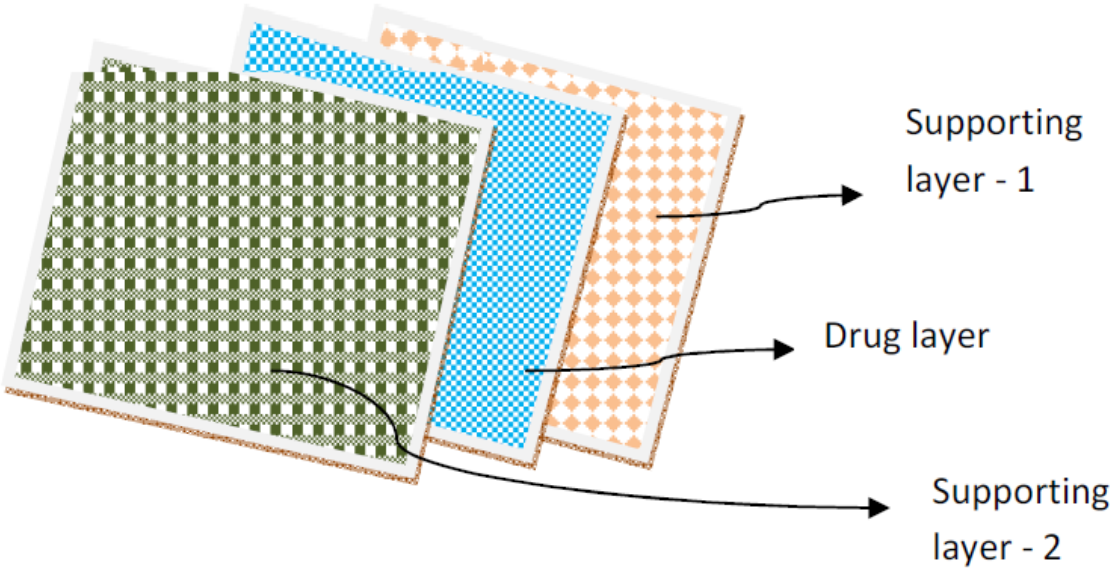

Figure 1: Oral thin films (Multi-layered) (Gupta et al., 2020)

In figure 1, different layers of a multilayered oral thin film are demonstrated.

Orodispersible films have a significant role in the field of antiemetic drugs. The drugs which are used to control emesis are called antiemetic drugs. They are different kinds of antiemetic drugs to control different kinds of emesis like nausea, vomiting, motion sickness, sea

sickness, post-surgery weakness etc. and different class of drugs like lorazepam, imidazole, metachlorpromide, glycine etc. The patients associated with these kinds of diseases or disorders are prone to vomit the tablet itself. If we can replace the dosage form from tablets to OTF, the patient becomes more benefited. The onset of action of OTF is quicker than any other oral dose and gives fast relief from sickness. Newborn babies, pregnant women, chemotherapy and elderly patients are mostly benefited by the use of orodispersible thin films as the antiemetic dosage form.

1.2 Mechanism of Action

The oral mucosal lining consists of a layer of the stratified squamous epithelium as the outermost layer which is followed by a base membrane at first, then a lamina propria and lastly the innermost layer or submucosa. Permeability of the buccal mucosa is higher than skin (approximately 4-4000 times higher) comparing to the permeability of the skin, which is different in each region. The thickness also varies in different parts of the oral cavity, for example, the mucosa membrane thickness of the hard & soft palates, the floor of the oral cavity, the upper palate of the tongue measure approximately 100-200 μm (Bhusnure et al., 2017). The order of permeability is such that: sublingual > buccal > palate according to the keratinization and thickness properties of these regions. Throughout the oral mucosa, there are two possible routes available for passive drug delivery and they are the Para and transcellular pathway. The nature of cytoplasm and the intercellular spaces is hydrophilic which helps hydrophilic drugs to penetrate while the cellular membrane is lipophilic in nature that allows the permeation of drugs that are lipophilic in nature. Oral mucosal lining is tolerant to potential allergens due to having high blood supply, robustness, lack of Langerhans cell and requiring a short time to recover after stress and damage. The pH of the

buccal mucosa is 6.28 +/- 0.36. There is one major limitation associated with buccal mucosal drug delivery which is the low flux leading to low drug bioavailability of some specific drugs. For them, the addition of a permeation enhancer like Aprotinin, Azole, Menthol, Cyclodextrin etc. might be needed (Chaurasiya et al., 2015).

