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FORMULATION OF AN ORALLY FAST-DISSOLVING FILM USING DIPHENHYDRAMINE HYDROCHLORIDE AS THE MODEL DRUG BY SOLVENT CASTING METHOD

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ABSTRACT

This study focused on the formulation of an orally fast-dissolving film using diphenhydramine HCl as the model drug by solvent casting method, utilizing the most commonly found excipients available in the country. This will enhance a drug's function for immediate release purposes and in cases wherein rapid action is required. The oral film was subjected to various physical and chemical quality control tests and pharmacokinetic tests such as the compatibility test of active ingredient and excipients. All of the ingredients except Acacia have two or more spots that signify no interaction between diphenhydramine HCl and the ingredients and therefore deemed compatible. The stability test for the physical parameter showed that the oral film is physically unstable at the 3rd month due to absorbance of moisture and loss of peppermint scent in light and relative humidity. The oral film is physically stable at temperatures of 2 to 8°C and 25 to 30°C but physically unstable to 40°C. They are rendered unstable because of their change in color, texture and scent. The stability for the chemical parameter showed that the oral film is chemically stable even under the varying influence of light, temperature and relative humidity during the 3-month duration of the stability study. The physical test of the oral film yielded an *In-vitro* disintegration time of 35.96 seconds, a mean weight of 0.3299g, and a mean thickness of 0.354 millimeters, folding endurance produced a mean of 20.5 folds, a

mean swelling index of 31.25%, a mean linear expansion coefficient in water of 0.06% at 30 seconds and 0.23% at 60 seconds and lastly a mean percentage moisture loss of 57.0%.

KEYWORDS: orally fast-dissolving films, formulation, solvent casting method, diphenhydramine HCl, disintegration, dissolution.

CHAPTER: 1 PROBLEM RATIONALE

1.1 INTRODUCTION

The oral route of drug administration is the most common and preferred method of delivery due to its convenience and ease of ingestion. It is the comfortable and familiar means of taking medication on the patient's perspective. Although oral route of administration is preferred, it may cause problems leading to inefficient drug delivery. There is a number of reasons for this phenomenon. Limited drug absorption resulting in poor bioavailability is paramount among the potential problems that can be encountered when delivering an active agent via the oral route (Miller, 2007). Drugs may also undergo first-pass effect or presystemic elimination. This is the rapid metabolism of an orally administered drug before reaching the general circulation. To overcome first-pass effect, the route of administration or dosage form of the drug may be changed (Shargel et al., 2004). Fast-dissolving drug- delivery systems were first developed in the late 1970s as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experience difficulty swallowing traditional oral solid-dosage forms (Arya et al., 2005).

Orally fast-dissolving films are made up of the water-soluble polymers which, when placed on the tongue, instantly dissolve or disintegrate the medication without the need of water (Radhakisan et al., 2012). The large surface area available in the film dosage form allows rapid wetting by the saliva, which then quickly disintegrates and dissolves. The drug is then made readily available and absorbed directly to enter the systemic circulation without undergoing first-pass hepatic metabolism, which increases bioavailability (Bhyan et al., 2011). In addition, this type of delivery system is favorable to patients since it is more stable, durable and quicker than other conventional dosage forms. It has pleasant mouth feel, accurate dosing and rapid onset of action (Bhura et al., 2012).

The dissolution of the conventional tablets is commonly slow, and they tend to retard the distribution of the drug into the system. The dissolution rate can be improved through excipients or by having a new formulation and new dosage form. The group suggests that a

new dosage form is the answer to the slow dissolution problem of the available capsule and tablet from the official monograph. The orally fast-dissolving film could alleviate the delay of the disintegration of the available dosage forms, hence may increase its availability to enter the systemic circulation.

Diphenhydramine hydrochloride is histamine H1 antagonist that occurs as a white, crystalline powder and is freely soluble in water and alcohol with a pH of 4.0 to 6.5. It is used to treat sneezing, runny nose, watery eyes, hives, skin rash, itching, and other cold or allergy symptoms (Hassan, 2015).

The general objective of this study was to develop and formulate an orally fast-dissolving film utilizing the most commonly found and economical chemical excipients available locally, employing the most convenient method. The group also aimed to determine the physicochemical properties of this newly formulated drug delivery system using the known antihistamine drug diphenhydramine hydrochloride as the model drug.

This research would benefit several areas of pharmacy, such as the pharmaceutical care industry, research and development, and manufacturing industry. The orally fast-dissolving film offers increased patient compliance through ease of administration, ommitance of water intake, no first-pass effect and for emergency purposes. It will also provide an attainable and readily available formulation with easily acquirable chemical excipients within the country, which can be a newly formulated dosage form that can be utilized by various active ingredients.

1.1 Research Impediments

This research study developed different formulations on the known antihistamine drug, diphenhydramine HCl, which is available in capsule and chewable tablet as stated from the official monograph, into an orally fast- dissolving film with the aid of solvent casting method. The group also conducted a three month stability testing and dissolution testing to determine the drug release information alone regarding the film formulated.

The research based the methods on previous journals parallel to the study and the objectives the researchers desired to achieve, because no exact same method was performed on similar pharmacologically related drug. This study is a prospective experimental and descriptive research, employing procedural concepts and descriptions. The group relied mostly on the

data gathered on which formulation produced the film with the best physical characteristics based solely on organoleptic evaluation, and was then subjected to the further test parameters that the group has chosen for the film evaluation.

This study was limited to the formulation of an orally fast-dissolving film and the concept of using diphenhydramine HCl as an active ingredient as a model drug. The group aimed to determine the film's drug release rates through its dissolution profile alone and no bioavailability studies, animal studies, and toxicity studies were performed.

The non-active ingredient and excipients used were also not assayed; instead, compatibility study was performed.

CHAPTER: 2 RESEARCH QUESTIONS

2.1 Review of the Literature

2.1.1. Orally Fast-Dissolving Film

Dissolvable oral thin films (OTFs) evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers for delivering vitamins and personal care products (Arya et al., 2010). In the late 1970s, the oral thin film was developed as an alternative to conventional dosage forms for pediatric and geriatric patients who experience difficulties in swallowing traditional oral dosage forms. The novel technology of oral fast-dispersing dosage forms is also known as fast dissolve, rapid dissolve, rapid melt, or quick disintegration. However, the function and concept of all these dosage forms are similar. By definition, a solid dosage form that dissolves or disintegrates quickly in the oral cavity resulting in solution or suspension without the need for the administration of water is known as an oral fast-dispersing or fast-dissolving dosage form (Ghodake et al., 2013). Moreover, fast-dissolving oral films (FDOFs) are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improves the efficacy of active pharmaceutical ingredients by dissolving within the minute in oral cavity after the contact with saliva (Siddiqui et al., 2011). Siddiqui et al. (2011) added that oral thin film is a great prospective for drug manufacturers for it satisfies the need of the patients.

Keshavarao (2011) stressed that oral films are soluble in water at room temperature and must break up within 30 seconds and disappear in one minute. He added that the faster the drug goes into the solution, the quicker its absorption and onset of clinical effect. By altering the

condition and formulation factors, it is possible to slow down or speed up dissolving rate in the mouth. In another study performed by Arya et al. (2010), he claimed that the delivery system consists of a thin film by which dissolves within seconds after placing on top of the tongue, avoiding first-pass metabolism and may increase the bioavailability of the drug. Furthermore, Dixit (2009) stated in his work that the accessibility of larger surface area leads to quick disintegration and dissolution in the oral cavity within seconds due to rapid wetting by saliva. The large surface area available in the film dosage form allows rapidly wetted by saliva then quickly disintegrates and dissolves, and is absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism and increase the bioavailability (Bhyan, 2011). Suresh and Quick (2006) mentioned that this dosage form may be available in various sizes and shape, has an excellent mucoadhesion, and has fast disintegration and rapid-release property.

Demand for fast-dissolving oral films has been identified for a variety of reasons: it represents the category of dosage forms that offers high patient compliance, especially for patients having difficulty in swallowing or chewing; oral administration of a drug can be made without the use of water and, hence, can be taken anywhere anytime; very good substitute for the liquid dosage forms, hence is suitable for pediatric and geriatric patients; devoid of friability problems associated with orodispersible tablets (Patel, 2013). Likewise, Ghodake et al. (2013) elaborated that oral-dissolving film is flexible so they are not as fragile and need not any kind of special package for protection during transportation and storage as compared to fast-dissolving tablets. The novel also ensures no fear of choking as compared to fast-dissolving tablets. Patients suffering from dysphagia, repeated emesis, hypertension, heart attack, asthma, motion sickness, paralysis, and mental disorders prefer this dosage form, as they are not capable to swallow large quantities of water. However, the disadvantage of oral thin film is that high dose cannot be incorporated into the strip and that it is moisture-sensitive (Siddiqui et al., 2011).

2.1.2. General Composition of an Orally-Fast Dissolving Film

The generalized composition of the system according to Ghodake et al. (2013) is enumerated in Table 1. He stated that mouth-dissolving film is a thin film with an area of 2 to 8 cm^2 containing an active ingredient. The immediate dissolution in water or saliva is reached through a special matrix from water- soluble polymers. Drugs can be incorporated up to a single dose of 30 mg.

Components of Mouth-Dissolving Film Include

1. Active Pharmaceutical Ingredient

Active pharmaceutical substance can be from any class of pharmaceutically active substances that can be administered orally or through the buccal mucosa. The selected drug should possess the following characteristics: (1) should have pleasant taste, (2) has low dose generally less than 30 mg, (3) smaller and moderate molecular weight should be preferable, (4) stable and soluble in water as well as in saliva, (5) partially unionized at the pH of oral cavity, (6) and has the ability to permeate oral mucosal tissue.

