# PREPARATION AND CHARACTERIZATION OF FAST-DISSOLVING DESLORATADINE ORAL FILM FOR GERIATRIC USE

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**MASTER THESIS**

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## ABSTRACT

PREPARATION AND CHARACTERIZATION OF FAST-DISSOLVING DESLORATADINE ORAL FILM FOR GERIATRIC USE

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The aim of this study was to develop 5 mg desloratadine orodispersible film (ODF) with fast disintegration time and suitable mechanical strength to treat allergic symptoms in geriatric and to increase patient compliance and convenience. Hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol, and Eudragit RS 100 were used as the film forming agent. HPMC was selected for further studies for being the best in terms of film forming ability, transparency, and lack of stickiness. Polyethylene glycol 400 and glycerol (Gly) were used as the plasticizers. Many batches of films with drug were prepared using different ratios of HPMC and plasticizers. The resultant films were evaluated for disintegration time, folding endurance, surface pH, weight variation, thickness, surface morphology using scanning electron microscopy, drug content, content uniformity, moisture loss, moisture uptake, drug-excipient compatibility using differential scanning calorimetry and fourier transform infrared spectroscopy, and dissolution. All the selected films started to disintegrate in less than 14 seconds. Most films exhibited good mechanical properties with a folding endurance value greater than 100. The uniformity in weight, thickness, and drug content in most of the selected films were obtained. Surface pH was within the normal range (6.4-6.8). Although there was no significant moisture loss in all films, moisture uptake has occurred in the films containing Gly as plasticizer. A smooth surface of the films was obtained and drug-excipient compatibility has been proved. The dissolution test wasn't done for all films due to the challenges associated with simulating the oral cavity physiological conditions using the conventional dissolution test apparatuses. However, more than 87% of the drug was released by the 4$^{th}$ minute.



**Keywords:** Orodispersible film, Desloratadine, Oral strip, Oral film, Allergic symptoms, Geriatric**.**

# ÖZET


GERİATRİK KULLANIM İÇİN HIZLI ÇÖZÜNEN DESLORATADİN ORAL FİLM HAZIRLANMASI VE KARAKTERİZASYONU

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Bu çalışmanın amacı, geriatride alerjik semptomları tedavi etmek için hızlı parçalanma süresi ve uygun mekanik mukavemete sahip 5 mg desloratadin yüklü ağızda dağılan film (ODF) geliştirmek ve hasta uyumunu ve rahatlığını artırmaktır. Film oluşturucu ajan olarak hidroksipropil metilselüloz (HPMC), polivinil alkol ve Eudragit RS 100 kullanılmıştır. HPMC, film oluşturma yeteneği, şeffaflık ve yapışkanlık açısından en iyi polimerlerden olduğu için tercih edilmiştir. Plastikleştirici olarak polietilen glikol 400 ve gliserol (Gly) kullanılmıştır. Etkin madde yüklü formülasyonlar, farklı oranlarda HPMC ve plastikleştiriciler kullanılarak hazırlanmıştır. Elde edilen filmler parçalanma süresi, katlanma dayanıklılığı, yüzey pH'sı, ağırlık değişimi, kalınlık, taramalı elektron mikroskobu kullanılarak yüzey morfolojisi değerlendirmesi, etkin madde mikra tayini, içerik tekdüzeliği, nem kaybı, nem alımı, ilaç-eksipiyan uyumluluğu için fizikokimyasal karakterizasyon açısından değerlendirilmiştir. Seçilen tüm filmler 14 saniyeden daha kısa sürede parçalanmıştır. Filmlerin çoğu, 100'den büyük bir katlanma dayanıklılığı değeriyle iyi mekanik özellikler sergilemiştir. Seçilen filmlerin çoğunda ağırlık, kalınlık ve etkin madde miktarında tekdüzelik elde edilmiştir. Yüzey pH'sı kabul edilebilir aralık içinde bulunmuştur (6.4-6.8). Tüm filmlerde önemli bir nem kaybı olmamasına rağmen, plastikleştirici olarak Gly içeren filmlerde nem alımı çekme meydana gelmiştir. Filmlerde pürüzsüz bir yüzey elde edilmiş ve etkin madde-eksipiyan uyumluluğu kanıtlanmıştır. Geleneksel çözünme testi aparatı kullanılarak ağız boşluğu fizyolojik koşullarının simüle edilmesiyle ilişkili zorluklar nedeniyle tüm filmler için çözünme testi yapılamamıştır. Bununla birlikte, ilacın % 87'inden fazlasının 4. dakikada salındığı tespit edilmiştir.



**Anahtar Sözcükler:** Ağızda dağılan film, Desloratadin, Oral strip, Oral film, Alerjik semptomlar, Geriatri.

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**10.06.2021**

## STATEMENT OF COMPLIANCE WITH ETHICAL PRINCIPLES AND RULES

I hereby truthfully declare that this thesis is an original work prepared by me; that I have behaved in accordance with the scientific ethical principles and rules throughout the stages of preparation, data collection, analysis, and presentation of my work; that I have cited the sources of all the data and information that could be obtained within the scope of this study, and included these sources in the references section; and that this study has been scanned for plagiarism with "scientific plagiarism detection program" used by Anadolu University, and that "it does not have any plagiarism" whatsoever. I also declare that, if a case contrary to my declaration is detected in my work at any time, I hereby express my consent to all the ethical and legal consequences that are involved.

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## LIST OF SYMBOLS AND ABBREVIATIONS

**API** : Active Pharmaceutical Ingredient

**AUC** : Area Under Curve

**BCS** : Biopharmaceutical Classification System

**CA** : Citric Acid

**CDER** : Center for Drug Evaluation and Research

**$C_{max}$** : Peak Plasma Concentration

**CMC** : Carboxymethylcellulose

**CYP** : Cytochrome P450

**DL** : Detection Limit

**DSC** : Differential Scanning Calorimetry

**DSL** : Desloratadine

**EMA** : European Medicines Agency

**FDA** : Food And Drug Administration

**FFDCA** : Federal Food, Drug, and Cosmetic Act

**FT-IR** : Fourier Transform Infrared Spectroscopy

**Gly** : Glycerol

**H** : Histamine

**HEC** : Hydroxyethyl Cellulose

**HPLC** : High Pressure Liquid Chromatography

**HPMC** : Hydroxypropyl Methyl Cellulose

**hr** : Hour

**ICH** : International Conference on Harmonization

**MC** : Methyl Cellulose

**min** : Minute

| | |
|---|---|
| **MW** | : Molecular weight |
| **n** | : Number of Trials |
| **ODF** | : Orodispersible Film |
| **ODTs** | : Oral Disintegrating Tablets |
| **OST** | : Oral Strip Technology |
| **PBS** | : Phosphate Buffer Solution |
| **PEG** | : Polyethylene Glycol |
| **PG** | : Propylene Glycol |
| **P-gp** | : P-Glycoprotein |
| **Ph. Eur.** | : European Pharmacopoeia |
| **PVA** | : Polyvinyl Alcohol |
| **PVP** | : Polyvinyl Pyrrolidine |
| **q.s.** | : Quantum Satis |
| **QL** | : Quantitation Limit |
| **$r^2$** | : Regression Square |
| **rpm** | : Revolutions Per Minute |
| **RSD** | : Relative Standard Deviation |
| **Rt** | : Retention Time |
| **SD** | : Standard Deviation |
| **SE** | : Standard Error |
| **Sec** | : Second |
| **SEM** | : Scanning Electron Microscope |
| **$t_{1/2}$** | : Half Life |
| **Tg** | : Glass Transition Temperature |
| **$T_{max}$** | : Time to Maximum Plasma Concentration |

| | |
|---|---|
| **USP** | : United States Pharmacopeia |
| **USP 2** | : Dissolution Paddle Apparatus |
| **v/v** | : Volume/Volume |
| **w/w** | : Weight/Weight |
| **η** | : Viscosity |

# 1. INTRODUCTION

Oral dosage forms keep to be the gold standard for the management and treatment of chronic and debilitating diseases, such as hypertension, hyperlipidemia, cancer, neurodegenerative, and psychotropic diseases as well as various infections (Alany, 2017). The oral route is the most patient-compliant and conventional route of drug administration, therefore about 60% of total dosage forms are administered orally. Among all the pharmaceutical dosage forms which delivered orally such as pills, tablets, capsules, solid powders, granules and liquids, the solid dosage forms are the most common used medications to obtain the desired therapeutic outcomes due to ease of administration (Darji et al., 2017; Kulkarni et al., 2010).

Special needs of the pediatric and geriatric patients led to the introduction of new oral dosage forms that have been expected to enhance therapeutic effects and improve patient compliance or develop currently available ones (Alany, 2017). Children and pediatrics are the most complicated to treat among all groups of patient populations primarily because they have a problem with swallowing solid dosage forms, accordingly they are generally prescribed liquid formulations. However, these dosage forms have their own drawbacks (Insufficient dose accuracy, spitting by the patients, spillage, stability issues, transportation difficulties, etc.) (Singh et al., 2013). Compared to pediatrics, elderly (over 65 years old) are the major consumers of medicines and while they represent 16% of the total population, they consume 31% of all of the medications. In addition to that, it's believed that the percentage of elderly is increasing significantly within the next 30 years in both developed and developing countries. This group resembles pediatrics in their medicine requirements and needs especially talking about lack of suitable formulations and the swallowing problem, while here the swallowing difficulties are related to age, disease related swallowing impairment (dysphagia), or simply due to polypharmacy in which the patient has to take several medications within the day to treat multiple conditions (Stegemann et al., 2010; Wahlich et al., 2013).

The development of oral disintegrating tablets (ODTs) has taken increased attention among researchers and pharmaceutical companies over the last years to overcome the swallowing problems and develop the most appropriate dosage form for the specific population where patient compliance is a problem. ODTs are defined as a solid dosage form

containing medicinal substances that disintegrate within seconds upon introduction on the tongue, as a consequence there is no need to chew the tablet, swallow an intact tablet, or swallow the tablet with water (Okuda et al., 2009; Gryczke et al., 2011)

However, continuous development of oral dosage forms has led to convention of oral strip technology (OST) as an alternative to ODTs and to overcome its disadvantages. The main drawback of ODTs is that they are fragile and breakable which needs special requirements related to packaging during storage and transportation (Dixit & Puthli, 2009). This problem develops from the fact that ODTs have high porosity and low mechanical hardness in order to achieve the desired rapid disintegration time. Moreover, special equipment's are needed to manufacture ODTs (Okuda et al., 2009; Al-Khattawi & Mohammed, 2013)

Allergies, including allergic rhinitis and urticaria, are very common high prevalence rate disorders that have a tremendous effect on the quality of life. Early diagnosis and treatment of allergic diseases using a medication of a high safety profile is of prime importance (Łagun, 2017). Histamine plays a main role in the development of allergy symptoms by the activation of H1 receptors. These symptoms include sneezing, rhinorrhea, mucosal edema, as well as swelling, pruritus, and redness of the skin. Histamine blockers are the essential medications for the treatment of allergic diseases. Desloratadine is one of the better-known second generation antihistamines that has been studied for being effective in relieving the allergic nasal and skin symptoms. It has a long-acting and non-sedative effect which makes it a safe and frequently used drug in the treatment of allergic rhinitis and urticaria (Buczak & Sybilski, 2018).