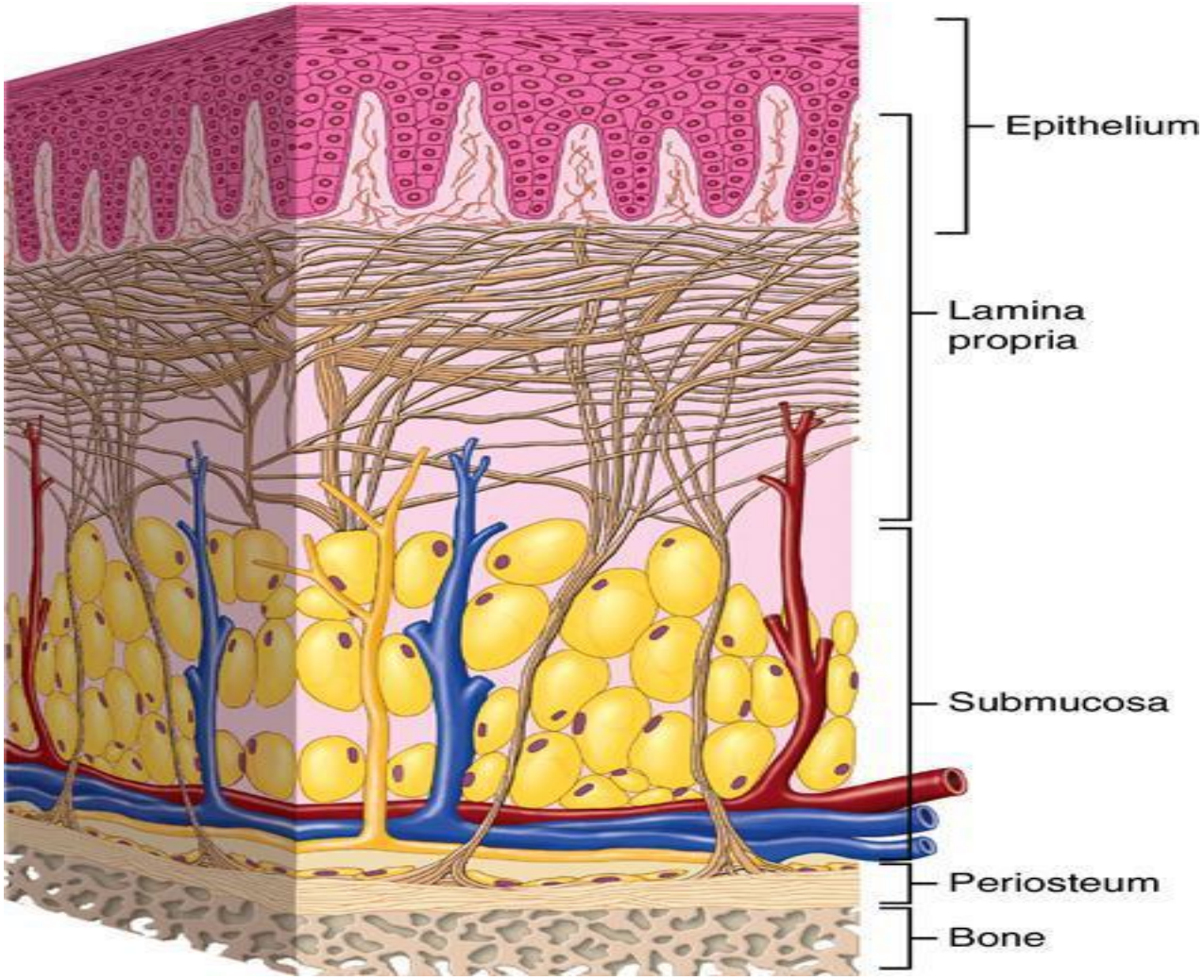

Figure 2: Structure of the oral mucosa (Bhusnure et al., 2017).

In figure 2, the structure of the oral mucosa is shown to understand the mechanism of action of oral thin films inside the oral cavity.

The mechanism of action of OTF is simple. The strip is kept on the patient's tongue's upper palate or any other tissue of the oral mucosa where it is wetted with saliva in few seconds. Then the film-forming polymer is rapidly dissolved within seconds and the API begins to

dissolve and release in the oral mucosa. Most of the drug is swallowed with the saliva and later absorbed from the GIT; however, absorption of an API fraction through the oral mucosa may occur which gives quick onset of action (Wasilewska & Winnicka , 2019).In this process, the drug quickly goes to the systemic circulation and gives rapid action. This is how OTF gives quick relief from emesis.

1.3 Classification of thin films

Generally, Orodispersible Thin Films can be classified into three classes and they are:

1.3.1 Type I: Based on dissolution potential of OTFs.

The base of this classification is dissolution potential. This type of oral thin films can further be classified into three categories. They are:

- Fast dissolving or flash release (1-30seconds)
- Moderately dissolving (1-30 minutes)
- Slow dissolving or sustained-release (more than 30 minutes)

The fast dissolving oral thin films are ultra-thin and dissolve immediately after getting in contact with saliva when placed inside the oral cavity followed by extemporary action of the APIs. Moderate and slow OTFs are used for making nicotine-based products to reduce or eliminate nicotine-based products to help giving up smoking or to chew tobacco (Gupta et al., 2020).

A table to better describe properties of OTFs based on dissolution potential is given below:

Properties	**Fast Dissolving**	**Moderately Dissolving**	**Slow Dissolving**
Area (cm^3)	2-8	2-7	2-4
Thickness (μm)	20-70	50-500	50-250
Structure	Single layer	Single or multilayer	Multilayer
Excipients	Soluble hydrophilic polymers	Soluble hydrophilic polymers	Low or nonsoluble polymers
Drug Phase	Solid solution	Solid solution or suspended drug particle	Solid solution or suspension
Application	Tongue	Gingival or buccal (under the tongue) region	Other regions of the oral cavity
Dissolution	1-30 seconds	1-30 minutes	Maximum 8-10 hours
Site of Action	Systemic or local	Systemic or local	Systemic or local

Table 1: Properties of OTFs based on dissolution potential (Bala et al., 2013).

In table 1, properties of oral thin films based on dissolution potential are listed to show the differences among them.