2. Water-soluble polymers

Water-soluble polymers achieve rapid disintegration, good mouth feel, and mechanical properties to the films. The disintegration rate of the polymers is decreased by increasing the molecular weight of polymer film bases. Some of the water-soluble polymers used as film former are HPMC E-3 and K-3, methyl cellulose A-3, A- 6 and A-15, pullulan, carboxymethyl-cellulosecekol 30, polyvinylpyrollidone K-90, pectin, gelatin, sodium alginate, hydroxypropylcellulose, polyvinyl alcohol, maltodextrins and eudragit-RD10 (Gavascar & Israel, 2009).

3. Plasticizers

Formulation considerations made with regard to the use of plasticizers have been reported as important factors affecting mechanical properties of films. The mechanical properties such as tensile strength and elongation to the films have also been improved by the addition of plasticizers. Variation in their concentration may affect these properties. The commonly used plasticizers are glycerol, di-butylpthallate, and polyethylene glycols etc.

4. Saliva-Stimulating Agent

More saliva production helps in the faster disintegration of fast-dissolving film formulations. Citric acid, malic acid, lactic acid, ascorbic acid, and tartaric acid are few examples of salivary stimulants, citric acid being the most preferred among them (Israel, 2009).

5. Flavoring Agents

Flavoring agents can be selected from synthetic flavor oils, oleo resins, extract derived from various parts of the plants like leaves, fruits, and flowers. Flavors such as essential oils or water-soluble extracts of menthol, intense mints such as peppermint, sweet mint, spearmint, wintergreen, cinnamon, clove, sour fruit flavor such as lemon, orange or sweet

confectionary flavors such as vanillin, chocolate, or fruit essence like apple, raspberry, cherry, and pineapple. The amount of flavor needed to mask the taste depends on the flavor type and its strength (Shimoda, 2009).

6. Sweetening Agents

The classical sources of sweetener are sucrose, dextrose, fructose, glucose, liquid glucose, and isomaltose. Artificial sweeteners have gained more popularity in pharmaceutical preparations. Saccharin, cyclamate, and aspartame are the first generation of the artificial sweeteners followed by acesulfame K, sucralose, alitame, and neotame which fall under the second generation artificial sweeteners (Gohel, 2010 & Nishimura, 2009).

7. Coloring Agents

Food Drugs & Cosmetics approved coloring agents are used (not exceeding concentration levels of 1 %); w/w in the manufacturing of orally-fast dissolving films.

8. Surfactants

Surfactants act as solubilizing or wetting or dispersing agent in the formulation so the film gets dissolved within seconds and releases active agent quickly. Some of the commonly used surfactants are sodium lauryl sulfate, benzalkonium chloride, tweens etc. One of the most important surfactant is polaxamer 407 that is used as solubilizing, wetting, and dispersing agent.

Table: 1 Generalized Detail of Different Ingredients of Oral Film

Ingredients	Amount(s) (w/w)
Drug (API)	5-30%
Water soluble polymer	45%
Plasticizer	0-20%
Saliva stimulating agent	2-6%
Surfactant	Q.S.
Sweetening agent	3-6%
Flavorant	Q.S
Colorant	Q.S.
Filler	Q.S

In this consideration, studies have been done on absorption, distribution, metabolism, and excretion. After absorption, a drug attains therapeutic level and therefore elicits pharmacological effect, so both rate and extent of absorption are important. In conventional dosage forms such as oral tablets, there is delay in disintegration and dissolution while orally fast-dissolving films rapidly disintegrate in oral cavity. Therefore, as a consequence, it

records faster dissolution. As a result of this increase in the disintegration rate of orally-fast dissolving film in the mouth, absorption is started from the mouth, pharynx, and esophagus. Some factors like age, gastrointestinal pH, and blood flow through gastrointestinal tract are taken into consideration. Drug distribution depends on many factors like tissue permeability, perfusion rate, binding of drug to tissue, disease state, drug interaction etc. (Ghodake et al., 2013).

With all this information known from an orally fast-dissolving film, a good candidate of a drug to utilize this dosage form is one that disintegrates at a slow rate, and a drug which has an indication for a condition which needs to have an immediate pharmacologic action, such as an antihistamine, antihypertensive, antidiabetic, and antiangina.

2.1.3. Diphenhydramine hydrochloride

Pharmacokinetic Profile

Diphenhydramine Hydrochloride is a histamine H1 antagonist which has a molar mass of 255.355 g/mol having the chemical name of 2- (Diphenylmethoxy)-N,N-dimethylethylamine hydrochloride and molecular formula of $C_{17}H_{21}NO \bullet HCl$. Diphenhydramine Hydrochloride occurs as a white, crystalline powder and is freely soluble in water and alcohol with a pH of 4.0 to 6.5. It is used as an antiemetic, antitussive, for dermatoses and pruritus, for hypersensitivity reactions, as a hypnotic, an antiparkinson, and as an ingredient in common cold preparations. Also, it has some undesired antimuscarinic and sedative effects. Diphenhydramine Hydrochloride is used to treat sneezing, runny nose, watery eyes, hives, skin rash, itching, and other cold or allergy symptoms (Hassan, 2015).

Diphenhydramine hydrochloride has the salt form if hydrochloride, an ethanolamine and first-generation histamine antagonist with anti-allergic activity. Diphenhydramine Hydrochloride competitively blocks H1 receptors, thus preventing the actions of histamine on bronchial smooth muscle, capillaries, and gastrointestinal smooth muscle. This prevents histamine-induced bronchoconstriction, vasodilation, increased capillary permeability, and GI smooth muscle spasms (Hassan, 2015).

Absorption

The currently available formulation of Diphenhydramine Hydrochloridecapsule appears to be reliably and almost completely absorbed in the systemic circulation after oral administration but has only a 40 to 60% of bioavailability due to first-pass metabolism. The onset of the

drug is within 15 to 30 minutes after administration and lasts for less than 12 hours if it is histamine- induced flare suppression and less than 10 hours if histamine-induced wheal suppression. Peak serum time of Diphenhydramine Hydrochloride is two hours (Watson, 1999).

Distribution

The drug is widely distributed throughout the body, crosses the placenta then deposited as breast milk, although the extent of distribution into milk has not been quantitated. Also, it is able to pass through the blood-brain barrier. The blood-brain barrier (BBB) is the system of brain microvascular endothelial cells (BMVEC) that protects the brain from toxic substances in the blood, supplies the brain tissues with nutrients, and then filters the harmful compounds from the brain back to the bloodstream. Volume of distribution is found to be 3.28 L/kg and plasma protein binding is 85 to 98% (Watson, 1999).

Highest concentrations of the drug were detected in the lungs, spleen, and brain in rats; however, small amounts were detected in the heart, muscle, and liver. It is also seen that the volume of distribution in Asian adults (about 480 L) is larger than in white adults (188 to 336 L). Less extensive protein binding reported in healthy Asian adults and in adults with liver cirrhosis (Watson, 1999).

Metabolism

Published journals show that diphenhydramine hydrochloride follows first-pass metabolism upon oral administration of the drug. In one study, data showed evidence that there was 50% of the drug being metabolized before reaching the systemic circulation. In comparison with the intravenous route of administration, the drug is found to be 100% bioavailable. Diphenhydramine is metabolized to nordiphenhydramine (active metabolite), dinordiphenhydramine, and diphenylmethoxyacetic acid. Presystemic metabolism is noted to be 50% and metabolism is reported extensively metabolized by the liver. As diphenhydramine is extensively metabolized by the liver, caution should be exercised when giving the drug to individuals with hepatic impairment (Watson, 1999).

Eliminatio

The unchanged portion of the dose and metabolites are excreted in the urine for 24 to 48 hours. The plasma half-life is 8.5 ± 3.2 hours; shorter half- lives were reported for

children and longer half-lives were reported for adults and the elderly. Fifty to seventy percent of the drug is excreted in the urine mainly as metabolites (Watson, 1999).

2.1.4. Solvent Casting Method

Many studies stated that orally fast-dissolving films are most preferred to be made through solvent casting method. Siemman (2005) stated that the solvent casting method is the oldest technology in the manufacture of plastic films. The continuous solvent cast process was developed more than a hundred years ago driven by the needs of the emerging photographic industry and is now being used in the formulation of orally fast-dissolving films. Nowadays, solvent cast technology is becoming increasingly attractive for the production of films with extremely high-quality requirements.

Water-soluble ingredients are dissolved to form a clear viscous solution and then the other ingredients are added in small amounts. Afterwards, the bulk drug is then added. The preparation is put in an oven at a constant temperature, and finally the solution is cut into the preferred size. The water-soluble ingredients help in the goal to improve the dissolution of diphenhydramine hydrochloride and an ease of administration due to its application in the oral route.

In order to produce an effective orally fast-dissolving film, the polymer utilized in the formulation must be nontoxic, nonirritant, hydrophilic, should have excellent film-forming capacity, good wetting and spreadability property, must be readily available, economically inexpensive, must have low molecular weight, and have sufficient shelf-life. It must also be tasteless, colorless, does not cause any secondary infection in oral mucosa and must exhibit adequate peel, shear, and tensile strengths. And to demonstrate if these properties have been established, various tests must be performed to assess if the newly formulated orally fast-dissolving film possesses good pharmacokinetic properties, and thus yield better bioavailability than commercially available oral capsules and tablets (Thakur, Bansal, Sharma, Yadav, & Khare, 2013).

According to the study conducted by Kumar et al. (2013), solvent casting method is the dissolution of the water-soluble polymer in water to form a clear viscous liquid solution. Simultaneously, diphenhydramine hydrochloride is weighed accurately and dissolved in distilled water. Other ingredients are dissolved in different containers with lesser amounts of the solution and are then combined with the majority of the dissolved liquid solution. The

resulting solution is then formed as a film and is allowed to dry, which is then cut into pieces of the desired size. The preferred finished film thickness is 12 to 100µm, although various thicknesses are probably to meet the dissolution needs. This method is performed because of its many advantages. Although it has its own disadvantages, these can be altered for the best outcome. Some of the advantages and disadvantages are as follows.