## 2. LITRETURE REVIEW

### 2.1. Oral Strip Technology

Oral strip is a thin film that is prepared using hydrophilic polymers that rapidly dissolves on the tongue or in the buccal cavity having an area ranging from 5 to 20 $cm^2$. Films are very similar to thin strip of postage stamp regarding shape, size and thickness. The strip is designed to be placed on the tongue or any oral mucosal tissue, immediately gets wet and hydrated after being in contact with the saliva. The thin strip then rapidly begins to disintegrate and dissolve to release the medication. In the literature several terms can be found to describe this technology, such as: oral film or strip, thin strip, orally dissolving film, orodispersible film (ODF), buccal film, mucoadhesive film, transmucosal film, flashrelease wafer, quick dissolve film, disintegrating film, melting film and melt-away film ( Liew et al., 2011; Patel & Modi, 2012; Irfan et al., 2016; Karki et al., 2016; Gholve et al., 2018). The last two terms are not preferably used by the Food and Drug Administration (FDA) because they indicate melting of the film instead of what actually happens; the film dese not melt but disintegrates and dissolves. Instead “soluble film” or “oral soluble film” are commonly used by the FDA to avoid any misunderstanding (Patel & Modi, 2012). The European Medicines Agency (EMA) prefers to use “orodispersible film” to describe the fast dissolving films not to confuse it with “buccal film” which is designed to stay longer on the mucosa (Karki et al., 2016). Furthermore, the European Pharmacopoeia (Ph. Eur.) 7.4 included the “orodispersible film” as a subchapter of “Oromucosal Preparations” whereas the mucoadhesive buccal films are included in the “Mucoadhesive preparations” and defined as “single-or multi-layer sheets that adhere to the buccal mucosa and may dissolve”. Figure 2.1. represents a simplified scheme of different oral films and properties (Borges et al., 2015).

This drug delivery system has been used for both systemic and local action. The medications start to get absorbed by mouth and then the saliva containing the dissolved medication is swallowed and continues its way down into the stomach passing by the pharynx and esophagus where the drug keeps being absorbed and that ensures higher bioavailabilities comparing to those observed from conventional dosage forms (Parejiya et al., 2013; Karki et al., 2016).

Beside the fact of fast disintegration and dissolving of the films, they should be stable to moisture overtime, produce an acceptable taste when placed on tongue, facilitate the handling by being flexible and exhibiting a suitable tensile stress, and do not stick to the packaging materials and fingers (Patel & Modi, 2012; Parejiya et al., 2013).

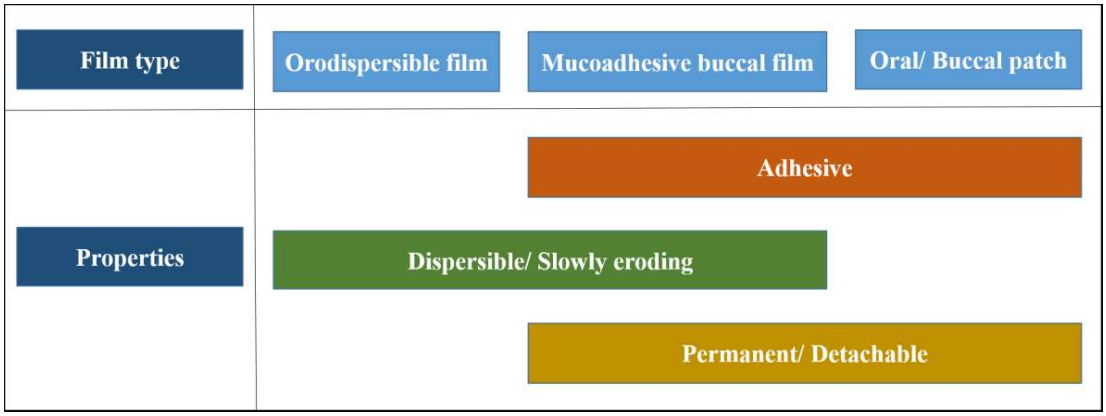


**Figure 2.1.** *A simplified scheme of different oral films and properties*

### 2.1.1. Advantages of oral strip technology

Oral films have many advantages comparing to other oral dosage forms as explained below:

- Rapid disintegrating and dissolution in the oral cavity thanks to the large surface area (Pandey et al., 2014).
- The absorption of the drug is higher as the dosage form dissolves in buccal cavity and the absorption takes place starting from buccal cavity to intestine (Liew et al., 2011). If the drug is absorbed through the oral mucosa, first-pass metabolism can be avoided for some drugs, which may improve bioavailability (Patel & Modi, 2012).
- A rapid onset of action could be achieved which is important in many cases such as sudden episodes of allergic attack or coughing, motion sickness, bronchitis or asthma as the drug is released within seconds to minutes into the oral cavity (Patel & Modi, 2012; Keshari et al., 2014).

- Superior to liquid dosage forms such as drops or syrups regarding the convenience of accurate dosing and stability (Liew et al., 2011; Patel & Modi, 2012).
- Oral films are patient-friendly dosage form; the dosage form is taken without water which is ideal for passengers or patients who have a problem with continuous access to water. The patient is not required to swallow, therefore there is no fear of choking or inhalation (Arya et al., 2010; Hoffmann et al., 2011).
- Flexible in handling and transportation (Pandey et al., 2014).
- The ability of taste masking (Arya et al., 2010).
- Available in different sizes and shapes (Keshari et al., 2014).

**Figure 2.2.** *Oral strips with different colors from the package until the absorption in buccal cavity* (http-1)

### 2.1.2. Challenges and limitations of oral strip technology

Using OST is mainly limited because of low dose capacity. Any increase in the dose requires larger films which is limited by the definition of the thin film with small size and low weight. Since the film dissolves in the mouth and has direct contact with oral mucosa, taste and several taste masking techniques should be considered. The film has stability concerns in environment with high humidity (Borges et al., 2015). Drugs which are classified as class II of Biopharmaceutical Classification System (BCS) (with low solubility and high permeability) show solubility problem that affects the ability to get the desired dose of the medication. Producing oral film requires long time in drying step affecting production rate in industries. To speed up this step hot air oven can be used. However, it's not an option for thermolabile drugs and drying at room temperature takes much more time

not less than a day usually. In OST co-administration of more than one active pharmaceutical ingredient (API) is problematic because it might affect the overall disintegration and dissolution time of the film. Content uniformity is an important challenge that depends on many factors such as cutting films into accurate desired size (Jadhav et al., 2013), otherwise therapeutic failure and sometimes toxic effects to the patient might be noticed (Karki et al., 2016).

### 2.1.3. Overview of oral cavity

As the oral cavity represented by the oral mucosa provides local and systemic drug delivery pathways, it's considered as one of the most essential route of drug administration. The overall surface area that is provided by the oral cavity is around 100 $cm^2$. This area which is lined by the mucus membranes guarantee the completion of diverse drugs absorption (Singh et al., 2017).

There are many sites inside the oral cavity that have been known for drug administration, they include the following (Haju et al., 2021):

- Buccal cavity.
- Sublingual cavity.
- Lingual area.
- The palate.
- Gingival region.

The oral mucosa that covers the oral cavity is made up of multilayers of epithelial tissues and it's additionally coated by the mucus. This epithelial layer is separated from the next inward layer known as lamina propria by a basement membrane. The lamina propria is a layer of connective tissue that functions as a mechanical support. The submucosal layer comes next and it's rich of blood vessels and nerves from the central nervous system. This high vascularity guarantees the completion of drug absorption. A cross-section of oral mucosa is shown in Figure 2.3. In general, the oral mucosa has two types of epithelium; keratinized and non-keratinized epithelium. Beside the relative thickness of the oral mucosa, the level of keratinization determines the permeability level of the oral mucosa. The oral mucosal permeability is 4-4000 times higher than skin. The keratinized epithelial layer

covers the gingival area and a part of the hard palate whereas the non-keratinized epithelium covers the soft palate, lips, cheeks and the floor of the mouth. Based on the level of keratinization and the relative thickness, the permeability order of the oral mucosa is sublingual>buccal> palatal (Haju et al., 2021).

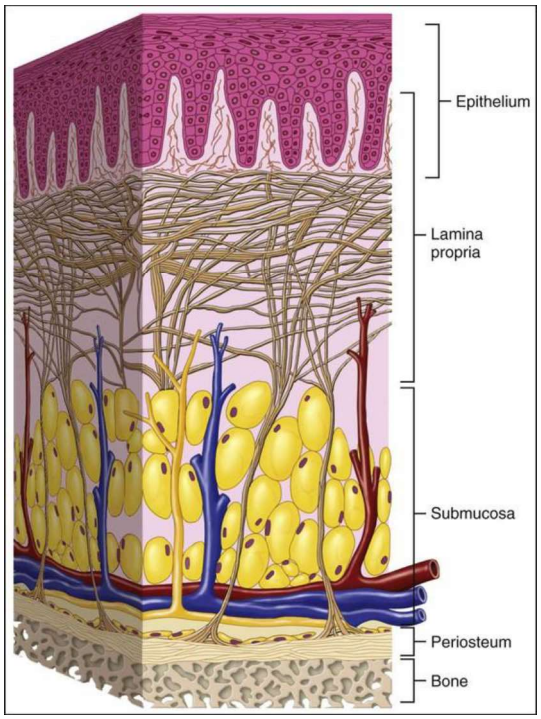


**Figure 2.3.** *Cross-section of oral mucosa (Mostafa, 2018)*

The mucus that covers the whole oral cavity as mentioned is a gel-like secretion that plays a major role in protecting the cells below. This viscoelastic gel is essentially containing water-insoluble glycoproteins in the range of 1-5%, water in the range of 95-99 % and many other components in small amounts, such as proteins, enzymes, electrolytes, and nucleic acids (Salamat-Miller et al., 2005).

Saliva, which is a digestive secretion made by the salivary glands is another important characteristic of the oral cavity. Saliva is fundamentally made up of water and 1% of organic and inorganic materials. The pH of the saliva ranges between 5.5-7. The available fluid to hydrate the oral mucosal drug dosage form is called salivary volume. Its daily volume ranges between 0.5-2 L depending on the flow rate. Depending on this water-rich medium,

hydrophilic polymers as a vehicle for buccal drug administration are mostly selected (Siddiqui et al., 2011).

## 2.2. Formulation of the Oral Strips

The API is incorporated into the film forming agent (polymer) along with other ingredients required for the formulation of the film. These excipients include plasticizers, sweetening agents, saliva stimulating agents, surfactants, flavoring agents, coloring etc…(Irfan et al., 2016).