1.3.2 Type II: Based on the number of thin layers in a strip.

OTFs can be categorized into three types based on the number of thin layers in them. They are:-

- Mono layered OTF
- Bi layered OTF
- Sandwich or multi-layered OTF

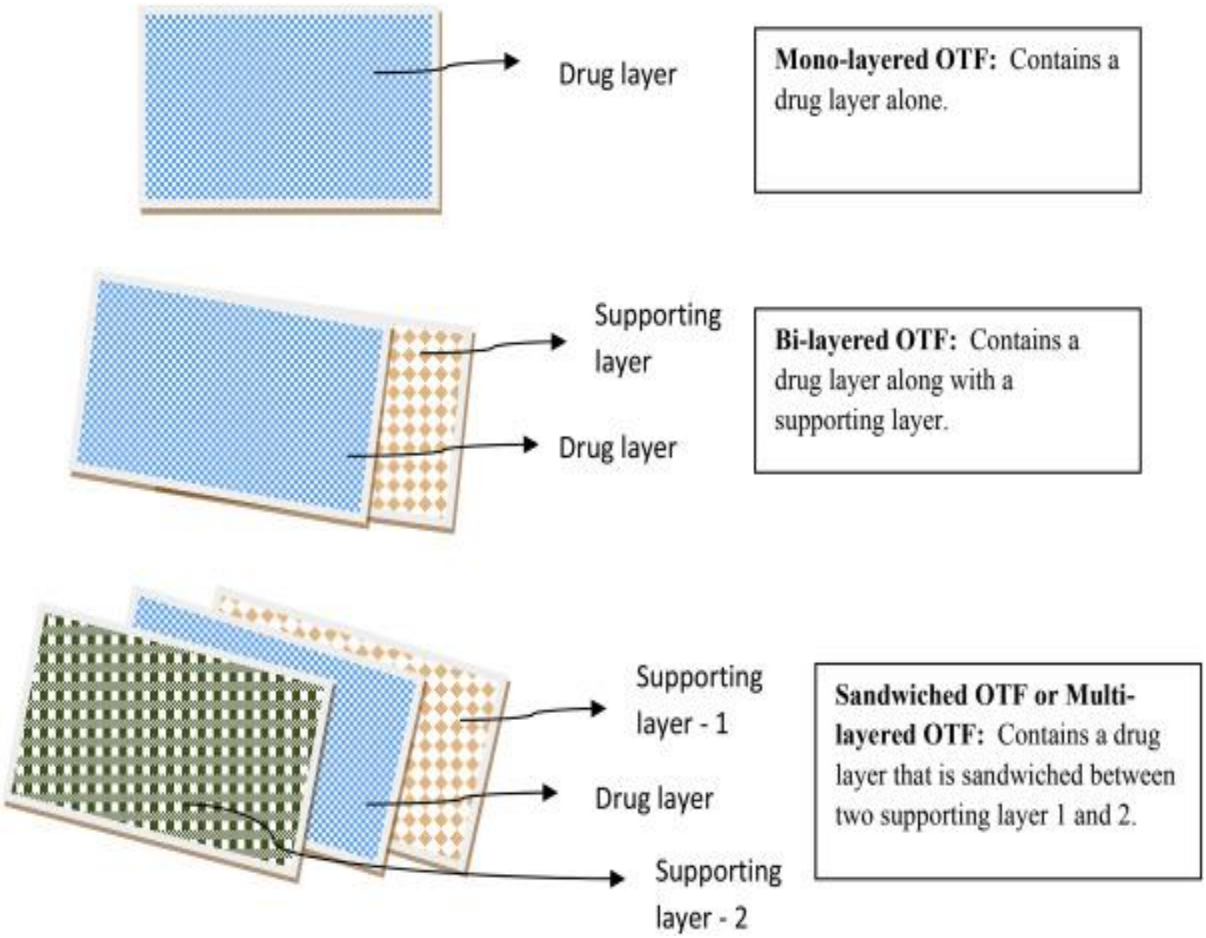

Figure 3: Classification of OTFs based on number of thin layers (Gupta et al., 2020)

In figure 3, the classification of oral thin films based on number of thin layers is shown with the identity of each layer.

The mono-layered OTFs are drugs that contain a single layer strip attached with various excipients like plasticizers, adhesives, polymers etc. The bi-layered OTFs contain a layer

along with the drug layer which can be taste-masking or permeation enhancer or simply a sticky layer. In the sandwich or multi-layered OTFs, the main layer or drug-carrying layer is sandwiched in between two layers known as supporting layers that has possibility to be taste-masking layer to reduce bitter taste, permeation enhancer layer to help the film dissolve more quickly or adhesive/sticky layers (Gupta et al., 2020).

1.3.3 Type III: Based on the characteristics of active ingredients existing in the OTFs

Depending on the nature or type of active ingredients, it is possible to categorize the OTFs as mentioned below:

a) Oral Thin Films that have an API or Active Pharmaceutical Ingredient, which comes from synthetic route .e.g. OTF of Sildenfil citrate.

b) OTFs that have an API came from the natural source. e.g. OTF of Tetrahydro Cannabinol

c) OTFs have some other materials which are known as micronutrients, fundamental vitamins, minerals, probiotics or vaccines. e.g. oral thin film of vitamin D.

Oral thin films with active pharmaceutical ingredients obtained from synthetic route include OTC (non-prescription drugs) and drugs that must be prescribed by a physician. They can be single drug either or combination drugs (Gupta et al., 2020).

1.4 Antiemetic drug

Drugs that prevent or suppress emesis are known as antiemetic drugs.This includes nausea (discomfort that felt before vomiting), anything from food poisoning, GI discomfort, head

injury or brain cancer (Mandal, 2019). There are various kinds of antiemetic drugs used for various reasons. The classification of antiemetic drugs is given below (Dnyaneshwar et al., 2014; Shetti et al., 2014):

1. Anti cholinergics (Highly effective in motion sickness): Hyoscine (Scopolamine), Dicyclomine
2. H1 Antihistaminics (Effective in both motion sickness and Morning sickness): Promethazine, Diphenhydramine, Dimenhydrinate, Doxylamine, Meclozine, Cinnarizine
3. Neuroleptics (D_2 Blockers): Chlorpromazine, Triflupromazine, Prochlorperazine, Haloperidol
4. Prokinetic drugs: Metoclopramide, Domperidone, Cisapride, Mosapride, Itopride
5. $5HT_3$ Antagonist: Ondansetron, Granisetron, Palonosetron, Ramosetron
6. Neurokinin (NK_1) Receptor antagonist: Aprepitant, Fosaprepitant
7. Adjunctive antiemetics: Dexamethasone, Benzodiazepines, Donabinol, Nabilone.