Advantages

1. The film has better consistency of thickness and better clarity than extrusion.
2. The film has fine gloss and it is free from flaws such as die lines.
3. The film has more flexibility and better physical properties.

Disadvantages

1. The polymer must be soluble in a volatile solvent or water.
2. A stable solution with a practical minimum solid content and viscosity should be formed.
3. Formation of a homogeneous film and release from the casting support must be possible.

Solvent casting method is primarily used in the production of orally fast- dissolving films because the film pH should be kept in mind while performing the method. Not only is the pH an important factor in the evaluation of the film but also its thickness and folding endurance. According to Shweta Kalyan and Mayank Bansal (2012), the surface pH of the oral-dissolving film is identified in order to investigate the risk of any side effects in-vivo. Since acidic or alkaline pH may cause irritation to the oral mucosa, it is determined to maintain the surface pH as close to neutral as possible. The test conducted by wetting the oral film slightly with water and the pH is measured by bringing the electrode in contact with the surface of the oral film.

The thickness of the orally fast-dissolving film is an important factor in the determination of the drug content uniformity and ideally should be maintained. Uniform and consistency should always be followed in the preparation of the orally fast-dissolving films.

The folding endurance is measured manually for the prepared films. A strip of film is cut and repeatedly folded at the same place till it brakes. According to Saini, Nanda, and Dhari, (2011), the number of times the film could be folded at the same place without breaking gives the value of folding endurance.

2.1.5. Drug-Excipient Compatibility Studies

Excipients are integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage form depends on the careful selection of excipients. In order to develop stable, safe, and effective dosage forms, the formulation scientist characterizes the physical, chemical, and mechanical properties of new drug substances. During this evaluation, possible interaction with various inert ingredients intended for use in final dosage form is considered. Assessment of possible incompatibilities between an active drug substance and different excipients plays an important part of the formulation stage during the development of solid dosage form. Fourier Transformer Infra Red Spectrum (FTIR), Differential Scanning Calorimeter (DSC), Thin Layer Chromatography (TLC) and X Ray Diffraction (X-RD) can be used to assess possible drug-excipient interaction.

2.1.6. Quality Control Test for Physical Properties of the Orally Fast- Dissolving Film

The first quality control test to determine the physical property of an orally fast-dissolving film is an inspection of its visual properties such as homogeneity, color, transparency, and surface of the oral films.

Secondly, morphology study, which determines the difference between the upper and lower side of the film, by using the scanning electron microscope (SEM) at a definite magnification. A weight variation test must be performed to ensure average weight uniformity.

A film thickness evaluation must also be performed since the thickness of film is directly related to the drug content uniformity; it is necessary to ascertain uniformity in the thickness of the films produced. It can be measured by micrometer screw gauge or calibrated digital vernier calipers.

The fifth test is a surface pH test for the orally dissolving film and this is determined to investigate the possibility of any side effects in-vivo. A combined pH electrode may be used for this purpose.

2.1.7. Mechanical Properties of the Film

Folding endurance test gives an indication of brittleness of the film. It is determined by repeated folding of the strip at the same place till the strip breaks. The number of times the

film is folded without breaking is computed as the folding endurance value (Koland et al., 2010).

Percent moisture uptake test is carried out to check the physical stability of the film at high humid conditions (Koland et al., 2010).

2.1.8. Pharmacokinetic Evaluation Studies

Assay for Drug Content and Content Uniformity is determined through the standard assay method using UV-Vis spectrophotometer.

Disintegration time determination is the variable directly related to the efficacy of the orally fast-dissolving film in delivering the active pharmaceutical ingredient (API) within the site of administration. However, there has been no official guideline available for orally fast-dissolving films. In lieu of this, an orally disintegrating tablet's information is utilized, wherein the time limit is ideally 30 seconds or less.

An *In-vitro* dissolution study may be performed by the use of USP Type-1 basket apparatus.

A stability study must be performed to determine the stability of the orally fast-dissolving film formulated. During storage period, various evaluating parameter like thickness, morphological properties, and dissolution behavior are checked.

Lastly, an in-vivo study design can be formulated to determine the concentration of drug and its effect on the subject made to take the orally fast- dissolving film formulated. This may be done by collecting blood samples at pre-determined time intervals (Kalyan & Bansal, 2012).

2.1.9. Recent Studies to the Application of Orally Fast-Dissolving Film as a Dosage Form

Based on the study of Siddiqui et al., (2011), each pharmaceutical company aims to formulate the novel oral dosage form, which has the higher bioavailability, quick action, and most patient compliance. So they formulate fast-dissolving tablets by using superdisintegrants and hydrophilic ingredients. In North America more than 80 oral thin film brands have been launched since 2003.

The market remains limited when compared to orally fast dissolving tablets. However, for future growth point of view the oral thin film (OTF) sector is well positioned. In the US market, OTC films for pain management and motion sickness are commercialized. Bhyan et al. (2011) mentioned that these are some of the commercially available orally fast-dissolving films products: Triaminic (Dextromethorphan HBr) by Novartis, Theraflu (Diphenhydramine HCl) by Novartis, Gas-X (Simethicone) by Novartis, Sudafed (Phenylephrine HCl) by Pfizer, Benadryl (Diphenhydramine HCl) by Pfizer, Chloraseptic (Benzocaine Menthol) by Prestige, Suppress (Menthol) by Innozen, Orajel (Menthol/Pectin) by Del, and Listerine (Cool mint) by Pfizer. Siddiqui et al. (2011) added that prescription OTFs have now been approved in the United States, the European Union, and Japan, which are the three major regions. These approved prescription films have a potential to dominate over other oral dosage forms of the same drugs. It seems that the value of the overall oral thin film market will grow significantly.

2.2 RESEARCH QUESTIONS

According to Reddy et al. (2013), the release and solubility of a drug molecule may becritical factorsin determining its usefulness since the solubility dictates the amount of compound that will dissolve and therefore the amount available for absorption. If a compound has slow and low water solubility, it may be subjected to dissolution rate limited absorption within the gastrointestinal residence time. One of the drug classifications which are a great candidate to be formulated into an orally fast-dissolving film is an antihistaminic drug for immediate action is desired for this drug and immediate relief is necessary.

In line with this, the general research question that the group aimed to answer is: What formulation ratio and excipient combination will yield the best film in terms of its organoleptic appearance?

And in relation to this general problem, the group also aimed to determine whether the oral film formed can contain and release the active ingredient incorporated in the dosage form.

CHAPTER: 3 RESEARCH METHODS

3.1Research Diagram

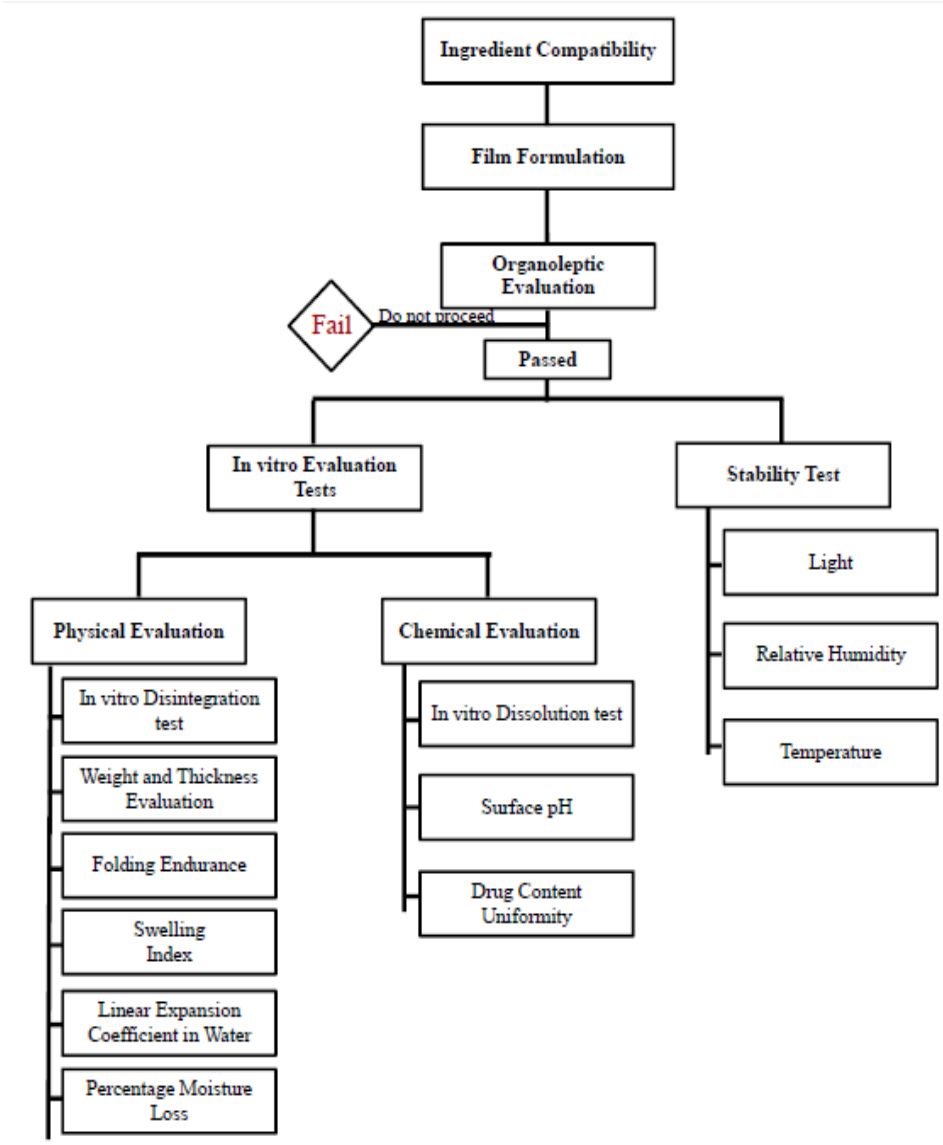


Figure 1: Research Diagram of the Research Methods

3.2 METHODS AND MATERIAL

3.2.1 Diphenhydramine Hydrochloride and Excipients

The researchers acquired the USP grade active ingredient Diphenhydramine Hydrochloride with a Certificate of Analysis from MDLD Interchemical Industries, Inc., and the analytical grade excipients from Belman Laboratories and Laboratory Equipment and Supplies Office (LESO) of the University of Santo Tomas.