### 2.2.1. Active pharmaceutical ingredient

API can be incorporated in the oral strip within limits, preferably about 5-30% by weight (Ghodake et al., 2013). As the major limitation of OST is incorporation high doses of APIs because of the small size of the dosage form, the ideal API has low dose preferably with low molecular weight. The majority of candidate APIs in OST has bitter taste. Thus, APIs should be compatible with different taste masking techniques. Micronized API is always preferred to enhance its dissolution, improve its uniformity, and also to get a better final texture of the strip. API should be soluble in water and saliva with good stability. It should be permeable into the oral mucosal tissue (Panda et al., 2012; Kumar & Yagnesh, 2019).

Various drugs with different therapeutic categories can be incorporated into oral strips e.g., anti-histamine, anti-diarrheal, anti-bacterial agents, anti-depressants, vasodilators, anti-asthmatic, anti-emetic, anti-allergic, anti-migraine, anti-epileptic, anti-parkinsonism agents, antiulcer agents, antacids, analgesics, diuretics, expectorants, antitussives, muscle relaxants, proton pump inhibitors, drugs used for erectile dysfunction, smoking cessation, etc. (Jyoti et al., 2011; Ghodake et al., 2013; Irfan et al., 2016).

Vitamins such as vitamin A, vitamin D, vitamin E, vitamin K, vitamin C, vitamin B1 (thiamin), vitamin B2 (riboflavin), vitamin B3 (niacin), vitamin B5 (panthotenic acid) vitamin B6, vitamin B7 (biotin), vitamin B9 (folic acid) and vitamin B12 can be incorporated in the oral strips. Minerals and trace elements are also suitable options for the incorporation in the oral strips. Examples include calcium, sodium, potassium,

phosphorous, magnesium, manganese, copper, zinc, iron, selenium, chromium. Some examples of specific API with different doses that can be delivered by rapidly dissolving oral strip are reviewed in Table 2.1 (Kulkarni et al., 2003b).

**Table 2.1.** *Examples of doses for specific pharmaceutically active ingredients that can be delivered by oral strips (Kulkarni et al., 2003a)*

| API | Dose (mg) |
|---|---|
| Loperamide | 2 |
| Chlorpheniramine Maleate | 4-12 |
| Brompheniramine Maleate | 4 |
| Dexchlorpheniramine | 2 |
| Dexbropheniramine | 2 |
| Triprolidine Hydrochloride | 2.5 |
| Cetirizine | 5-10 |
| Acrivastine | 8 |
| Azatadine Maleate | 1 |
| Loratadine | 5-10 |
| Phenylephrine Hydrochloride | 5-10 |
| Dextromethorphan Hydrobromide | 10-30 |
| Sildenafil | 25-100 |
| Ketoprofen | 12.5-25 |
| Sumatriptan Succinate | 35-70 |
| Zolmitriptan | 2.5 |
| Famotidine | 5-10 |
| Nicotine | 1-15 |
| Diphenhydramine Hydrochloride | 12.5-25 |
| Pseudoephedrine Hydrochloride | 15-60 |
| Atorvastatin | 5-80 |
| Valdecoxib | 5-20 |
| Amlodipine besylate | 2.5-10 |
| Rofecoxib | 5-25 |
| Setraline hydrochloride | 10-100 |
| Ziprasidone | 20-80 |
| Eletriptan | 10-40 |
| Nitroglycerin | 0.3-0.6 |

### 2.2.2. Polymers or film forming agent

Polymer is used as a carrier for the API. The nature and physiochemical of the polymers can be changed and used either individually or in combinations to get the desired film (Varun, V, Lavanya, & Ritu, 2011; Keshari et al., 2014). The film should be strong and elastic enough not to get broken or ruptured during storing, transportation, and administration. The mechanical properties of the film depend on the type of polymer and amount of polymer used. Mostly hydrophilic polymers are used as film forming agents (Keshari et al., 2014; Pandey et al., 2014). Both natural and synthetic polymers can be employed for film preparation. The ideal polymers should be non-toxic, non-irritant, and absence of leachable impurities is required. Water soluble polymers are required as film forming agents to produce a thin film with rapid disintegration, good mechanical strength, and good mouth feel effect (Karki et al., 2016). It's better for the polymer to have good mucoadehsion properties to enable the film to be adhered to the buccal mucosa in a quick manner (Sudhakar et al., 2006). The polymer should have good wetting and spreadability properties. It should exhibit sufficient peel, shear and tensile strengths. It should not cause any secondary infection in the oral cavity (Varun et al., 2011). The polymer should be available and inexpensive with good shelf life. Generally, a typical film contains 40-50% (w/w) of the film forming polymer (Joshua et al., 2016).

Some examples of polymers that have been used alone or in combination for ODF preparations include pullulan, gelatin, cellulose derivatives like hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), carboxymethyl cellulose (CMC) or methyl cellulose (MC), sodium alginate, polyvinyl pyrrolidine (PVP), polyvinyl alcohol (PVA), polyethylene glycol (PEG), povidone K-90, pectin, maltodextrin, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, methyl methacrylic copolymer, carboxyvinyl copolymer, etc. (Singh et al., 2013; Pathare et al., 2013). Among all the available polymer options, pullulan, gelatin and HPMC are most commonly used for preparation of oral films (Dixit & Puthli, 2009). Table 2.2. represents these polymers with additional descriptions and properties.

**Table 2.2.** *Proprieties of most commonly used polymers in oral strip formation (Karki et al., 2016; Kumar & Yagnesh, 2019)*

| Polymer | Properties |
|---|---|
| **HPMC** | White or creamy colored, odorless, and tasteless powder. |
| | Molecular weight (MW) 10,000–1,500,000 |
| | Soluble in cold water. |
| | Insoluble in chloroform and ethanol. |
| | Viscosity (η) 3–100,000 mPa·s |
| | Non-ionic polymer with moderate mucoadhesive properties |
| | Solutions are stable at pH 3.0- 11.0 |
| | Film forming ability at 2–20% concentrations |
| **Pullulan** | White, odorless, and tasteless powder |
| | MW 8000–2,000,000 |
| | Soluble in hot as well as cold water |
| | η 100–180 mm2/s (10% aqueous solution at 30 °C) |
| | Contain > 6% w/w of moisture. |
| | 5–25% (w/w) solution forms flexible films |
| **Gelatin** | A light amber to faintly yellow colored powder |
| | MW 15,000–250,000 |
| | Soluble in glycerin, acid, alkali and hot water |
| | η 4.3–4.7 mPa s (6.67% (w/v) aqueous solution at 60 °C) |
| | Moisture content 9–11% (w/w) |
| | It has a very good film forming ability |

ODFs of flupentixol dihydrochloride were prepared to improve its bioavailability and therapeutic effect and increase the convenience and compliance by the mentally ill, disable, elderly, and pediatric patients. Six formulas with different concentrations of HPMC and CMC were used and the resulting films were characterized. Films of 2% HPMC exhibited best compatibility between the drug and the excipients, best stability, best uniformity and fast disintegration in water. The in vivo studies in healthy human volunteers indicated that rapid and enhanced absorption of flupentixol could be achieved from the oral films with lower time to maximum plasma concentration ($T_{max}$) and 1.51-fold increase bioavailability than that gained of commercially marketed tablets. These findings support using oral films to ensure patient satisfaction (Abdelbary et al., 2014).

### 2.2.3. Plasticizers

Plasticizer is a primary ingredient in OST formulation which is responsible to convert the hard and breakable films to more pliable and tougher form (Liew, Tan, & Peh, 2014). The addition of plasticizers increases the mobility of polar polymer chains and reduces the intermolecular forces which leads to reducing the glass transition temperature (Tg) of the polymer. Accordingly, the presence of plasticizers overcomes the films' brittleness and improves their flexibility and mechanical properties. Plasticizers must be compatible with the polymers, API, and the other excipients. The concentration of plasticizer usually ranges from 0-20% (w/w) (Laohakunjit & Noomhorm, 2004; Galgatte et al., 2013). Among all available plasticizers, glycerol (Gly), propylene glycol (PG), sorbitol, and PEG are the most commonly used ones (Liew et al., 2014). Other available options include dimethyl, dibutyl, diethyl phthalate, tributyl, triethyl, actyl citrate, triacetin and castor oil. Splitting, peeling and cracking of the film might happen because of inappropriate selection of the plasticizer (Joshua et al., 2016). Although increasing the elasticity of the film has been reported by increasing the amount of the plasticizer (Liew et al., 2014), too much amount of it might cause overhydrating of the film. Besides, there might be slight increase in the film thickness (Karki et al., 2016).

### 2.2.4. Sweetening agents

In general, sweetener is utilized to mask the bitter taste of certain drugs and to provide the level of desired sweetness for the formulation. The amount will vary according to the chosen sweetener. The effective amount is normally about 3-6% (w/w) of the film. Natural and artificial sweeteners can be used either individually or in combination (Kulkarni et al., 2003b ; Joshua et al., 2016). Different natural and artificial sweeteners which can be used in OST are shown in Table 2.3.

Using natural sweeteners in diabetic patients needs to be reduced. Due to this reason, the artificial sweeteners have earned more acceptance in pharmaceutical preparations (Mahboob et al., 2016). These artificial sweeteners are known as high-potency sweeteners. Their sweetness potency is determined depending on sucrose. Saccharin is 300 times sweeter than sucrose. Aspartame and acesulfame-K are 200 times sweeter compared to sucrose. Sucralose has a potency equals to 600. Neotame is 8000 time sweeter then sucrose.

However, considering the disadvantages of artificial sweeteners, rebiana (common name of high-purity rebaudioside A), a natural sweetener with 200–300 sweetness potency could be an interesting alternative. It provides no calories and has a clean, sweet taste with no significant undesirable taste characteristics. The previous potencies are given approximately (Prakash et al., 2008; Neacsu & Madar, 2014).

**Table 2.3.** *Examples of sweetening agents used in oral strips (Joshua et al., 2016)*

| Sweeteners | Examples |
|---|---|
| **Natural sweeteners** | Sucrose, fructose, dextrose, glucose, maltose, xylose, ribose, mannose, galactose, partially hydrolyzed starch, or corn syrup solids. |
| **Synthetic sweeteners** | -First generation: Saccharin, cyclamate and aspartame.<br>-Second generation: Acesulfame-K, sucralose, alitame, neotame. |

### 2.2.5. Saliva stimulating agent

Rapid disintegration of the oral film formulations can be enhanced by more saliva in the oral cavity. Thus, salivary stimulating agents might be added to the formulation just as acids used in the preparation of food as salivary stimulants. Citric acid (CA), malic acid, lactic acid, ascorbic acid and tartaric acid are few examples of salivary stimulants. Among these, citric acid is the most common used one. The concentration of saliva stimulating agents usually ranges from 2-6% (w/w) (Siddiqui et al., 2011).