The vomiting center receives input from GI mucosa, Chemoreceptor trigger zone (CTZ) and Vestibular apparatus, where both vomiting center and CTZ are present in the medulla oblongata (Dnyaneshwar et al., 2014).

The use of various antiemetic drugs with their purpose of use is given below (Saur et al., 1996):

- Drugs used for nausea, vomiting associated with GI Tract- Metachlorprimide, Domperidone.

- Drugs used for motion sickness and morning sickness- Hyoscine,Cyclizine, Dimenhydrinate, Promethazine.
- Drugs used in vomiting associated with pregnancy- Doxylamine, Cyclizine, Meclizine.
- Drugs induced vomiting due to general anesthesia- Ondansetron, Metachlorpromide.
- Drug-induced vomiting due to intake of morphine- Cyclizine.

1.5 Use of antiemetic drugs in OTF dosage form

Scientists are trying to convert previously used oral antiemetic drugs into orodispersible thin film form. Some OTF antiemetic drugs are being used for the cancer patients who have undergone chemotherapy. For example, Palonosetron antiemetic drug is a tricyclic 5-HT_3 receptor antagonist applied as an antiemetic drug, which has therapeutic and prophylactic effects on nausea, vomiting and other emesis. Particularly Palonosetron is an effective anti-emetic agent for post-surgery, radiotherapy and chemotherapy patients' nausea and vomiting (Bhoumik et al., 2019).

Metoclopramide hydrochloride is a dopaminergic blocker of BCS class III drug which produces antiemetic effects by inhibition of D2 and 5-HT3 receptors in the CTZ (Alam et al., 2014). Its OTF version is also available which a sandwiched layered OTF is and being used to prevent nausea & vomiting associated with GIT irritation.

Mostly, children and elderly patients are using the OTFs. People who have problem with swallowing are highly encouraged to take OTFs instead of tablets.

There are some Ideal characteristics that an antiemetic OTF should have:

- The film should be thin and readily dissolved or disintegrated in the oral cavity (Bala et al., 2013)
- It should stick to the oral cavity (Liew et al., 2013)
- Should be able to disintegrate or dissolve immediately when gets in contact with saliva without the presence of water. (Irfan et al., 2016).
- Every part of the strip should be dissolved or disintegrated in the oral cavity and there should be no residue left at all (Abdulrahman, Patel, 2015).
- Should be free from bad odor and bitter taste.
- There should be high bioavailability and long therapeutic index.
- Taste masking is required if the drug has a bitter taste (Barnhart et al., 209-216).
- OTF must be stable against humidity and temperature (Panchal et al., 2012)

There are usually five methods that are commonly used to manufacture OTFs:

(a) Semisolid Casting:

- Firstly, in this process, a film-forming polymer solution is prepared which is water-soluble in nature.
- Thereafter, the obtained product is mixed with an acid-insoluble polymer solution made of sodium or ammonium hydroxide (Bhusnure et al., 2017).
- The ratio of 1:4 ought to be maintained for the two types of polymers where a gel mass is acquired after adding the plasticizer in the right measure.

- Finally, using the thermally regulated barrels it is then cast on desired thin films. So, this process is called the semisolid casting method (Bhusnure et al., 2017).

(b) Solvent Casting:

- Here, an aqueous or hydro-alcoholic solution of various excipients likes polymers; plasticizers etc. which are needed for making the orodispersible film is taken along with drug solution (Thakur & Tyagi, 2019).
- Then both of the above-mentioned solutions are compounded, properly stirred and then cast into the Petridis or Petri plate to be dried at 60^0C temperature (Bhusnure et al., 2017).
- Finally, they are cut into desired pieces.
- It is the most common Oral thin film manufacturing method.

Figure 1

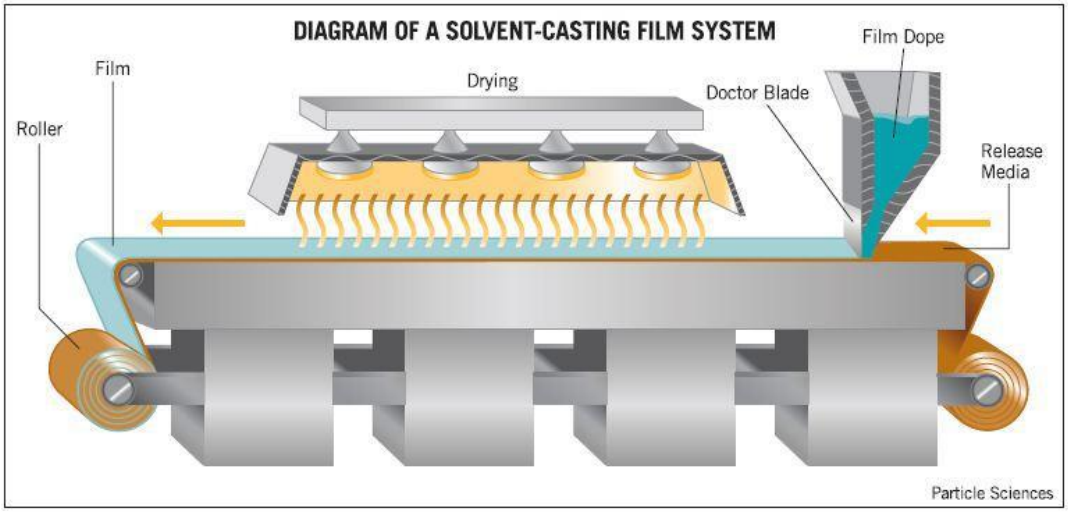

Figure 4: Solvent casting method (Bhusnure et al., 2017)

In figure 4, solvent casting method with a machine's model is shown.