The description and use of each excipient is as follows:

Table 2. Description and Use of Each Excipient

Excipients	Description	Use
Acacia	White or yellowish-white thin flakes, spheroidal tears, granules, powder, or spray-dried powder. It is odorless and has a bland taste.	Viscosity-increasing agent
Sodium	White to almost white, odorless,	Disintegrating agent and water
Citric acid monohydrate	Colorless or translucent crystals, or as a white crystalline, efflorescent powder. It is odorless and has a strong acidic taste. The crystal structure is orthorhombic.	Saliva-stimulating agent
FD&C approved coloring agents	Artificial colors contain various chemicals and are commonly derived from petroleum products. They are	Colorant
Glycerol	Colorless, odorless, viscous liquid with a sweet taste.	Humectant and plasticizing agent
Malic acid	White or nearly white, crystalline powder or granules having a slight odor and a strongly acidic taste. It is hygroscopic. The synthetic material produced commercially in Europe and the US is a racemic mixture, whereas the naturally occurring material found in apples and many other fruits and plants is levorotatory.	Saliva-stimulating agent
Polyethylene glycol 400	Part of the liquid grades, occurs as a clear, colorless or slightly yellow-colored, viscous liquid. It has a slight but characteristic odor and a bitter, slightly burning taste.	Plasticizing agent and water-soluble polymer
Propylene glycol	Clear, colorless, viscous, practically odorless liquid, with a sweet, slightly acrid taste resembling that of glycerin.	Preservative and plasticizing agent

Saccharin	Occurs as odorless white crystals or a white crystalline powder. It has an intensely sweet taste, with a metallic or bitter aftertaste that at normal levels of use can be detected by approximately 25% of the population.	Sweetening agent
Sodium Lauryl Sulfate	A white powder that lowers surface tension of an aqueous solution	Surfactant
Peppermint oil	Volatile oil distilled with steam from the fresh overground parts of the flowering plant of Menthapiperita Linné (Fam. Labiatae), rectified by distillation and neither partially nor wholly dementholized. It yields not less than 5.0 percent of esters, calculated as menthyl acetate ($C_{12}H_{22}O_2$), and not less than 50.0 percent of total menthol ($C_{10}H_{20}O$), free and as esters.	Flavoring agent
Distilled Water	Colorless and odorless liquid, having the pH of 7 and a boiling point of 100°Cand underwent the process of distillation in removing its impurities.	Solvent, vehicle

3.2.2 Formulation of Orally Fast-Dissolving Film

The group developed 12 different formulations to determine the most suitable combination of ingredients and its corresponding ratio for the optimum output of the oral film. As shown in Table 2, the amount of active ingredient, sweetening agent, saliva stimulating agent, and distilled water is constant in all of the formulations, while the amount of water-soluble polymer and plasticizer is of varying quantities for several formulations.

Table 3. Formulations of Diphenhydramine HCl Orally Fast-Dissolving Film in mg

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Diphenhydramine HCl	25	25	25	25	25	25	25	25	25	25	25	25
CMC	166.67	83.20	124.95		104.16				124.95			104.16
Acacia				124.95		104.16	166.67	83.20		124.95	104.16	
PEG 400	83.20	166.67		124.95		145.83				124.95		145.83
Glycerol			124.95		145.83		83.20	166.67	124.95		145.83	
Saccharin	4.17	4.17	4.17	4.17	4.17	4.17	4.17	4.17	4.17	4.17	4.17	4.17
Citric Acid	25.05	25.05	25.05		25.05					25.05		25.05
Malic Acid				25.05		25.05	25.05	25.05	25.05		25.05	
SLS	74.97	74.97	74.97	74.97	74.97	74.97	74.97	74.97	74.97	74.97	74.97	74.97

3.2.3 Dose Calculation for Oral Film Active Ingredient and Excipients

The amount of each excipient was computed based on the varying ratios the group has decided to assign per formulation, considering the suggested ratio from previous studies. It was then multiplied until a favorable outcome was obtained. The final formulation ratio was then based on the standard concentration of the active ingredient which was 30%, and the excipients were then adjusted to complete the 100% ingredient formulation.

3.2.4 Preparation of Film by Solvent Casting Method

A suitable amount of water was placed in a container and heated up to 75°C. The excipients such as the water-soluble polymer, sweetening agent, saliva-stimulating agent, flavorant, surfactant, and colorant were weighed one by one and added to the heated water while stirring the solution continuously and rapidly. When the solution has already been mixed thoroughly, the active ingredient, diphenhydramine hydrochloride was dissolved in the plasticizer then added into the solution and mixed until homogenous and cooled to room temperature. The final film solution was then transferred to the desired container to be cast and dried in an oven at 70°C. The final outcome was a polymer film. This was based from the study of Kumar et al. (2013), and modified by the group in order to yield a more feasible and desired outcome.

3.3 Analysis

3.3.1 Compatibility of API and Excipients

Compatibility Test

Every excipient was combined with the active pharmaceutical ingredient (API) in 1:1 concentration ratio; and in one preparation, all of the proposed excipients in Table 2

were combined. These preparations underwent Thin Layer Chromatography (TLC) for assessment of the compatibility of each of the excipient with the API

Table 4. One is to One Ratio of API and Excipients

Ingredients	Ratio
Drug (API) + Water soluble polymer	1:1
Drug (API) + Plasticizer	1:1
Drug (API) + Saliva stimulating agent	1:1
Drug (API) + Surfactant	1:1
Drug (API) + Sweetening agent	1:1
Drug (API) + Flavorant	1:1
Drug (API) + Colorant	1:1
Drug (API) + all excipients	1:1

3.3.2 Stability Test for the Orally Fast-Dissolving Film Formed

Stability Test

Stability testing was assessed based upon the exposure of light, relative humidity, and temperature, each having a triplicate of the formulations for 3 months. Visual evaluation, specifically transparency and color, was conducted before each procedure, first month, second month, and third month. After which, the preparations in the first and second month were subjected to Thin Layer Chromatography (TLC) and on the third month, were subjected to Fourier Transformer Infrared Spectrum (FTIR) (Kalyan & Bansal, 2012).

Light

Formulation 3 was contained in amber and flint bottle inside a stability cabinet where the preparations were exposed to light in varying distances from 1, 2, and 3 feet.

Relative Humidity

Formulation 3 was contained in a petri dish wrapped in aluminum foil and was placed in a dessicator with $40^{O}C \pm 2^{O}C/75\%$ RH ± 5% RH. This is according to the ASEAN Guideline on Stability of Drug Product as of May 2013.

Temperature

Each formulation was exposed to cold temperature (2 to 8°C), room temperature (25 to 30°C), and extreme condition (40°C).

3.4 *In-vitro* Evaluation Tests for Orally Fast-Dissolving Film

To assess the physical and chemical characteristics of the orally fast- dissolving film formulated, the group performed different tests as follows:

3.4.1 Physical Tests

***In-vitro* Disintegration Time**

The *In-vitro* disintegration time of orally fast-dissolving films was determined visually in an aluminum container of 25 mL 6.8 pH phosphate buffer with constant swirling action. The disintegration time was determined when the film started to disintegrate. The determination was performed in triplicate and the average value was used (Kalyan & Bansal, 2012).

Weight and Thickness Evaluation

For evaluation of film weight, three films of every formulation weretaken and weighed individually on an analytical balance. The average weights were calculated. Similarly, three films of each formulation were taken and the film thickness was measured using a vernier caliper. The average weights were calculated. The determination was performed in triplicate and the average value was used (Bhura, Sanghvi, Patel, Parmar & Patel, 2012).

Folding Endurance

The folding endurance was determined by repeatedly folding the film at the same place until the film broke. The number of times the film was folded without breaking was the folding endurance value (Bhura et al., 2012).

Swelling Index

After determination of the original film weight, the oral film samples were allowed to swell on the surface of a petri dish kept in an incubator maintained at 37 ± 0.2ºC for 5 hours. The determination was performed in triplicate and the percent swelling, % S was calculated using the equation (Bhura et al., 2012).

$$[\%S] = \frac{Initial\ weight\ of\ swollen\ film\ after\ time\ (t) - Initial\ film\ weight\ at\ zero\ time\ (t/)}{Initial\ film\ weight\ at\ zero\ time\ (t/)} \times 100$$

Linear Expansion Coefficient in Water

The film was immersed in distilled water. The sample was then taken 2,4, 6, 8, 10, 15, 30, and 60 seconds after and the size of side length was measured. The equation used is as follows:

$$L\% = \frac{\text{Side length after immersion (L1)} - \text{side length before immersion (L0)}}{L0} \times 100$$

Percentage Moisture Loss

To determine the percentage moisture loss if the films with an area 2 × 2 cm, two films were cut and weighed accurately on an analytical balance. After weighing, the films were kept in desiccators containing anhydrous calcium chloride. The films were kept for 72 hours in the dessicator. After 72 hours, the films were taken out, weighed again, and the percentage moisture loss of films was measured using the formula:

Percent moisture loss = (Initial weight - Final weight) X 100

4.2. Chemical Tests

***In-vitro* Dissolution Study / Drug Content Uniformity**

The dissolution test procedure for the diphenhydramine hydrochloride oral film was taken from USP 37 of diphenhydramine hydrochloride capsule. The medium used for the dissolution testing was 500 mL distilled water using apparatus 1 (basket apparatus) for 30 minutes in 100 rpm. At the end of the said time period, an aliquot portion of the 5mL of the fluid was withdrawn, and was subjected to UV-Vis spectrophotometer and the concentrations of the sample were calculated and became the basis for the drug release action of the film formulated.