### 2.2.6. Flavoring agents

Flavor is an important factor to be taken into consideration when talking about patient acceptance of the formulation. It depends on the initial flavor observed within the first few seconds after the application of the film and on the after taste that lasts for about 10 minutes. Age has been observed to be the most significant factor in selecting the suitable flavor. For example, geriatric population prefers mint and orange while children prefer fruity essence flavors. The selected flavor can be from synthetic flavor oils, oleo resins, or extracts obtained from leaves, fruits, and flowers of many plants. The amount of the flavoring agent which can be added individually or in combination to mask the taste is related to the flavor

type itself and its strength. Therefore, the concentration of the flavoring agents is usually described as quantum satis (q.s.). Examples of flavor oils are peppermint oil, cinnamon oil, spearmint oil, and nutmeg oil. Fruity flavors such as vanilla, cocoa, coffee, chocolate and citrus. Fruit essence type flavors such as apple, raspberry, cherry, pineapple (Jyoti et al., 2011; Ghodake et al., 2013).

### 2.2.7. Coloring agents

It's preferred for the film to be dyed according to the used flavor as the film's color associated with the expected flavor film enhances the acceptance of the oral strips by the patients. For example, red color for cherry flavor and orange color for orange flavor (Garsuch, 2009). Any pigment that has been approved by Federal Food, Drug, and Cosmetic Act (FFDCA) can be used. Titanium oxide is an example. The concentration of the coloring agent is Q.S. but should not exceed 1% w/w of the oral strip (Bhyan et al., 2011).

### 2.2.8. Other excipients

The stabilizing and thickening agents are incorporated into the formulation to improve the consistency and viscosity of dispersion or solution of the strip preparation. Examples include natural gums such as xanthum gum, locust bean gum, carragenan and cellulosic derivatives (Panda et al., 2012).

Surfactants can be added to the formulation as they act as solubilizing or wetting or dispersing agent in order to increase the ability of the film to be dissolved within seconds and release the API quickly. Polaxamer 407 is one of the most used surfactant. Other commonly used surfactants are sodium lauryl sulfate, benzalkonium chloride, tweens etc. (Siddiqui et al., 2011).

## 2.3. Manufacturing of Oral Films

One or more method can be used in the manufacturing of oral films. Solvent casting and hot extrusion methods are the most commonly used. These methods alongside the other available methods will be explained below (Mishra & Amin, 2011).

### 2.3.1. Solvent casting method

This method is considered as the most preferred one in manufacturing. The water soluble ingredients (polymer) and plasticizer are dissolved in a proper volatile solvent such as distilled water or ethanol and stirred to form a clear, viscous solution. The API and other ingredients are dissolved in an aqueous solvent. This mixture is added to the previously prepared viscous solution. Selection of a proper solvent depends significantly on the properties of the API (Mishra & Amin, 2011; Joshua et al., 2016). The API and other ingredients can be added directly to the polymer solution and mixed well to get a homogeneous solution. The entrapped air bubbles which from because of mixing should be removed before casting the resulting solution into a suitable mold which is usually a petri dish to get a uniform thickness. (Panda et al., 2012). The film is allowed to dry and eventually cut to the desired dimensions. Scaling up the production involves using rollers and inert bases for film casting. Once the solution is prepared, the roller guides the solution on the inert substrate and the clearance between them determines the thickness of the film as shown in Figure 2.4. Glass, plastic, or teflon plates can be used as an inert material base. The film is subjected then to the drying system to be cut and packaged after (Mishra & Amin, 2011).

Moisture is an important aspect to be considered when using this method as moisture is present in the solution and it affects both stability and the mechanical properties of the film. Another factor to be considered is temperature as controlled temperature is required to maintain the viscosity of the solution and for the temperature sensitivity of the API. The challenges of this method develop when moving to production scale. Casting the film, maintaining a uniform film thickness, and the selecting a suitable drying system are the major limitations of this technique (Mishra & Amin, 2011).

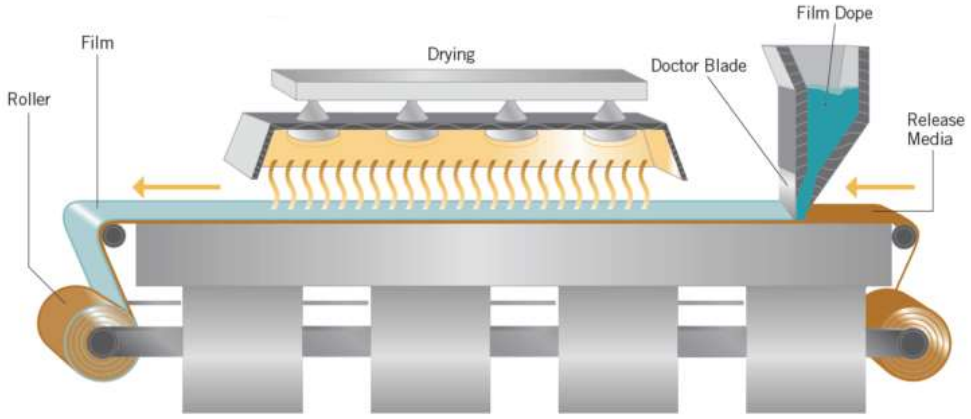


**Figure 2.4.** *Diagram of solvent casting method (Mostafa, 2018)*

### 2.3.2. Hot melt extrusion method

In this method all the ingredients are mixed in the dry state where they are subjected to heat within the extruder to form a molten mass. This mass is formed into films while extruding out through the dies as shown in Figure 2.5. The films are left to cool down and finally cut into the desired dimensions (Varun et al., 2011; Thakur & Narwal, 2012). The application of hot melt extrusion is increasing due to its advantages which include no need for solvent, continuous operation with fewer units, and better content uniformity (Jani & Patel, 2015). However, thermoliable drugs can't be processed by this technique while both thermoliable and thermostable drugs can be processed in solvent casting method (Mishra & Amin, 2011).

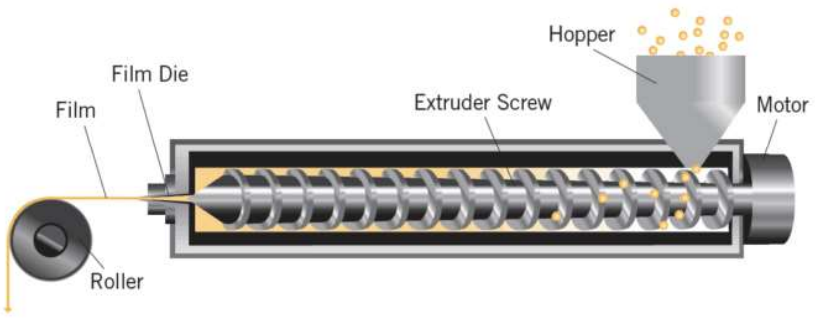


**Figure 2.5.** *Diagram of hot melt extrusion method (Mostafa, 2018)*

### 2.3.3. Semisolid casting method

In this method a solution of acid insoluble polymer such as cellulose acetate phthalate, cellulose acetate butyrate is prepared in ammonium or sodium hydroxide. A solution of water-soluble polymer should be prepared and added to the previous solution. The ratio of the acid insoluble polymer to the film forming polymer should be 1:4. A gel mass is obtained by adding the required amount of plasticizer. Once the gel mass is ready, it will be casted into films by the help of heat controlled drums (Kumar & Yagnesh, 2019).

### 2.3.4. Solid dispersion extrusion method

The term solid dispersion refers to the dispersion of one or more APIs in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers using methods such as hot melt extrusion. In solid dispersion extrusion method, solid dispersion of immiscible components is prepared by dissolving the drug in a proper solvent and add the resulting solution to the melt of suitable polymer and extruded together. This step happens under 70°C without removing the solvent. Finally, The solid dispersions are shaped into films by means of dies (Mishra & Amin, 2011).

### 2.3.5. Rolling method

In this method a premix, which contains the polymer, polar solvent (water and mixture of water with alcohol), and the other excipients is prepared and added to the feed tank where it will be fed by a metering pumps to either one or both of the mixers. The required amount of the API is then added to the premix preparation and mixed well to obtain a uniform matrix that will be fed into a pan by second metering pumps. The film starts to be formed and carried away by the help of support rollers. The formed wet film is then subjected to controlled bottom drying system in order to be cut to the desired dimensions at the end (Ghodake et al., 2013; Mostafa, 2018).

### 2.3.6. Spray method

In a suitable solvent, API, polymers and all other excipients are dissolved to obtain a clear solution. The next step is to spray the resulting solution onto a proper material such as glass, polyethylene film of non-siliconized Kraft paper or teflon sheet etc. The film is dried and peeled off, and cut to the desired dimensions (Irfan et al., 2016).

### 2.3.7. Printing method

Printing may play an essential role in the future for oral film formulation. With printing, depending on the choice of technology, a very high precision for depositing a desired ratio of API and excipients onto suitable substrates can be achieved in a controlled manner. Inject printer is an example of this technology where small amount of liquid (ink formulation) which represents here the API and excipients is deposited onto a carrier based on digitally predesigned printing patterns (Preis et al., 2015).

## 2.4. Commercially Available Products

Commercial fast dissolving oral strips are available in the United States of America, Europe and Japan (Panda et al., 2012). Some commercially available fast dissolving film are listed in Table 2.4.

**Table 2.4.** *List of some commercially available fast dissolving film*

| Trade name | Active ingredient/Dose | Application | Company |
|---|---|---|---|
| Benadryl® Allergy quick dissolve strips | Diphenyhydramine HCl/ 12.5 or 25 mg | Anti-allergic | Pfizer |
| Sudafedpe® quick-dissolve strips | Phenylephrine HCl/ 10 mg | Decongestant | Pfizer |
| Gas-X® thin strips | Simethicone/ 62.5 mg | Anti-bloating | Novartis |
| Triaminic® thin strips allergy | Diphenyhydramine HCl/ 12.5 mg | Anti-allergic | Novartis |

**Table 2.5. (Continued)** *List of some commercially available fast dissolving film*

| | | | |
|---|---|---|---|
| Triaminic® thin strips day time cold and cough | *Dextromethorphan/ 3.67 mg<br>*Phenylephrine HCl/ 2.5 mg | *Cough suppressant<br>*Nasal decongestant | Novartis |
| Pedia-Lax® quick dissolve Strips | Standardized sennosides/ 8.6 mg | Laxative | C.B. Fleet |
| Chloraseptic® Sore Throat Relief Strips | *Benzocaine/ 3mg<br>*Menthol/ 3mg | Sore throat reliving | Prestige |
| Zuplenz® oral soluble strips | Ondansetron 4 or 8 mg | Nausea and/or vomiting prevention | Strativa |

## 2.5. Drug Profile

### 2.5.1. Chemistry of desloratadine

The International Union of Pure and Applied Chemistry Name (IUPAC Name) of desloratdaine (DSL) is 13-chloro-2-piperidin-4-ylidene-4-azatricyclo[9.4.0.0$^{3,8}$]pentadeca 1(11),3(8),4,6,12,14-hexaene. The molecular formula of DSL is C19H19ClN2, its molecular weight is 310.8 g/mol, and its structural formula is presented in Figure 2.6. DSL is derivative of loratadine with one structural change where the ethoxycarbonyl group connected to the piperidine ring is substituted by hydrogen (http-2).