(c) **Hot melt extraction method:** In this method, a mixture of polymers, drugs and other excipients are shaped into a film by melting all the components by a heater and passed it through the orifice to obtain a homogenous matrix. Which is then cut into desired shapes and sizes through dies (Dixit et al., 2009) (Parmar et al., 2012) (Nagendrakumar et al., 2015). Both these techniques used to prepare orodispersible thin films come with good characteristics but the solvent casting method is mostly used because it is cost-effective if we compare it with the hot-melt extrusion method (Thakur & Tyagi, 2019).

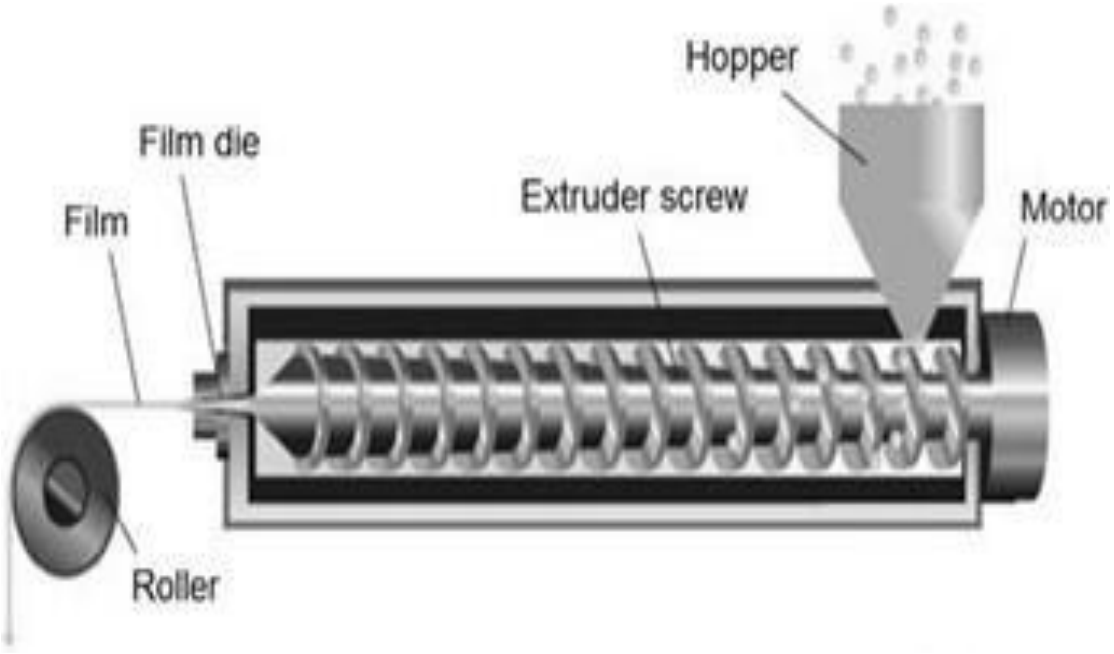

Figure5: Hot melt extraction machine (Thakur & Tyagi, 2019)

In figure 5, a labeled diagram of a hot melt extraction machine is shown.

(d) **Rolling:** In this method, drug solution or suspension having the film-forming polymer undergoes metallic roller where the film is dried and then cut into desired shapes and sizes (Bidhakar et al., 2018).

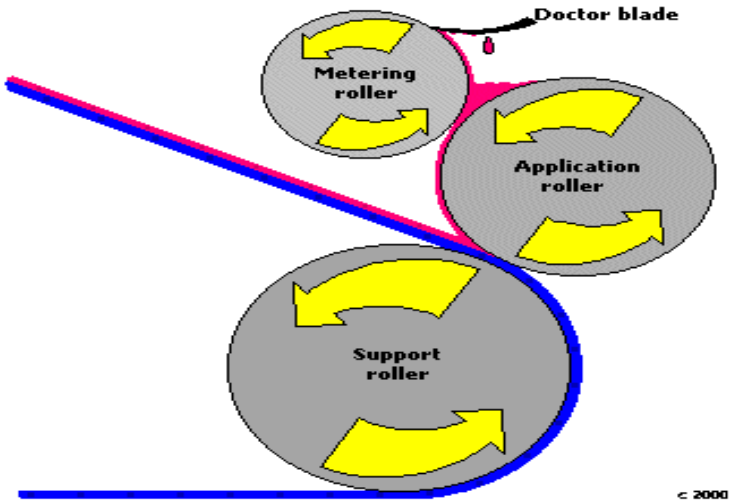

Figure 6: Three roller coating films forming the unit (Bhusnure et al., 2017)

In figure 6, a diagram of forming film using the rolling method is given.

(e) Solid Dispersion extraction:

- At first, preparation of solid dispersion is done by putting the unmixable components along with the drug.
- Then they are given shape into films by using the dies (Dixit et al., 2009).

There is another technique named 3D printing of Orodiapersible thin films, which is getting popularity. Different types of 3D printing technology are available now. With the help of a 3D printer, it is now becoming easier to prepare customized OTF drugs and films containing a higher dose of drugs.

1.6 Advantages of OTF

Orodispersible thin films containing antiemetic drugs have some advantages over the conventional dosage forms available in the market. They are:-

- Orodispersible thin films offer fast, accurate dosing in a safe format, without the need of water. This is one of the reasons why the pharmaceutical companies and consumers

have become interested on it over the other dosage forms (Abdulrahman & Patil, 2015).