Surface pH test

A Milwaukee pH600 pH tester was used to determine the pH of the oral films. The pH meter was immersed into a solution where the film was made wet; the electrode was put into contact with the film and waited for stabilization of the display. The pH readings were recorded and the electrode was rinsed with water to minimize contamination afterwards.

3.3.3 Statistical Analysis

Only the mean of the results gathered from the different evaluation tests was used to describe the data.

CHAPTER 4: RESULTS AND DISCUSSION

4.1 Compatibility Study of the Excipients

For the compatibility testing of the excipients and active ingredient, the researchers used the samples from the stability tests. Ingredients of the chosen formulation were individually placed in an amber and flint bottle separately. After the duration of the stability tests, the

samples were collected and used for the thin layer chromatography test. The objective of the compatibility test was to compare the samples from the amber and flint bottles whether there was a chemical reaction between the active ingredient and excipient inside its container. According to Pharmaquest, a chemical reaction is positive in a thin layer chromatography test if there is only one spot that was exposed in the TLC plate even if the sample is composed of two ingredients. On the other hand, there is no chemical reaction between the active ingredient and excipient if two spots were seen vertically in the TLC plate. A reference of the excipients and active ingredient results in the TLC plate were also used for comparison with the samples from the stability tests.

Table 5. Comparison of Excipients with the API from Amber and Flint Bottles and their Corresponding Reactions

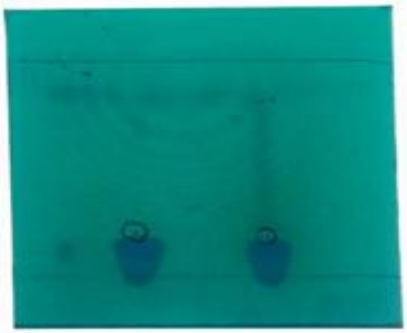
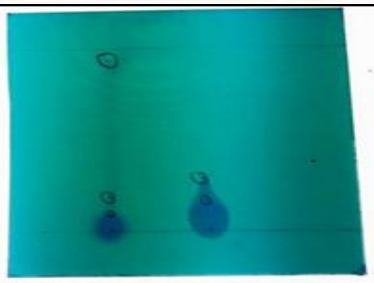
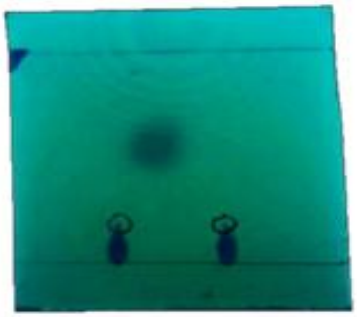
Excipient +Diphenhydramine HCl (API)	Number of Spots from Amber	Number of Spots from Flint	(+) Reaction	(-) Reaction
1. Acacia	1	1	✓	
2. Malic Acid	3	2		✓
3. Carboxymethyl Cellulose	2	2		✓
4. Polyethylene Glycol	1	1		✓
5. Glycerol	2	2		✓
6. Saccharin	2	2		✓
7. Polypropylene Glycol	2	2		✓
8. Citric Acid	2	2		✓
9. Sodium Lauryl Sulfate	2	2		✓
10. Peppermint oil	2	2		✓

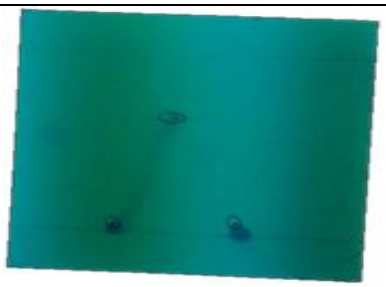
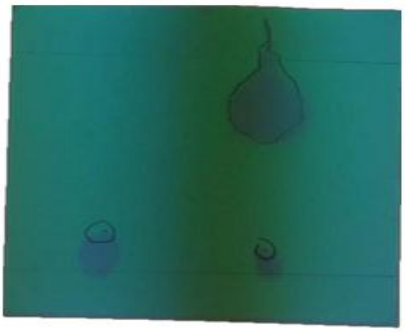
Based on the table, acacia produced only one spot from the amber and flint bottles. This results in the incompatibility of acacia to diphenhydramine hydrochloride. It was then compared to the reference TLC result of pure acacia and it produced almost the same height, meaning there is a reaction between acacia and the active ingredient. Carboxymethyl Cellulose replaced acacia because it did not present any reactions with the API. The possible cause of acacia being incompatible is the methanol used while doing the spotting in the TLC plate. In the process mentioned in the methodology, spotting consists of putting methanol while mixing with the ingredient. While doing this process, the methanol reacted with acacia producing only one spot in the TLC plate. According to rxistsource, pharmaceutical incompatibility with acacia includes alcohol or any alcoholic precipitate. It is when the alcohol amounts to more than about 50% of the total volume that the solution is affected by dilution with water. This renders the compatibility test of acacia and

diphenhydramine HCl false negative since methanol and ethyl acetate were used during the TLC test and it may have been a catalyst for a chemical reaction.

Hence, all of the excipients in Table 5 are compatible with diphenhydramine HCl.

Table 6. Comparison of Excipients with the API from Amber and Flint Bottles and their Corresponding Physical Reactions.

Excipient	Amber (Left); Flint (Right)
CMC	
PPG	
PEG	
Citric Acid	

Glycerol	
Diphenhydramine HCl (left) Peppermint (right)	
Saccharin	

The table of the list of excipients shows that all of the ingredients except acacia have two or more spots that signify no interaction between diphenhydramine HCl and each of the ingredients. Acacia was not used in the formulation that was chosen because of the seen interaction with methanol.

4.2 Film Formulation

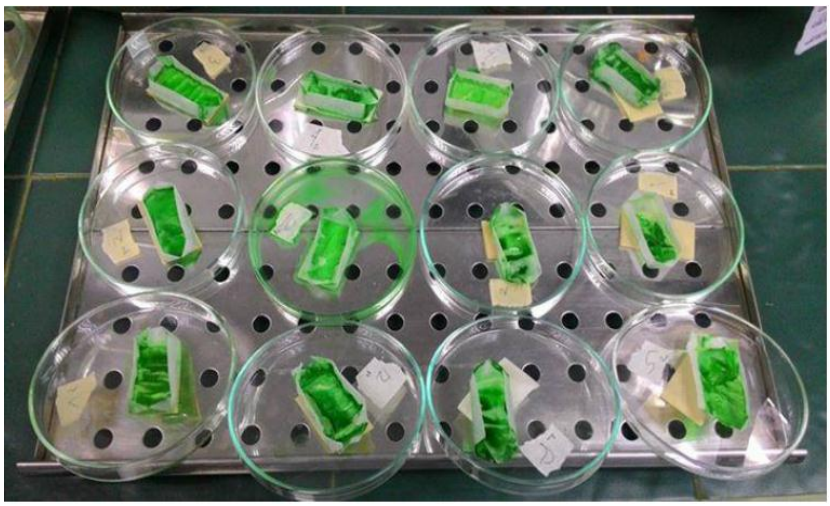


Figure: 2 Actual 12 Film Formulation Stips

Among the 12 formulations developed, three good potential films were produced; namely, Formulation 3, 9 and 12. But after repeating the methods, only Formulation 3 was able to produce consistent results. Formulation 3 yielded the acceptable physical film characteristics.

4.3 Organoleptic Evaluation

The group chose the film formulation based solely on organoleptic evaluation, such as film appearance, texture, consistency, and scent.

4.4 *In-vitro* Evaluation Tests for the Orally Fast-Dissolving Films

4.4.1 Physical Tests

***In-vitro* Disintegration Time**

Disintegration time is the time when an oral film starts breaking when brought to contact with water or saliva. Disintegration time for fast-dissolving oral strips varies depending on the formulation, but typically the disintegration range is from 5 to 30 seconds, although no official guidance is available for oral fast disintegrating films strips (Bhyan et al., 2011). The film, after subjecting to phosphate buffer, produced a disintegration time of 32.63 to 41.88 seconds having an average of 35.96 seconds.

Weight and Thickness Evaluation

The weight and thickness of the film were evaluated to determine the uniformity of the formulation. The film, after being weighed four times, produced a reading of 0.3232 to 0.0.3358 g having an average of 0.3299 g. The film was also measured to be 0.347-0.362 mm thick having an average of 0.354 mm.

Folding Endurance

The folding endurance of the film was determined to be 18 to 24 folds having an average of 20.5 folds.

Swelling Index

The weight of the film was determined before and after it was subjected to swelling and was then calculated giving a percent swelling index of 16.00 to 58.00% having an average of 31.25%.

Linear Expansion Coefficient in Water

After being immersed in water, the film retained the size of its side length in 2, 4, 6, 8, 10, and 15 seconds, but was measured to have a linear expansion coefficient of 0.04 to 0.12%

having an average of 0.06% at 30 seconds, and a linear expansion coefficient of 0.20 to 0.32% having an average of 0.23% at 60 seconds.

Percentage Moisture Loss

The film was measured to have a moisture loss of 2.10 to 168.84% having an average of 57.0%.