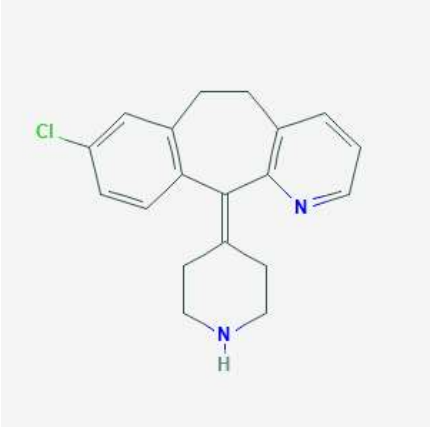


**Figure 2.6.** *Structural formula of desloratadine* (http-2)

### 2.5.2. Description of DSL

DSL has white to off-white color and bitter taste (Etman et al., 2014). It's slightly soluble in water and sparingly soluble in methanol, ethanol, propylene glycol, acetonitrile and toluene (Committee for medicinal products for human use [CHMP], 2012). According to the BCS, DSL is classified as a Class I drug; in which the drug is characterized by high solubility and high permeability (Falcão et al., 2017).

### 2.5.3. Pharmacodynamics and clinical use of DSL

DSL is piperidine derivative with selective histamine 1 antagonist (H1) properties and characterized by long-acting and non-sedating properties. Histamine is one of the chemicals that play a role in signs of the allergic reactions in the body, like tissue swelling. DSL reduces the typical histamine-associated effects that occur because of activation of H1 receptors in bronchial and gastrointestinal smooth muscle and capillaries which include: dilation of blood vessels, bronchoconstriction, contractions of gastrointestinal smooth muscle, increased permeability of blood vessels, pain and itching. DSL works without entering the central nervous system readily and that is the factor behind its non-drowsy property (http-2). These factors suggest DSL as an anti-allergic and anti-inflammatory non-sedating antihistamine that first became commercially available in 2001 for the treatment of allergic rhinitis. DSL is presently approved for the treatment of allergic rhinitis symptoms regardless its duration weather it's intermittent or persistent and its seasonality weather it's seasonal or perennial and for treatment of chronic idiopathic urticaria symptoms (Geha & Meltzer, 2001; Canonica et al., 2007). DSL is available in tablets and syrups dosage forms with 5 mg dose for adults and children aged 12 and over (Kolašinac et al., 2012).

### 2.5.4. Pharmacokinetics of DSL

DSL is quickly absorbed after oral administration, and it has linear pharmacokinetic profile across a single-dose within the range of 5–20mg. In general, multiple and single dose pharmacokinetic profiles of DSL are similar. Steady state of plasma concentration can be attained at the $7^{th}$ day after 5 mg of daily DSL oral dose for 10 days. Mean of peak plasma concentrations ($C_{max}$) of DSL equals to 3.98 μg/L is reached at a mean of 3.17 hours ($t_{max}$)

after administration. The area under the plasma concentration-time curve from 0 to 24 hours ($AUC_{24h}$) is 56.9 μg/L · hr. DSL can be administrated with or without food since food and grapefruit juice do not significantly affect its oral bioavailability. About 82–87% of DSL dose is bound to plasma proteins (Melton et al., 2002; Murdoch et al., 2003).

DSL is known to be subjected to extensive hepatic metabolism. (Berginc, Sibinovska, Žakelj, Trontelj, & Legen, 2020). The cytochrome P450 (CYP) isoenzyme that metabolizes DSL has not been specified, but CYP3A4 and CYP2D6 are unlikely to be extensively involved (Murdoch et al., 2003). The main pathway of DSL metabolism has been determined by the metabolite profiles found in plasma, urine, and feces includes formation of 3-hydroxy DSL which is subsequently converted to its inactive form by glucuronidation. There are three other hydroxylated metabolites that account for less than 6% of the dose execration for each. DSL has six fewer metabolites comparing to loratadine. (Geha & Meltzer, 2001).

Around 45% and 40% of DSL administered dose is excreted as metabolites in the feces and urine respectively (Murdoch et al., 2003). Very low concentrations of unchanged drug detected in feces and urine; (< 7%) and (< 2%) respectively (Berginc et al., 2020). The mean half-lives ($t_{1/2}$) of DSL is 26.8 hours (Melton et al., 2002). Age, sex and race seem to have no considerable effects on the pharmacokinetics of DSL (Murdoch et al., 2003).

### 2.5.5. Interactions of DSL

After the discovery of possible fatal interaction between terfenadine (non-sedating antihistamine) and the CYP 3A4 inhibitors, erythromycin and ketoconazole, comprehensive assessment of possible drug interactions of non-sedating antihistamines has been a critical element of their evaluation. Simultaneous administration of DSL and inhibitors of CYP3A4 or CYP2D6, such as erythromycin, ketoconazole, cimetidine and fluoxetine, or with azithromycin showed no significant changes in the electrocardiographic parameters which indicated no clinically relevant interactions between DSL and these compounds (Geha & Meltzer, 2001; Murdoch et al., 2003).

Many drug interactions are mediated wholly or partially by effects on CYP–mediated drug metabolism. However, a group of active drug transporters that can be recognized as critical targets for drug interactions have been identified. P-glycoprotein (P-gp) transporters

are one of these transporters across cell membranes that play a critical role in determining the pharmacokinetics of a drug. Although the pharmacokinetics of some antihistamines might be affected by stimulation or inhibitions of these transporters, DSL is not a significant substrate of P-gp transporters. Therefore, no significant interactions have been detected between DSL and the drugs that interact with the P-gp transporter system, such as cyclosporine (Geha & Meltzer, 2001).

# 3. MATERIALS AND DEVICES

## 3.1. Materials

| Substance | Company |
|---|---|
| Acetonitrile | Sigma-Aldrich, Germany |
| Anhydrous calcium chloride | Sigma-Aldrich, Germany |
| Citric acid | Sigma-Aldrich, Germany |
| Desloratadine | Berko İlaç, Turkey |
| Ethanol | Sigma-Aldrich, Germany |
| Eudragit RS 100 | Sigma, USA |
| Glycerol | Sigma, USA |
| Hydroxypropyl methyl cellulose | Sigma, USA |
| Methanol | Sigma-Aldrich, Germany |
| Ortho phosphoric acid | Sigma-Aldrich, Germany |
| pH 6.8 phosphate buffer tablets | Sigma-Aldrich, Germany |
| Polyethylene Glycol 400 | Sigma, USA |
| Polyvinyl Alcohol | Sigma, USA |
| Potassium di-hydrogen phospates | Sigma, USA |
| Propylene Glycol | Sigma-Aldrich, Germany |
| Sodium hydroxide | Sigma, USA |
| Sorbitole | Sigma, USA |
| Tween 80 | Sigma-Aldrich, Germany |

### 3.2. Devices

| Device | Company |
|---|---|
| Aluminum autosampler crimp pans | Shimadzu, Japan |
| Column | Merck, Millipore, Germany |
| Desiccator set | İsolab, Turkey |
| Digital clipper | China Factory, Guangzhou, China |
| Differential Scanning Calorimetry | Shimadzu DSC-60, Japan |
| Dissolution Apparatus | Pharma test, Germany |
| Fourier Transform Infrared Spectroscopy | Shimadzu, Japan |
| High Performance Liquid Chromatography | Shimadzu, LC 20-AT, Japan |
| Hot air oven | Nüve, FN 500, Turkey |
| Humidity chamber | İsolab, Turkey |
| Magnetic stirrer | Wisd Laboratory Instruments, Daihan SMH5-3, Korea |
| Micropipette set | Eppendorf, Germany |
| Petri dishes | İsolab, Turkey |
| pH meter | Mettler Toledo, USA |
| Pure Water Device | Millipore, France |
| Refrigerator | Arçelik 5274 NMS No Frost, Turkey |
| Scanning Electron Microscope | Zeiss, Supratm 50 VP, Germany |
| Sensitive balances | Mettler Toledo, USA |
| Syringe filter (0.45 μm) | Sigma-Aldrich, Germany |
| Ultrasonic bath | Wisd Laboratory Instruments, South Korea |
| Vortex | Jeiotech VM-96B, South Korea |

# 4. METHODS

## 4.1. Analytical Validation Studies

Analytical validation studies are the systematic process of establishing that an analytical method is acceptable for its intended purpose. Typical validation characteristics which should be considered are: linearity, range, accuracy, precision, detection limit, quantitation limit and specificity the analytical validation studies were carried out using high pressure liquid chromatography (HPLC) under specific conditions as determined in Table 4.1. The following analytical parameters were evaluated according to the Validation of Analytical Procedures: Text and Methodology Q2(R1) of International conference on harmonization (ICH) (ICH, 2005).

**Table 4.1.** *HPLC operating conditions*

| | |
|---|---|
| **Device** | Shimadzu, LC 20-AT, Japan |
| **Column** | 150×4.6 mm LiChrospher® 100 RP-18 octadecyl silane column (5 µm particle size) |
| **Oven temperature** | 25 ± 2°C |
| **Mobile phase** | pH 3 phosphate buffer*: Acetonitrile: Methanol in the ratio of 50:40:10 v/v/v |
| **Detector** | Diode array detector |
| **Wavelength** | 247 nm |
| **Flow rate** | 0.8 mL/min |
| **Injection volume** | 20 µL |

**pH 3 phosphate buffer of the mobile phase was prepared by dissolving 8 g of potassium dihydrogen phospahte in 100 mL of water and volume was made up to 1000 mL with water followed by adjusting the solution to pH 3 using dilute ortho phosphoric acid. The buffer was filtered using 0.45µm filter to remove all fine particles* (Bondili & Mentada, 2011).

### 4.1.1. Linearity

The linearity of an analytical procedure is its ability to obtain test results (peak areas) which are directly proportional to the concentration in the sample in order to determine the straight-line equation to be used thought the entire study (ICH, 2005).

In our study, 7 different DSL concentrations within the level of 50 to 700 μg/mL in mobile phase were used to construct the calibration curves. Calibration curves were constructed for DSL in the mobile by plotting their concentrations versus their respective relative peak areas/retention time (AUC/Rt) using a linear least squares regression analysis. HPLC was used to analyze the sample of each concentration and the whole work was repeated three times.

### 4.1.2. Range

The range of an analytical procedure describes the interval of the lowest and highest amounts of analyte in the sample including the limits in which the analytical procedure provides acceptable level of accuracy, precision and linearity. The range is mainly determined based on the intended application of the procedure by the help of the linearity studies. When the range is determined, some specific ranges should be taken into consideration as following (ICH, 2005):

- Usually, 80-120% of the test concentration for the analysis of a drug or finished product.
- At least 70-130% of the test concentration for the content uniformity analysis. Sometimes wider range could be justified depending on the dosage form.

### 4.1.3. Accuracy

Accuracy or trueness of an analytical procedure describes the closeness of the resulted value to the conventional true value or accepted reference value. Accuracy should be determined covering the specified range of the procedure which is accomplished by calculating the amounts of the analyte resulted from analyzing known concentrations using the straight-line equation and compare them to the actual quantities. At least, 3 different concentrations across the specified range repeated for 3 times should be used when

establishing the accuracy (ICH, 2005). Results are given as percent recovery (% recovery), standard error (SE), standard deviation (SD) and relative standard deviation (RSD).