- Fast disintegration in the oral cavity is achievable due to the accessibility of greater surface area of the film that enhances the onset of action, reduces the dose size and upgrades the effectiveness of the medicine (Sheoran, 2018).
- OTFs can avoid the fast pass effect due to tremendously vascularized oral mucosa (Arora & Chakraborti, 2017).
- OTFs are ideal for patients suffering from dysphagia, recurrent emesis, mental disorders and motion sickness as they can't swallow a sufficient amount of water (Arora & Chakraborti, 2017).
- This is a new business window for the pharmaceutical companies to reach more close to the customers (Abdulrahman & Patel, 2015).
- Loss due to friability is less as drugs are kept into layers (Sheoran, 2018).
- No chance of distress due to choking which is common for oral solid doses. (Panda et al., 2012).
- It can replace local anesthetics that are used during oral or dental surgery (Pallavi et al., 2017).
- A small amount of excipients are needed (Sheron, 2018).
- Feels good in the mouth, easy to use, fast absorption, quicker action and enhanced bioavailability with a large therapeutic window (Pallavi et al., 2017).

1.7 Disadvantages, limitations and challenges

Despite many other advantages, orodispersible thin films have some disadvantages, limitations and challenges. They are:

- A higher dose can not be usually incorporated into orodispersible thin films which is comparatively easily possible in other oral drugs like tablets and capsules (Arora & Chakraborti, 2017).
- Packaging of OTFs requires special equipment's and they are difficult to pack compared to others (Thakur & Tyagi, 2019).
- As OTFs are hygroscopic in nature, special packaging is required for longer preservation (Arora & Chakraborti, 2017).
- There are restrictions in eating and drinking for patients after consuming OTFs (Arora & Chakraborti, 2017).
- Expensive technique to prepare OTFs compared to normal tablet production (Arora et al., 2017).
- Mucosal irritation occurring drugs cannot be administered (Thakur et al., 2019).
- It is difficult to combine more than two drugs as both the dissolution rate and disintegration time are obstruct by the co-administration of a drug in films (Thakur & Tyagi, 2019).
- Just like conventional dosage form, antiemetic OTF dosage cannot do anything to the patients if they vomit.

Some of the above limitations can be solved by the recently innovated 3D printing technology with which we can increase the dose and make more stable OTFs. Researchers are trying to increase the loading capacity of the oral thin films to incorporate higher doses (Ouda et al., 2020).

1.8 Points to improve

Nowadays, solvent casting is a more popular technology to produce OTFs. It is cost-effective and more economical than the other technology's. But it looks like 3D printed OTFs will lead in the future because of their flexibility to prepare the desired product. The two major drawbacks of OTFs are:

(i) Size of dose

(ii) The cost of manufacture.

A higher dose cannot be incorporated in OTFs, but researchers are trying to make the larger dose of OTFs so that more drugs become available in OTF form. Another one is the manufacturing cost. Still, oral thin films cost more while manufacturing compared to other oral solid dosage forms. This is a major drawback to make OTFs available to the patients. In future, if a more cost-effective OTF manufacturing method comes, it will play a revolutionary role in the medical sector.

1.9 Current scenario and future of antiemetic OTF drugs in Bangladesh

During my study I have found that Beximco Pharmaceuticals is the first pharmaceutical company in Bangladesh to introduce Oral Soluble Film (OSF) or Orodispersible Thin Film (OTF).The Drug Onsat OSF (Ondansetron), an anti-emetic drug, is available as 4 and 8 mg soluble films. This drug is used for post-operative nausea and vomiting and controlling vomiting due to cytotoxic agents.

There are some other pharmaceutical companies like Novartis, Pfizer etc. who make OTF drugs. But the use of OTFs is not that much common in our country and our pharmaceutical companies don't manufacture them at all. That is why our people are deprived of

experiencing this novel drug delivery technology. Bangladesh is a densely populated country and people here need antiemetic drugs a lot. For many people, motion sickness is a curse and people would be very much benefited if more antiemetic OTF drugs were available in our country. The population is our asset and our pharmaceutical companies should not forget it. If they bring various types of OTF drugs, many people will be benefited from it. From a marketing perspective, this new orodispersible film technology can bring more revenue for them (Thakur et al., 2019).

1.10 Literature review

The making of Palonesteron Hydrochloride Oral thin film was discussed by Bhowmik et.,al (2019) in the article "Preparation and Evaluation of Palonosetron Hydrochloride Oral Thin Film", where the motto of the study was to develop an orodispersible thin film that contains Palonosetron hydrochloride. It will have satisfactory mechanical properties, rapid dissolution & disintegration and all drug contents should have a good level of uniformity (Bhowmik et al., 2019). At first, the ingredients were collected from different sources. The most common and cost-effective method, the "solvent casting method" was used for preparing film and balance within excipients and drugs were HPLC and FTIR studied. At the end, oral thin films of Palonosteron hydrochloride was successfully prepared which contain polymer of various concentrations and rest of the elements. In the study, the researchers evaluated the film for various properties like p^H, weight variation, thickness etc. and found everything perfect. The outcome of the drug content uniformity and weight test demonstrated that it was the homogenous thin film where the drug was uniformly distributed. The product as well as with the Oral Thin Film technology satisfied the researchers. The antiemetic OTF drug of Polonosetron hydrochloride which contains polymer 'A' for film shaping and plasticizer 'B'

as the most ideal decision taken by them that give quicker drug release in the middle of a small timeframe with better agreeableness in a straightforward, minor tedious and practical way that was believed by them(Bhowmik et al., 2019).

In the study "Formulation and Evaluation of Swellable Oral Thin Film of Metoclopramide Hydrochloride" (Alam et al., 2014), the production of antiemetic OTF dosage form of Metoclopromide hydroxide was discussed. It is commonly used for migraine, cancer patients and post-operative nausea and vomiting. In this case, the researchers used solvent casting method using different concentrations of povidon K-90 in the drug layer, polyvinyl alcohol as gel-forming polymer and glycerin as plasticizer. Citric acid was used as saliva stimulating agent and other excipients were used accordingly to formulate a sandwiched swellable oral thin film of metoclopramide hydroxide. At the end, the necessity of further study to make the newly formulated oral thin film is expressed by the researchers (Alam et al., 2014).