4.4.2 Chemical Tests Drug Release Via *In-vitro* Dissolution and Drug Content Uniformity

Table: 7. Absorbance and Concentration of Samples

Absorbance Value of 25mg Diphenhydramine Hydrochloride Oral Film (220nm)	Concentration of 25mg Diphenhydramine Hydrochloride Oral Film	Percentage of Drug Released from the Oral Film
0.825	0.0463 mg / mL	92.60%
0.785	0.0441 mg / mL	88.20%
0.788	0.0442 mg / mL	88.40%
0.795	0.0446 mg / mL	89.20%
Mean:	**0.0413 mg / mL**	**89.60%**

After performing dissolution testing, the test samples were subjected to UV-VIS analysis and the following absorbances were collected as stated in Table 7. To be able to determine the amount of drug released from the oral film, the researchers derived the formula:

$$\frac{Absorbance\,of\,Sample}{Absorbance\,of\,Standard} = \frac{Concentration\,of\,Sample}{Concentration\,of\,Standard}$$

where the sample and standard were the oral film and pure diphenhydramine hydrochloride, respectively. The standard used has an absorbance value of 0.891 and a concentration of 0.05 mg/mL. A mean of 89.60% of the drug was released from the film. As seen in Table 7, the drug concentration was close to one another defining the film's drug content uniformity, thus signifying the repeatability of the formulation.

Surface pH

Table 8. Surface pH of Oral Films

Film 1	4.6
Film 2	4.1
Film 3	4.2
Film 4	4.2
Mean	**4.28**

Using the Milwaukee pH meter, the following pH were measured as stated in Table 8. The mean pH of the film was 4.28 which, according to Hassan (2015) is within the pH range of the suitable vehicle for diphenhydramine HCl which is 4 to 6.

4.5 Stability Testing for the Orally Fast-Dissolving Film

Stability studies were performed with the film Formulation 3 wherein it was subjected to varying measures of light, temperature, and relative humidity. The results were characterized through physical and chemical parameters of stability studies.

The objective of the physical parameter of the stability study was to observe, if there would be changes in the appearance of the oral film from the initial period to the third month. As for the chemical parameter of the stability study, the objective was to confirm if diphenhydramine hydrochloride was present during the initial period to the third month through the use of Thin Layer Chromatography (TLC) that qualitatively measures the presence of diphenhydramine hydrochloride.

Table:9. Storage Condition and Schedule of Stability

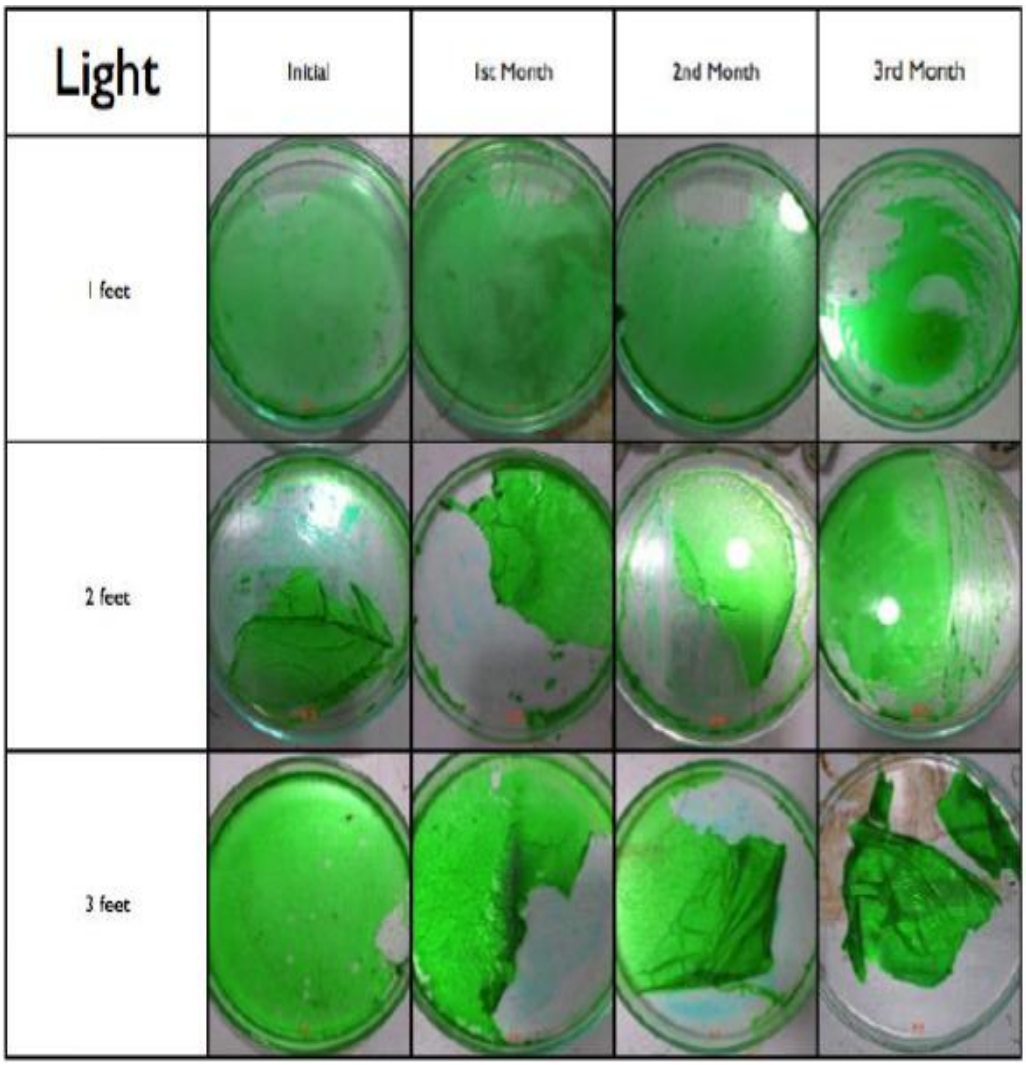
Storage		Schedule			
		Film Number			
Period	Condition	0	1	2	3
initial	accelerated	Aug. 14 2015	Sep.12 2015	Oct.12 2015	Nov. 3 2015
first month	accelerated	Aug. 14 2015	Sep.12 2015	Oct.12 2015	Nov. 3 2015
Second month	accelerated	Aug. 14 2015	Sep.12 2015	Oct.12 2015	Nov. 3 2015
Third month	accelerated	Aug. 14 2015	Sep.12 2015	Oct.12 2015	Nov. 3 2015

4.5.1 Light

From the initial period to the first month, the film presented the same color, same smooth texture with significant peppermint scent on all temperature ranges. On the second month, the film presented the same color, moisture was observed on the film and significant peppermint

scent was still observed on all ranges but on the third month, the films on all ranges presented a tacky texture and diminished peppermint smell.

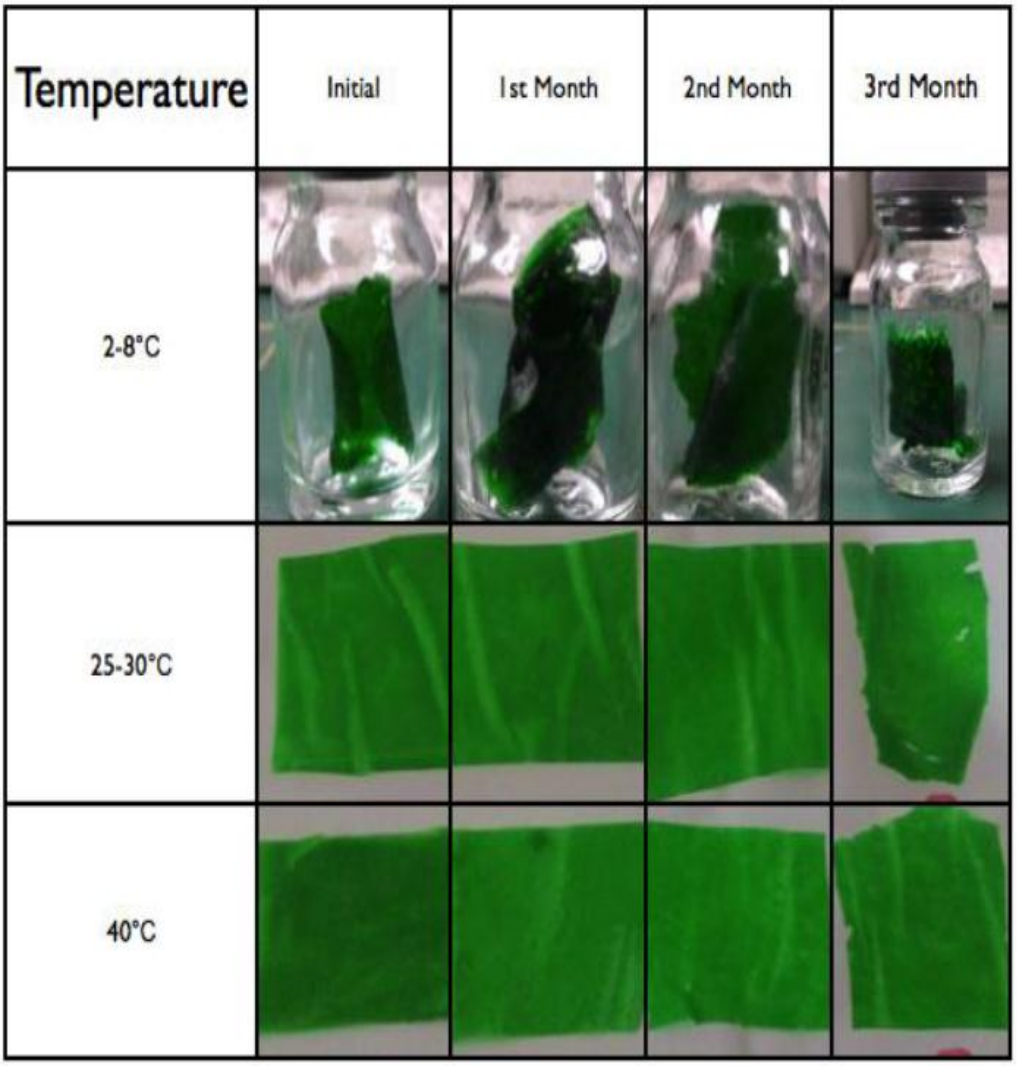
Table: 10. Physical Test for Oral Film through Light under the Stability Cabinet for Three Months with Varying Heights of 1, 2 and 3 Feet



The oral film is physically stable in the first 2 months, having the same color, texture and significant peppermint scent regardless of varying heights but at the second month moisture is already observed at the first feet while the second and third feet have the same texture as the initial. The film is rendered physically unstable on the third month due to absorbance of moisture and loss of peppermint scent.