### 4.1.4. Precision

The precision of an analytical procedure shows the degree of scatter (closeness of agreement) between a set of measurements obtained from various sampling of the same homogeneous authentic sample under particular conditions. If it's difficult to obtain a homogenous sample for the precision study, an artificially prepared sample or a sample solution could be used instead. Precision may be studied at many levels as following (ICH, 2005):

- Intra-assay precision: in which the precision is studied under the same specified conditions over a short period of time. It's also called repeatability.
- Intermediate precision: in which the precision shows the variations within the same laboratory; different days, different equipment, etc.
- Reproducibility: it shows the precision between different laboratories.

In our work, a standard solution of DSL was used for the precision study. Intra-assay precision (intra-day precision) and intermediate precision (inter-day precision) were investigated using 3 different concentrations repeated for 6 times for 3 days. RSD was used to express the precision.

### 4.1.5. Detection limit

The detection limit (DL) of analytical procedure is the minimum amount of analyte in a sample which can be detected but not quantitatively determined. A variety of methods can be used to determine the DL depending on whether the procedure is instrumental or not. These methods are based on: visual evaluation, signal-to-noise, or on the SD of the response and the slope in which the SD is determined based on the response of blank samples or on the calibration curve of the analyte (ICH, 2005).

In our work, equation (4.1) was used to determine the detection limit (ICH, 2005):

$$DL = \frac{3.3 * \text{SD}}{\text{Slope}} \quad (4.1)$$

In equation (4.1), SD is the standard deviation of y-intercepts of regression lines and slope is estimated from the calibration curve of the analyte.

### 4.1.6. Quantitation limit

The quantitation limit (QL) of analytical procedure expresses the minimum amount of analyte in a sample which can be detected in exact quantity with suitable accuracy and precision. Whether the procedure is instrumental or not, the same methods that used in determining the DL can be applied to determine the QL(ICH, 2005).

In our work, equation (4.2) was used to calculate the QL (ICH, 2005):

$$QL = \frac{10 * \text{SD}}{\text{Slope}} \quad (4.2)$$

In equation (4.2), SD is the standard deviation of y-intercepts of regression lines and slope is estimated from the calibration curve of the analyte.

### 4.1.7. Specificity

The specificity of analytical procedure aims to provide a proper level of discrimination of the analyte in the sample in the presence of any other materials that expected to be present such as impurities, excipients, degradation products, etc. The selectivity may be confirmed by coupling the positive results obtained from the sample containing the analyte with the negative results that obtained from the sample without the analyte. The discrimination between the analyte and the related materials of similar structures can be confirmed by obtaining a negative response. Representative chromatograms should be used for specificity studies of chromatographic procedures. The peak of the chromatogram in purity test is a useful way to show that the analyte's peak is attributable to one component. Other approaches can be used to establish the specificity depending on the purpose of the analytical procedure (ICH, 2005).

In our study, the specificity test was carried out by HPLC operating method using a sample of standard DSL in mobile phase, mobile phase itself, and placebo solutions of the other components in the mobile phase.

### 4.2. Preparation of the Oral Film

Solvent casting method has been used in our work. Different polymers and plasticizers with different ratios have been studied as presented in Table 4.2. in order to choose the formula with the best film forming properties and high transparency.

**Table 4.2.** *Formulation trials for selecting polymer and plasticizer*

| Ingredients | Formula 1 | Formula 2 | Formula 3 | Formula 4 |
|---|---|---|---|---|
| **HPMC (mg)** | 1250 | 1250 | - | - |
| **PEG 400 (µL)** | 500 | - | - | - |
| **Gly (µL)** | | 500 | 500 | 500 |
| **PVA (mg)** | - | - | 1250 | - |
| **Eudragit RS 100 (mg)** | - | - | - | 1250 |
| **CA (mg)** | 100 | 100 | 50 | 50 |
| **Sorbitol (µL)** | 1000 | 1000 | 2000 | 2000 |
| **Tween 80 (µL)** | 50 | 50 | 50 | 50 |
| **Water (mL)** | 25 | 25 | 40 | 40 |
| **Ethanol (mL)** | 25 | 25 | - | 20 |

The polymer was dissolved in distilled water with/without alcohol by the help of 3 hours stirring using the magnetic stirrer at speed of 500 rpm. The homogenous solution kept aside to get rid of any entrapped air bubbles. Meanwhile, in another beaker the excipients were dissolved and stirred for 30 min at 150 rpm. After the completion of stirring, both solutions are mixed and stirred together for 1 hour at 150 rpm. Finally, the solution is casted on 8.5 cm X-plate petri dish (4 compartments) by pipetting 3000,4000, and 6000 µL of each

formula and kept in a hot air oven at 40°C for 24 hours. The dried films were gently separated from the petri dish.

After selecting the best polymer, it has been studied with different ratios of plasticizer as presented in Table 4.3. using the same previous method. However, the active ingredient has been added to the second beaker and 0.1 M NaOH was added to the final solution to adjust its pH. The final solution was casted on 3 cm petri dish by pipetting 3000 µL of each formula. The dried films were gently separated from the petri dish and cut into desired sizes (2×2 cm). Each petri dish provided us with one film. The films left inside the desiccator containing anhydrous calcium chloride wrapped in aluminum foil at room temperature until further use.

**Table 4.3.** *Formulation trials of HPMC as a film forming agent*

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| **HPMC (mg)** | 1250 | 1250 | 1250 | 1250 | 1250 | 1250 |
| **PEG 400 (µL)** | 500 | 1000 | 1500 | - | - | - |
| **Gly (µL)** | - | - | - | 500 | 100 | 1500 |
| **DSL (mg)** | 5 | 5 | 5 | 5 | 5 | 5 |
| **CA (mg)** | 50 | 50 | 50 | 50 | 50 | 50 |
| **Sorbitol (µL)** | 2000 | 2000 | 2000 | 2000 | 2000 | 2000 |
| **Tween 80 (µL)** | 50 | 50 | 50 | 50 | 50 | 50 |
| **Water (mL)** | 25 | 25 | 25 | 25 | 25 | 25 |
| **Ethanol (mL)** | 25 | 25 | 25 | 25 | 25 | 25 |
| **NaOH (µL)** | 4500 | 4500 | 4500 | 4500 | 4500 | 4500 |

In order to enhance the film properties, new formulations (A1-C6) with desired dose of DSL have been studied as presented in Table 4.4. The method of preparation has been modified as following:

- Required amount of HPMC was weighed and dispersed in the solvent mixture of ethanol and water. By the help of magnetic stirrer, a homogeneous viscos solution formed.
- Required amounts of plasticizer and DSL were added to the solution and mixed to get a clear solution.
- The solution was degassed by sonicating it for 5 minutes by the help of a bath sonicator.
- The solution was poured into a petri dish of 8.5 cm diameter and dried at 60°C for the first 30 minutes then at 40°C for the next 24 hours.
- The dried films were gently separated from the petri dish and cut into desired sizes (2×2 cm) and left inside the desiccator containing anhydrous calcium chloride wrapped in aluminum foil at room temperature until further use.

The total amount of drug required for the film has been calculated according to the following:

1. The dose of drug required per film = 5 mg
2. 4 films of 4 $cm^2$ (2×2 cm) can be obtained from every petri dish.
3. Area of the Petri dish = ($\pi \times radius^2$) = 3.14 × 4.25 = 56.72 $cm^2$
4. Area of required 4 films = 4 $cm^2$ × 4 = 16 $cm^2$
5. Amount of drug in the required area = 20 mg
6. Unrequired area = Total area of petri dish - Required area= 56.77 - 16 = 40.72 $cm^2$
7. Accordingly, amount of drug in the unrequired area = 50.96 mg (If 4 $cm^2$ contains 5 mg of drug then 40.77 $cm^2$ contains 50.9 mg of drug).
8. Total drug amount = (Amount of drug in the required area) + (Amount of drug in the unrequired area) = 50.9 + 20 = 70.9 mg
9. Additional 17 mg of drug has been added for its approximate loss in the viscous solution retained in the beaker and as a part of the dried film on the side surface of the petri dish.

**Table 4.4**. *Formulation trials of HPMC with desired dose of DSL*

| Formulation Code | DSL (mg) | HPMC (mg) | PEG 400 (mg) | Gly (mg) | PG (mg) | Water (mL) | Ethanol (mL) |
|---|---|---|---|---|---|---|---|
| **A1** | 88 | 300 | 45 | - | - | 3 | 7 |
| **A2** | 88 | 300 | - | 45 | - | 3 | 7 |
| **A3** | 88 | 300 | - | - | 45 | 3 | 7 |
| **A4** | 88 | 600 | 45 | - | - | 3 | 7 |
| **A5** | 88 | 600 | - | 45 | - | 3 | 7 |
| **A6** | 88 | 600 | - | - | 45 | 3 | 7 |
| **B1** | 88 | 300 | 67.5 | - | - | 3 | 7 |
| **B2** | 88 | 300 | - | 67.5 | - | 3 | 7 |
| **B3** | 88 | 300 | - | - | 67.5 | 3 | 7 |
| **B4** | 88 | 600 | 67.5 | - | - | 3 | 7 |
| **B5** | 88 | 600 | - | 67.5 | - | 3 | 7 |
| **B6** | 88 | 600 | - | - | 67.5 | 3 | 7 |
| **C1** | 88 | 300 | 90 | - | - | 3 | 7 |
| **C2** | 88 | 300 | - | 90 | - | 3 | 7 |
| **C3** | 88 | 300 | - | - | 90 | 3 | 7 |
| **C4** | 88 | 600 | 90 | - | - | 3 | 7 |
| **C5** | 88 | 600 | - | 90 | - | 3 | 7 |
| **C6** | 88 | 600 | - | - | 90 | 3 | 7 |
| **D1** | 88 | 300 | 120 | - | - | 3 | 7 |
| **D2** | 88 | 300 | - | 120 | - | 3 | 7 |

25 mg of CA was added to the second batch of the selected formulations among A1-C6 and 2 new formulations (D1, D2) with 25 mg CA were added for further studying.

### 4.3. Characterization of DSL Oral Film

#### 4.3.1. Disintegration time

In our study, the film of 4 $cm^2$ was placed in a petri dish containing 10 mL of distilled water with swirling every 10 sec. The time required for the film to break was considered as the disintegration time. Four films of selected formulas were subjected to disintegration test. Mean and SD were calculated.

#### 4.3.2. Mechanical properties evaluation

In our study, manual folding endurance was done to study the mechanical properties of the films. The film was folded at the same place until the it starts to break. Number of times before the film breaks or develops a visible crack is considered as the folding endurance value (Centkowska et al., 2020). Four films of selected formulas were subjected to folding endurance test. Mean and SD were calculated.