1.11 Purpose of the study

The purpose of this study is to discuss as follows:

- To discuss about the Orodispersible Thin Films for effective drug delivery.
- To demonstrate the application of Orodispersible Thin Films as a dosage form for antiemetic drugs.
- To show OTFs' acceptance over conventional dosage forms available in the market.
- To show that conventional dosage forms can be made as OTF drugs.
- To introduce this novel drug delivery system.
- To say that our pharmaceutical companies should emphasize manufacturing OTF dosages to ensure more patient comfort.

This Orodispersible Thin Film can create a great change in the healthcare sector. It is going to be a lifesaver dosage form for certain patients in future if emphasized properly.

Chapter 2

Methodology

The study was carried out by emphasizing on latest published research articles as well as review articles focusing on orodispersible thin film for effective drug delivery. The literature search was performed on renowned journals, published research papers and different kinds of research databases like Pubmed, Research Gate, Google Scholar, Science Direct, Academic Search and Bangladesh Pharmaceutical Journal etc. Keywords like oral thin film, orodispersible thin film, oral strip, swallowable film, antiemetic drugs, emesis etc. led to hundreds and hundreds of articles. All the articles those seemed relevant to the research topic, were gone through and collected them for writing a review on Orodispersible Thin Film. Search for knowledge gaps was done and research questions were prepared. Have gone through around 100 articles and collected information from more than 50 articles to know about this novel technology and after that they were assembled. The draft was edited several times to reduce the errors with the help of the supervisor's feedback on it. After going through all these processes, the final write-up is prepared.

A flow chart of the screening process for writing the review article is given on the next page which helps to better understand the whole procedure:

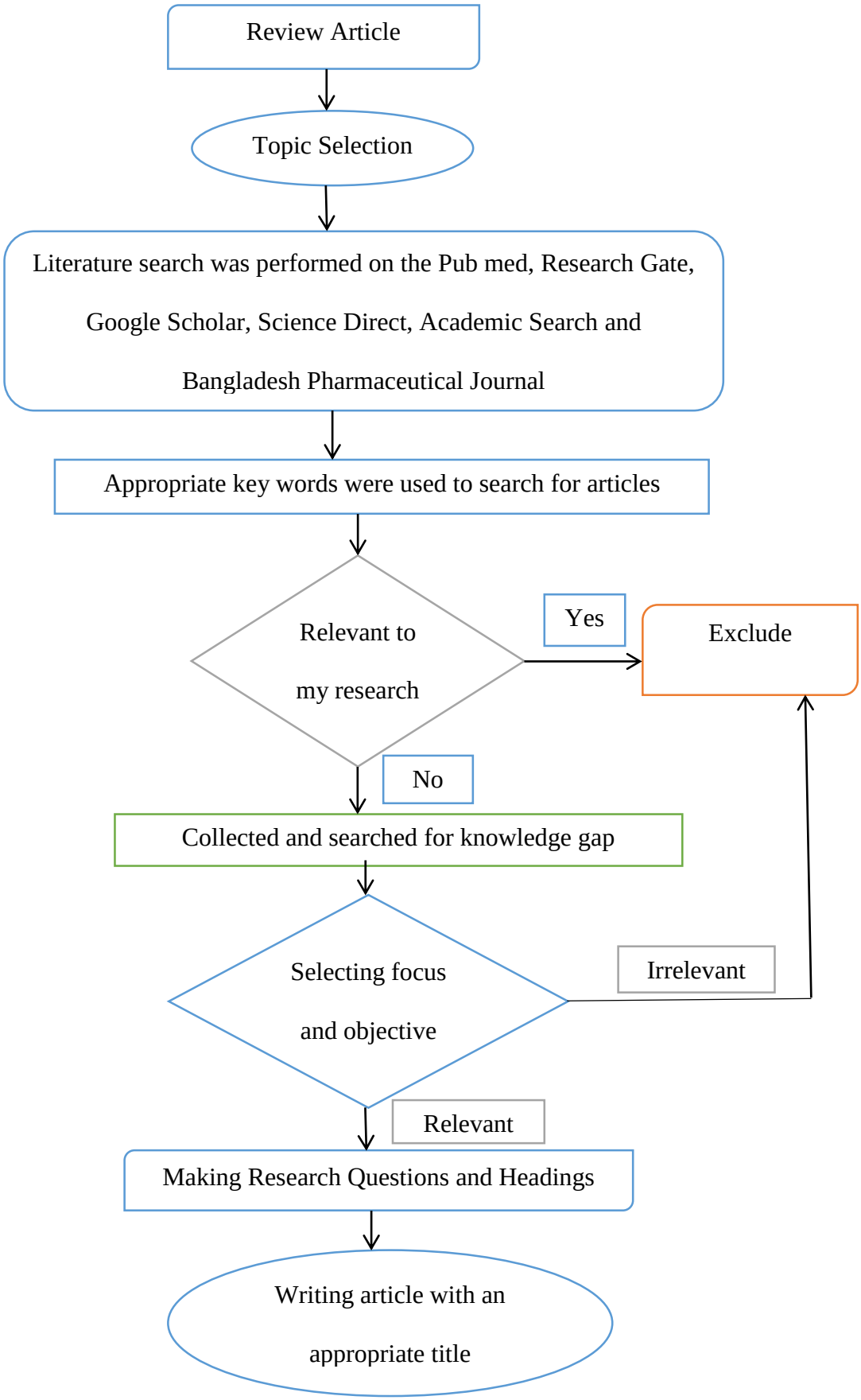

Figure 8: Flowchart of Article Screening Process

Here, some of the methods that were used in different articles are summarized by:

In one article the researchers have discussed about the background of oral thin films. It was said by the author that the most desired route of drug administration is oral route and almost 60% dosage forms available are solid dosage forms that are taken through oral route (Bhusnure et al., 2017). Its low bioavailability, small therapeutic window, delayed onset of action time and patients with dysphagia made the manufacturers interested at liquid oral and parenteral dosage form followed by orodispersible thin film (OTF). The OTF relieved the children, elderly patients and people who have swallowing problem. Later information about oral mucosa from the same article was collected and found that OTFs can be directly absorbed by oral mucosa and avoid fast pass mechanism.