4.5.2 Temperature

Table: 11. Physical Test for Oral Film through Temperature for Three Months with Varying Temperatures of 2-8°C, 25-30°C and 40°C

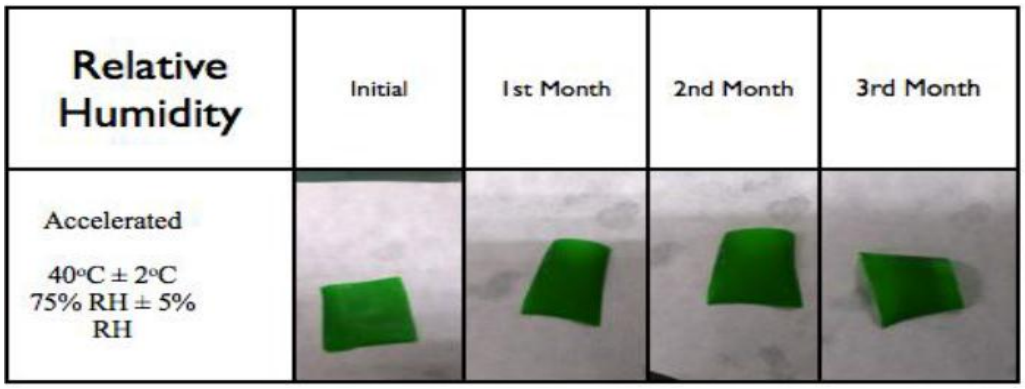


From the initial period to the first month, the film presented the same color, same smooth texture with significant peppermint scent on all temperature ranges. On the second month, the film presented the same color, texture, and significant peppermint scent was still observed on all ranges but the 40°C film presented a tacky texture. On the third month, the same color was still observed on all ranges, the same texture and significant peppermint scent was still observed in 2 to 8°C and 25 to 30°C film. The 40°C film swelled and had a diminished peppermint scent.

The oral film is physically stable at temperatures of 2 to 8°C and 25 to 30°C but physically unstable to 40°C.

4.5.3 Relative Humidity

Table:12. Physical Test for Oral Film through Relative Humidity for Three Months Using Accelerated Study (40^{o}C ± 2^{o}C 75% RH ± 5% RH)



From the initial period to the second month, the film presented the same color, same smooth texture with significant peppermint scent, while on the third month, the film present the same color, but with a tacky texture and diminished peppermint scent.

The oral film on the third month is physically unstable due to loss of scent and absorbance of moisture making the film susceptible to microbial growth.

Table:13. Chemical Test for Oral Film through Light Using TLC

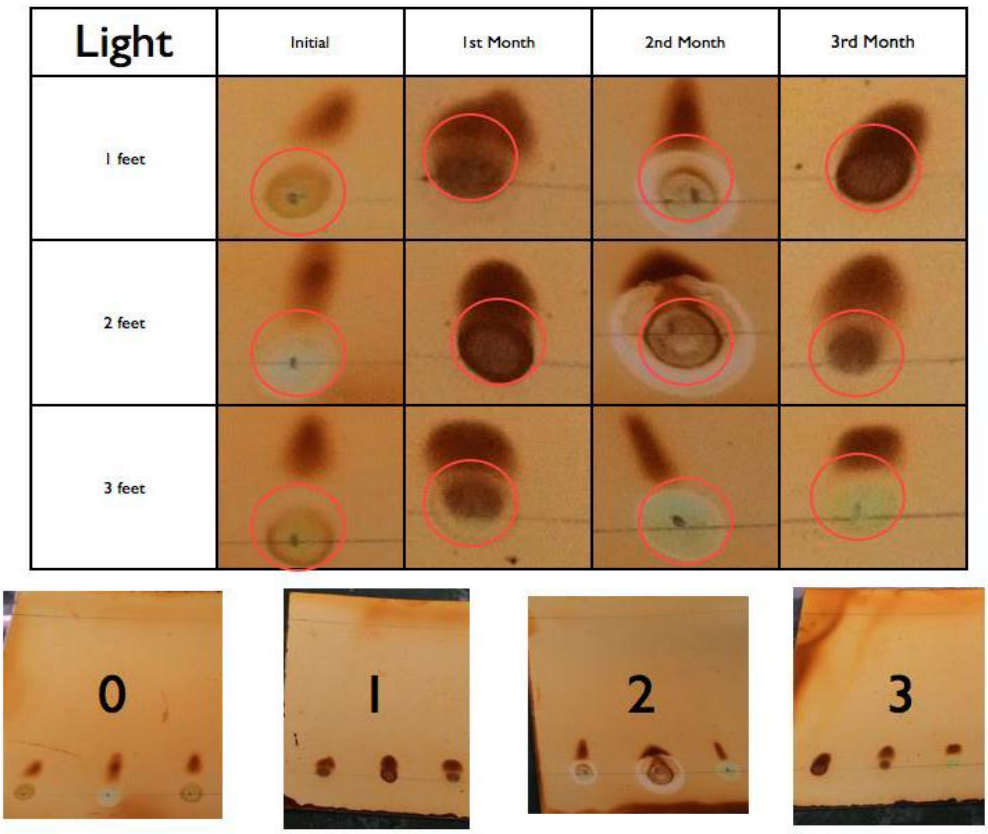
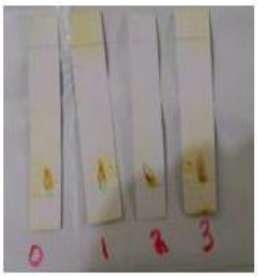


Table:14. Chemical Test for Oral Film through Temperature Using TLC

Temperature	Initial	1st Month	2nd Month	3rd Month
2-8°C				
25-30°C				
40°C				

Table: 15. Chemical Test for Oral Film through Relative Humidity Using TLC

Relative Humidity	Initial	1st Month	2nd Month	3rd Month
Accelerated 40°C ± 2°C 75% RH ± 5% RH				



The chemical tests (light, temperature, and relative humidity) confirmed the presence of diphenhydramine hydrochloride. Diphenhydramine hydrochloride is considered a moderately polar compound, while the excipients used were less polar than diphenhydramine hydrochloride. Therefore, it is expected that diphenhydramine hydrochloride would stick more tightly to the TLC plate and not move freely to the top, while the less polar excipients would move away from the bottom towards the top.

The oral film is therefore chemically stable under the varying influence of light, temperature, and relative humidity during the 3-month duration of the stability study.

4.6. Identification of Diphenhydramine Hydrochloride using Fourier Transformer Infra Red Spectrum (FTIR)

Fourier Transformer Infra Red Spectrum (FTIR) was used as a qualitative fingerprint check for the identity of raw material for identifying drugs used (Watson, 1999).