#### 4.3.3. Surface pH

The surface pH is measured to investigate any possible of side effects of ODFSs upon oral consumption. In our study, the pH of the film was measured by allowing the film to get wet first by placing it in a petri dish containing 1 mL of distilled water for 1 minute. Then, the pH meter electrode was brought near the surface of the oral film and the value recorded after equilibration Three films of selected formulas were subjected to surface pH test. Mean and SD were calculated (Sjöholm & Sandler, 2019).

#### 4.3.4. Weight variation

In our study, 10 films of each selected formula were randomly selected from different batches and their weights were recorded using sensitive balance. Mean of weights, SD, and % of weight variation were calculated (Singh et al., 2013).

### 4.3.5. Thickness

In our study, 6 films of each selected formula were randomly selected from different batches and their thicknesses were recorded using digital Vernier caliper. The thickness was measured at 5 different locations of the film; the four corners and the center. Mean of thickness and SD were calculated to evaluate the variation in thickness (Alhayali et al., 2019).

### 4.3.6. Scanning electron microscopy

SEM test is performed to evaluate the surface morphology of the film (Bharti et al., 2019). In our study, a small piece of the film was coated with gold on carbon tape and placed on a circular aluminum stub in a high vacuum evaporator. Accelerating voltage of 15 kV was used for imaging. The morphological images of the film were obtained by SEM at 3 definite magnifications; 1.2 K X, 2.5 K X, AND 5.0 K X (K=1000). In order to give a proper judgment, 2 films of the excluded ones because of their visible roughness on one side were subjected to SEM test at 100 X, 200 X, 500 X and 1.2 K X magnifications to provide an indicator of smoothness/roughness of the selected films.

### 4.3.7. Drug content and content uniformity

In order to run the drug content test, phosphate buffer solution (PBS) of pH 6.8 was prepared using phosphate buffer tablets of pH 6.8. One tablet was dissolved in 100 mL distilled water by the help of a magnetic stirrer. Each film was placed inside a volumetric flask and 10 mL of PBS was added. The flask kept a side for 5 min followed by 1-minute mixing using the vortex mixer to ensure complete dissolving of the film. Entrapped air bubbles were removed by the help of bath sonicator for 20 minutes. The solution was filtered through 0.45µm filter and 1 mL of each film solution was taken for HPLC analysis (Singh et al., 2013; Patil et al., 2013). The test has been done 3 times for each film formulation and 3 samples of each film solution were taken. The drug content in each film was calculated using the linearity equation. % Drug content was calculated as each film is claimed to contain 5 mg of DSL using equation 4.3 (Centkowska et al., 2020). Mean, SD and RSD were calculated to evaluate the drug content and its uniformity.

$$Drug\ content\ \% = \frac{Found\ drug\ content\ (mg)}{Claimed\ \ drug\ content\ in\ 2 \times 2\ cm\ film\ (mg)} \times 100 \quad (4.3)$$

### 4.3.8. Moisture loss and moisture uptake

Moisture content tests (moisture loss and moisture uptake) are important in determination the suitable type of packaging and storage conditions a particular dosage form requires (Singh et al., 2013). Moisture loss test is important to guarantee film dryness. (Al-Mogherah et al., 2020).

In our study, moisture loss test was performed by recording the weights of the films (which represent the initial weight) and then keep them wrapped in aluminum foil inside the desiccator at room temperature for 72 hours. After 72 hours, their weights were recorded again (which represent the final weight) and % moisture loss was calculated as % weight loss using equation 4.4 (Bharti et al., 2019). The test was repeated 3 times for each formulation. Mean and SD were calculated.

$$Moisture\ loss\ \% = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100 \quad (4.4)$$

The moisture uptake test is important to evaluate the hygroscopic properties of the film (Al-Mogherah et al., 2020).

In our study, moisture uptake test was performed by recording the weights of the films (which represents the initial weight) and then keep them wrapped in aluminum foil inside the humidity chamber at room temperature under 75% relative humidity conditions for 72 hours. After 72 hours, their weights were recorded again (which represent the final weight) and % moisture uptake was calculated as % weight gain using equation 4.5 (Reddy et al., 2016). The test was repeated 3 times for each formulation. Mean and SD were calculated.

$$Moisture\ uptake\ \% = \frac{Final\ weight - Initial\ weight}{Initial\ weight} \times 100 \quad (4.5)$$

### 4.3.9. Differential scanning calorimetry

Differential scanning calorimetry (DSC) is one of the thermal analysis techniques that determines the heat flow connected to a material transition as a function of time and temperature. DSC measures the heat (absorbed or radiated) by the sample depending on a temperature difference between the sample and a reference. DSC detects the transition temperature (melting point) of the sample in a solution, solid, or mixed phase (Pooria et al., 2010).

DSC test was carried out to investigate the compatibility of the pure substances (drug and polymer) and to detect any possible physical or chemical interactions between the components after film formation. The analysis was done by analyzing pure DSL, DSL+HPMC physical mixture, and using a small part of each film (Panchal et al., 2012; Al-Mogherah et al., 2020). Each sample was placed in an aluminum cell that has been closed with pressure. The thermal analysis was done at a temperature range of 25 to 200ºC with a temperature increase of 10ºC/min. An empty aluminum sample cell was used as a reference.

### 4.3.10. Fourier transform infrared spectroscopy

FT-IR analysis is another thermal technique to investigate any potential interactions between the drug and the other components. Any changes in the absorption bands or the appearance of new ones are an indication of interactions between the drug and the other components (Veronez et al., 2014).

FT-IR test was done to investigate the compatibility of the pure substances (drug and polymer) and to detect any possible interactions between the components after the film formation by analyzing pure DSL, its physical mixture with HPMC, and a sample of drug-loaded film (Panchal et al., 2012). The test was performed by scanning samples at the wavelength range of 4000 - 400 $cm^{-1}$ and FT-IR spectra were recorded.

### 4.3.11. Dissolution test

Basket apparatus (USP 1) was used to carry out the dissolution test. The films were placed inside the baskets and the vessels were filled of 500 mL of PBS (pH 6.8). The test

was carried out at 37.5 ± 1 °C with speed of 50 rpm (Adrover et al., 2015). Samples of 1 mL were collected at time intervals of 15 sec, 30 sec, 1 min, 2 min, 4 min, 8 min, 16 min and 30 min. 1 mL prefilled syringes of blank solution were prepared to replace the taken sample in order to maintain the sink-conditions after each sampling. The samples were filtered using 0.45µm filter and analyzed for the drug concentration using HPLC analysis. % Cumulative drug release was calculated. The drug release studies were performed 3 times and mean values were taken.

# 5. RESULTS AND DISCUSSION

## 5.1. Analytical Validation Studies

Quantitative HPLC was used in our study as it's known to be simple, rapid, and reliable (Bondili & Mentada, 2011). Our methods were validated and evaluated according to ICH recommendations. The used methods were confirmed to be suitable according to these recommendations as will discussed in details (ICH, 2005).

### 5.1.1. Linearity

In our study, solutions of DSL of different concentrations were prepared in the mobile phase and analyzed by HPLC. Concentrations of 50, 100, 200, 300, 400, 500, 600, and 700 µg/mL were used. ICH recommends using at least 5 different concentrations (ICH, 2005). Plotting concentrations versus AUC/Rt was used to obtain the linearity graph. The linearity was examined by using the least square regression equation. The DSL chromatogram is shown in Figure 5.1 and the AUC/Rt values obtained by HPLC analysis for the DSL concentrations are shown in Table 5.1.

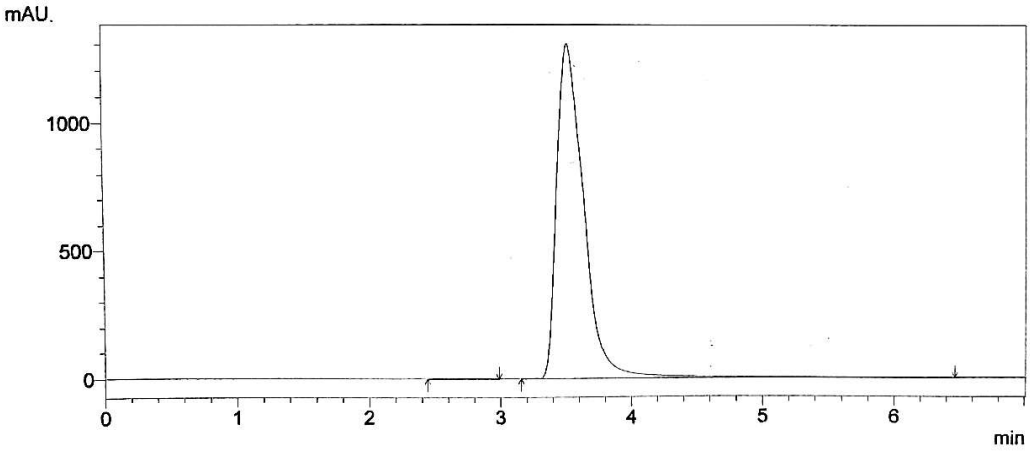


**Figure 5.1.** *Chromatogram of standard DSL*

The right equation in the result of the work done is y=13322x-74448 and regression square ($r^2$) = 0.9999. A value equals to 0.9996 is considered good enough to ensure linearity

(Sjöholm & Sandler, 2019). Accordingly, our method has excellent linearity. The linearity graph is shown in Figure 5.2.