About the classification of thin layers and their basis of classification were known from another article. Basically they can be classified into three types and each type can be classified into another three types (Gupta et al., 2020).

In the article "orodispersible film dosage form: a review" (Dnyaneshwar et al., 2014**)** it was spoke by the author about emesis, cause of emesis, and antiemetic drugs. Search for antiemetic OTF drugs in Bangladesh led to find only one, BEXIMCO Pharmaceutical's 'Onsat OSF'. Found nothing like orodispersible thin film or oral thin film after searching in bddrugs.com.

Several different articles were found related to the development of orodispersible thin film and orodispersible antiemetic thin film. Some of them are titled as:

- "Orally dissolving strips: A new approach to oral drug delivery system" (Bala et al., 2013).
- "Formulation and Evaluation of Swellable Oral Thin Film of Metoclopramide Hydrochloride" (Alam et al., 2014).

- “Preparation and Evaluation of Palonosetron Hydrochloride Oral Thin Film” (Bhowmik et al., 2019).

In these articles, the authors discussed about the preparation of those antiemetic OTF drugs and their potential.

Thus, the data and information for the review article to overview the use of orodispersible thin film or oral thin film for effective drug delivery of antiemetic drugs were collected.

Chapter 3

Discussion

Orodispersible thin film is a novel drug therapy. It has changed the way of oral dosage form. Previously there were only two types of oral dosages:

(i) Oral solid dose (tablets and capsules)

(ii) Liquid dose.

They were swallowed using water and after absorption through GIT, they start their onset of action. They have poor bioavailability and a low therapeutic window. Chocking is very common for administering oral solid dosage and children, elderly people and pregnant women face many difficulties. Approximately 28% of people suffer from swelling difficulties (Gupta et al., 2020). Study shows that in 20% case children have to take adult dose due to lack of availability. Oral route or oral cavity is considered as an ideal route for drug administration especially for those rugs which are degraded in gastric p^H. Some of the conventional dosage forms, for example, disintegrating tablets can be replaced by ODFs as these are most convenient to all age groups (Bala et al., 2013). The large surface area of oral cavity which is 214.7 ± 12.9 cm^2 facilitates the larger amount of drug (Batista et al., 2019). Usually larger amount of drug can not be incorporated into oral thin films but a small amount can easily be incorporated into OTFs as well as into oral cavity (Karki et al., 2016). When someone is feeling nausea it is hard for him or her to swallow a tablet. Pregnant women and chemotherapy patients suffer a lot from their morning sickness and post-operative sickness due to difficulty to take medicine (Nishigaki et al., 2012).

On the other hand, Oral thin films or orodispersible thin films are free from these difficulties. There is no fear of choking during taking medicine because OTF doesn’t need water to

swallow it. It can easily replace the conventional solid antiemetic doses because antiemetic drugs don’t require a higher dose, so they can be easily incorporated into oral thin film strips.

To mention, 3D printing technology for producing oral thin films has taken this dosage form a new level. Complex structure and dosage form can be formulated in fewer time frames along with making it better and it can be constructed pretty fast than conventional manufacturing process at the same time using the 3D printing technology (Ehtezazi et al., 2018). This 3D printing technology might be beneficial from early drug development to personalized drug production (Lamichhane et al., 2019).

There are advantages, disadvantages and limitations of antiemetic OTFs. The main advantage of oral thin films are, they are ideal for all ages including patients suffering from dysphagia, recurrent emesis, mental disorders and motion sickness as they can't swallow a sufficient amount of water (Arora & Chakraborti, 2017).The major disadvantage is, it is difficult to incorporate a higher dose and more than two types of drugs in one strip (Arora & Chakraborti, 2017). Requirement of special packaging is also a limitation for oral thin films (Thakur & Tyagi, 2019).

Antiemetic OTFs are blessings for those who have motion sickness as it can readily get absorbed by the oral mucosa and give rapid onset of action. Sometimes, patients like pregnant women, chemotherapy patients vomit the antiemetic tablet itself. Here OTFs can play an important role in patient safety, comfort and effective drug delivery. OTFs can be commercially significant with time when it will be more available and more popular to the patients and the physicians (Abdulrahman & Patel, 2015).

Chapter 4

Conclusion and Future aspect

4.1 Conclusion

To conclude, it can be said that the antiemetic oral thin films are blessing for mankind. The technology is still novel and there are so many scopes to work and improve its performance. It has enlightened hope to many patients who have difficulties in swallowing oral solid dose.

4.2 Future aspect

From my perspective, OTFs are the future of antiemetic drugs. The OTFs are invented due to swallowing problem and patients who are prone to nausea or vomiting can not swallow properly. Many times the patients vomit out the tablet itself where OTF is readily soluble on the tongue in the presence of saliva. In future more pharmaceutical companies will come forward and more and more investment will come. Hope so the manufacturing cost will decrease in future and everyone will have access to have OTFs. The 3D printing technology is booming and using 3D printing technology to prepare OTFs may provide a better alternative to injections and syrups. OTFs can increase the bioavailability of drugs. Further in vitro studies should be carried out using the orodispersible film for determining dose accuracy, film strength, moisture content, and surface pH for effective oral drug delivery.

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