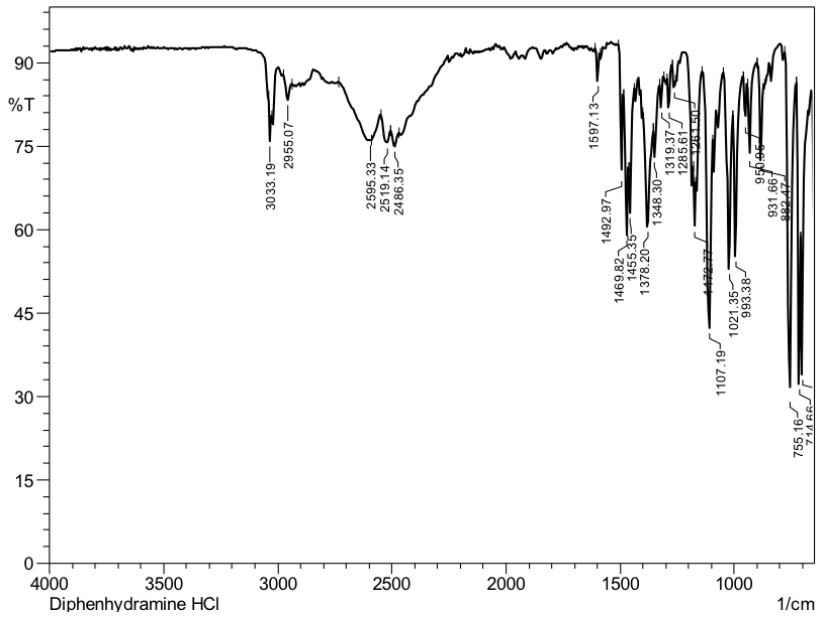


Figure 3.FTIR Analysis of Diphenhydramine Hydrochloride

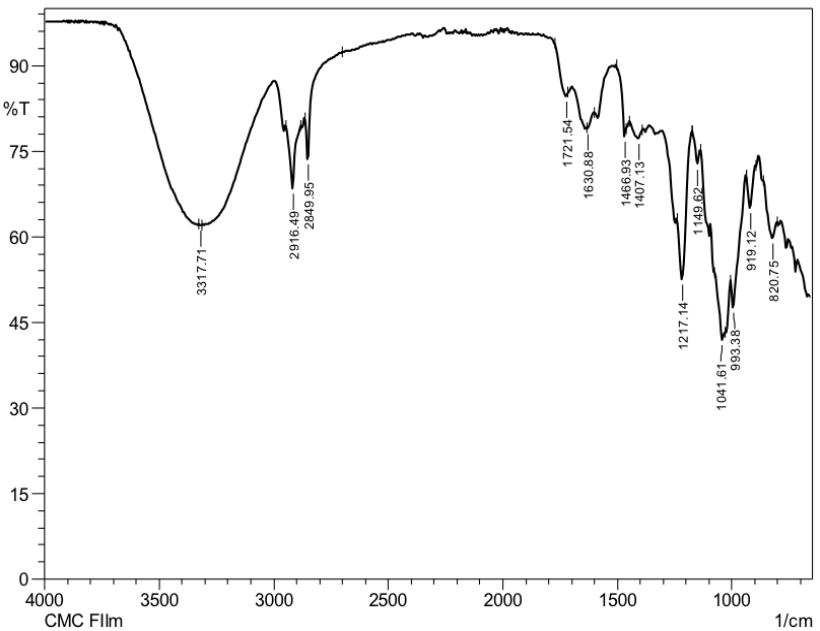


Figure 4. FTIR Analysis of Oral Film at the Initial Period Under Light Parameter

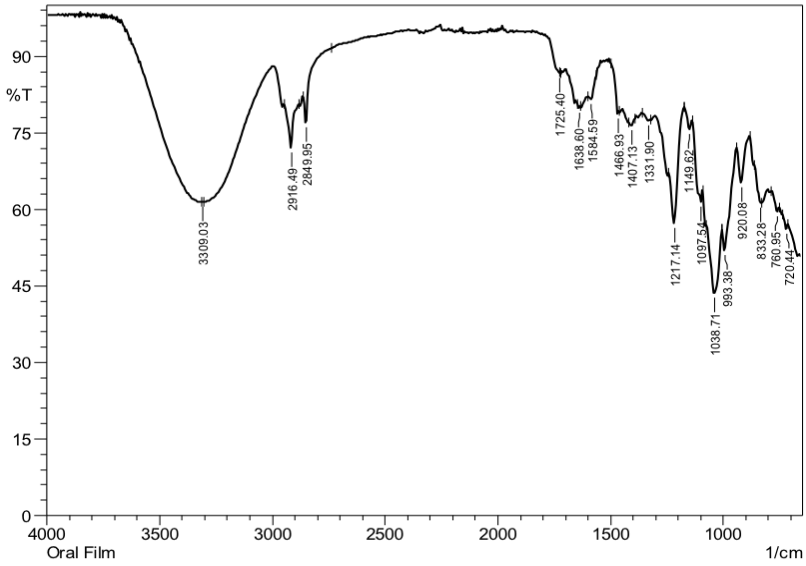


Figure: 5. FTIR Analysis of Oral Film at the Third Month Under Light Parameter

DOCUMENTATION OF EXPERIMENTATION

Figure 6. Film subjected to phosphate buffer with a pH of 6.8.

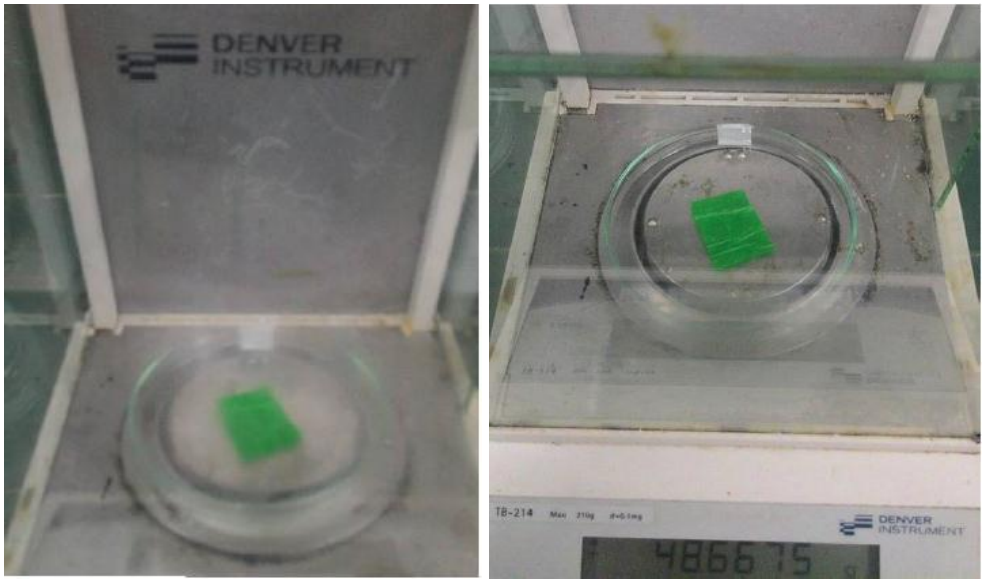


Figure 7. Weight and thickness Evaluation.

Swelling index

Figure 8. The films subjected to swelling in a petri dish and left in the Memmert oven.

Linear Expansion Coefficient In Water

Figure 9. Preparation of the films for linear expansion coefficient testing in water

Percentage Moisture Loss

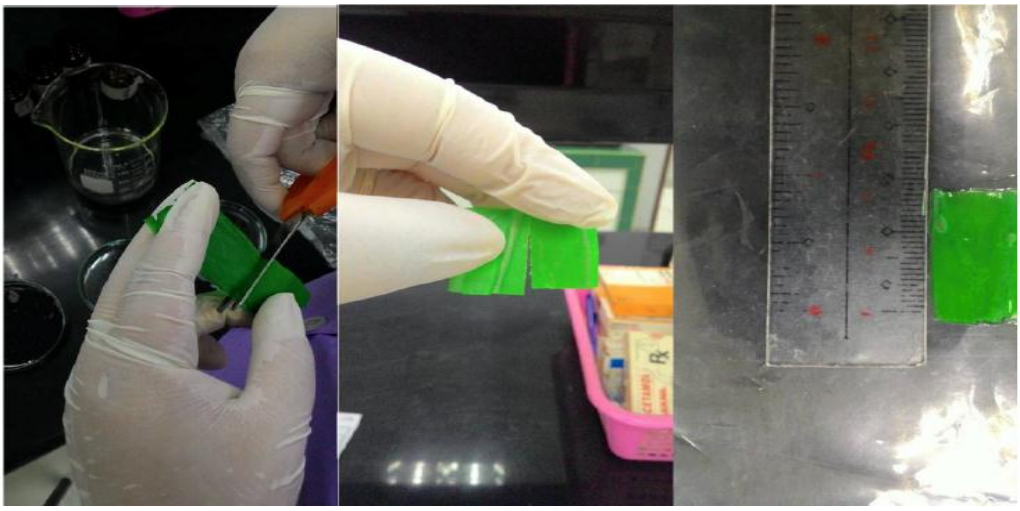


Figure 9. Preparation of the films for percentage moisture loss test.

Figure: 10 Subjecting of the films to anhydrous calcium chloride maintained in the same container.

Figure 11. Leaving of the films inside the dessicator for 72 hours.

The presence of diphenhydramine hydrochloride was qualitatively measured using Shimadzu IR Prestige-21 Fourier Transform Infrared Spectrum equipped with Single Reflection ATR Accessory from the Department of Science and Technology-Forest Products Research and Development Institute (DOST-FPRDI).

The oral films in the light parameter were subjected to FTIR to confirm if the active ingredient was present, since they yielded an inconsistent physical appearance compared to the other parameters. Figure 4 and figure 5 was compared to Figure 3, which was used as the basis for the identification of Diphenhydramine hydrochloride in the oral film. The peak of diphenhydramine hydrochloride can be clearly seen; therefore, diphenhydramine hydrochloride was present from the initial period to the third month.

CHAPTER: 5 CONCLUSIONS AND RECOMMENDATIONS

Summary of Findings

The compatibility test of active ingredient and excipients exhibited that all of the ingredients except acacia have two or more spots that signify no interaction between Diphenhydramine Hydrochloride and each of the ingredients and are therefore deemed compatible.

The stability test for the physical parameter showed that the oral film is physically unstable on the third month due to absorbance of moisture and loss of peppermint scent in light and relative humidity. The oral film is physically stable at temperatures of 2 to 8°C and 25 to 30°C but physically unstable to 40°C. They are rendered unstable because of their change in color, texture, and scent.

The stability for the chemical parameter showed that the oral film is chemically stable under the varying influence of light, temperature, and relative humidity during the 3-month duration of the stability study.

The physical test of the oral film yielded an *In-vitro* disintegration time of 35.96 seconds, an average weight of 0.3299 g and an average thickness of 0.354 mm, folding endurance produced an average of 20.5 folds, an average swelling index of 31.25%, an average linear expansion coefficient in water of 0.06% at 30 seconds and 0.23% at 60 seconds, and lastly, an average percentage moisture loss of 57.0%.

CONCLUSION

Twelve formulations were subjected to organoleptic evaluation and the formulation that passed was the Formulation 3 which is composed of a 1:1 proportion of carboxymethyl cellulose and glycerol with diphenhydramine hydrochloride, saccharin, citric acid, peppermint oil, and sodium lauryl sulfate. The oral film yielded the concentration of 89.60% thus proving the capacity of the film in containing and releasing the active ingredient.

RECOMMENDATION

The researchers recommend using United States Pharmacopeial (USP) grade excipients to establish purity and quality. All the raw materials should be assayed to confirm its identity and purity before formulation. Another active ingredient should be substituted to test

whether the film could contain a variety of active ingredient and therefore prove it's effective as a drug delivery system. Bioavailability studies should be conducted to measure the pharmacokinetic profile of the drug. Toxicity studies should be conducted to assess the lethality and predict the therapeutic index of the drug. Six month accelerated stability or a long-term stability should be conducted to determine the extent of the drug delivery system to be stable. Differential Scanning Calorimeter (DSC) should be used in place of TLC and FTIR to quantitatively measure the results.

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