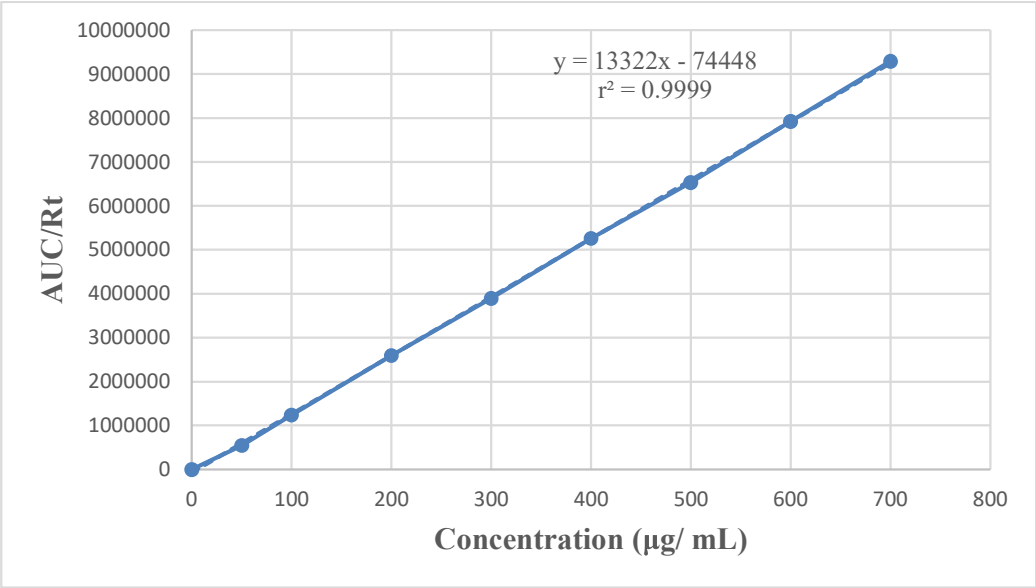


**Figure 5.2.** *Calibration curve and linearity equation of DSL*

**Table 5.1.** *AUC and Rt values obtained by HPLC analysis of DSL*

| DSL concentration (µg/mL) | AUC | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1. Set | | | 2. *S*et | | | 3. *S*et | | | Mean ± SE |
| | AUC | Rt | AUC/ Rt | AUC | Rt | AUC/ Rt | AUC | Rt | AUC/ Rt | |
| **50** | 1969911 | 3.67 | 536760.4905 | 2051304 | 3.64 | 563545.0549 | 1953119 | 3.63 | 538049.3113 | 546118.2856 ± 8721.3242 |
| **100** | 4479689 | 3.647 | 1228321.6340 | 4570918 | 3.653 | 1251277.8540 | 4567726 | 3.643 | 1253836.3990 | 1244478.6290 ± 8112.1903 |
| **200** | 9365608 | 3.658 | 2560308.3650 | 9620751 | 3.660 | 2628620.4920 | 9511778 | 3.658 | 2600267.3590 | 2596398.7390 ± 19814.6522 |
| **300** | 14193758 | 3.667 | 3870673.0300 | 14251373 | 3.665 | 3888505.5930 | 13916993 | 3.543 | 3928025.1200 | 3895734.5810 ± 16946.0837 |
| **400** | 19091357 | 3.64 | 5244878.2970 | 18837030 | 3.496 | 5388166.4760 | 18854044 | 3.656 | 5157014.2230 | 5263352.9990 ± 67364.2510 |
| **500** | 23692071 | 3.61 | 6562900.5540 | 23395393 | 3.608 | 6484310.6980 | 23172386 | 3.535 | 6555130.4100 | 6534113.8880 ± 25002.4133 |
| **600** | 27570304 | 3.537 | 7794827.2550 | 28255210 | 3.525 | 8015662.4110 | 28047425 | 3.521 | 7965755.4670 | 7925415.0440 ± 66864.4247 |
| **700** | 33125691 | 3.571 | 9276306.6370 | 32849193 | 3.535 | 9292558.1330 | 32915086 | 3.536 | 9308565.0450 | 9292476.6050 ± 9312.2896 |

### 5.1.2. Range

The range of the analytical procedure was 50 to 700 µg/mL and the calibration curve was selected at the same concentration limits.

### 5.1.3. Accuracy

Three different concentrations (150, 350, and 550 µg/mL) of DSL were prepared for HPLC analysis for 3 repetitions for each. Using the linearity equation, the actual concentrations were calculated and the accuracy of the method was determined by comparing the results with known concentrations in terms of % recovery. As stated in literature; 97-103% of % recovery is an accepted interval for a method to be accurate (Bondili & Mentada, 2011). According to the obtained results presented in Table 5.2. the method has been approved to be accurate with accepted level of recovery.

**Table 5.2.** *% Recovery of DSL by HPLC Analysis*

| **Added concentration (µg/mL)** | **150** | **350** | **550** |
|---|---|---|---|
| **Found concentration (µg/mL) (Mean±SD)** | 151.9963±1.3197 | 350.7301±1.7247 | 554.0389±0.7782 |
| **% Recovery** | 101.3309 | 100.2086 | 100.7343 |
| **SE** | 0.7619 | 0.9958 | 0.4493 |
| **RSD** | 0.8683 | 0.4918 | 0.1405 |

### 5.1.4. Precision

Intra-assay precision (intra-day precision) and intermediate precision (inter-day precision were investigated using 3 solutions of DSL at concentrations of 200, 400, and 600 µg/mL. The samples were analyzed 6 times for each concentration and the whole same process repeated on 3 consecutive days. The calculated RSD is less than 2% which indicates an accepted level of precision of the analytical method (Bondili & Mentada, 2011). The results are shown in Tables 5.3, 5.4, and 5.5.

**Table 5.3.** *Results of precision study for 200 µg/mL of DSL*

| 200 µg/mL | Intra-day (n=6) | | | Inter-day (n=18) |
|---|---|---|---|---|
| | AUC/Rt | | | AUC/Rt |
| | 1.Day | 2.Day | 3.Day | |
| **Mean** | 2886502.5 | 2876109.539 | 2803399.753 | 2855337.264 |
| **SD** | 21481.7681 | 35825.3999 | 24434.2302 | 46453.8293 |
| **SE** | 8769.8951 | 15045.7242 | 9975.2327 | 10949.2726 |
| **RSD** | 0.7442 | 1.2814 | 0.8716 | 1.6269 |

**Table 5.4.** *Results of precision study for 400 µg/mL of DSL*

| 400 µg/mL | Intra-day (n=6) | | | Inter-day (n=18) |
|---|---|---|---|---|
| | AUC/Rt | | | AUC/Rt |
| | 1.Day | 2.Day | 3.Day | |
| **Mean** | 5625207.632 | 5651224.494 | 5583777.952 | 5620070.026 |
| **SD** | 49105.6712 | 29706.649 | 41323.0361 | 47830.5153 |
| **SE** | 20047.3063 | 12127.6887 | 16870.0589 | 11273.7606 |
| **RSD** | 0.8729 | 0.5257 | 0.7401 | 0.8511 |

**Table 5.5.** *Results of precision study for 600 µg/mL of DSL*

| 600 µg/mL | Intra-day (n=6) | | | Inter-day (n=18) |
|---|---|---|---|---|
| | AUC/Rt | | | AUC/Rt |
| | 1.Day | 2.Day | 3.Day | |
| **Mean** | 8511187.459 | 8534048.414 | 8414755.554 | 8486663.8090 |
| **SD** | 68664.2079 | 64051.2659 | 74847.6527 | 84087.6960 |
| **SE** | 28032.0455 | 26148.8198 | 30556.4263 | 19819.6600 |
| **RSD** | 0.8068 | 0.7505 | 0.8895 | 0.9908 |

### 5.1.5. Detection limit

The DL was calculated using equation 4.1 which was mentioned in section 4.1.5. DL equals to 2.7892 μg/mL.

### 5.1.6. Quantitation limit

The QL was calculated using equation 4.2 which was mentioned in section 4.1.6. QL equals to 8.4520 μg/mL. Therefore, concentration ≈ 8.5 μg/mL is considered as the lowest concentration that can be measured with acceptable level of accuracy and precision. The calculated DL value (≈2.8 μg/mL) is lower than this value which indicates that our method is sensitive.

### 5.1.7. Specificity

Analysis of standard DSL for specificity studies were performed by HPLC operating method. The chromatograms showed that there were no interfering peaks at the retention time of DSL so the HPLC operating method was confirmed to be specific for DSL. The chromatograms related to specificity test are shown in Figure 5.3.

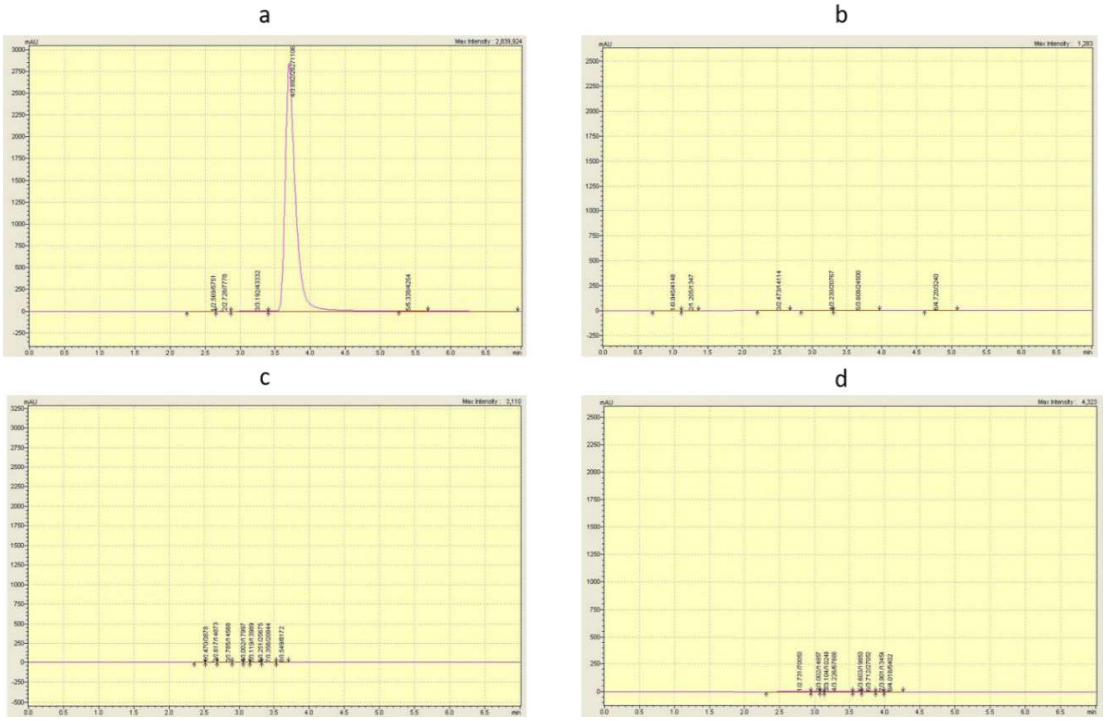


**Figure 5.3.** *Chromatograms of analyzes of the selectivity studies: a: DSL, b: HPMC, c: Mobile phase, d: Glycerol*

## 5.2. Preparation of the Oral Film and Selecting the Best Formulations

Selecting the best formulas among all the formulations prepared was the most challenging step during this study. First of all, we need to pay attention to the physical appearance and general homogeneity of the films by visual examination and by touch (Chaudhary et al., 2013)**.** A film of good properties should be smooth with no visible roughness and transparent in appearance (Galgatte et al., 2013; Abdelbary et al., 2014). Sticky films are unsuitable for this application (Garsuch & Breitkreutz, 2010)**.** The results are presented in Tables 5.6 and 5.7. We aimed to get smooth, transparent, non-sticky, and rapidly dissolved film with good mechanical properties.

According to these results, HPMC was selected as the polymer of study. All F1-F6 formulations were transparent and non- sticky. However, NaOH was added to formulations F1-F6 to adjust the pH and there was a slight effect on the transparency. Taking into consideration the very low pH values of the viscous solution before poring it into the petri

dish and most importantly the long disintegration time and poor mechanical properties of the films as will be discussed in the characterization section led us to formulations A1-D2.

**Table 5.6.** *Physical appearance and texture analysis of formulas 1-4*

| | | Film formation | Transparency | Stickiness |
|---|---|---|---|---|
| **Formula 1** | | Yes | Transparent | Not sticky |
| **Formula 2** | | Yes | Transparent | Not sticky |
| **Formula 3** | **Pipetting 3000 µL** | Yes, but after 36 hours | Not totally transparent | Not sticky |
| | **Pipetting 4000, 6000 µL** | Yes, but after 48 hours | Not totally transparent | sticky |
| **Formula 4** | **Pipetting 3000 µL** | No, even after 72 hours | - | - |
| | **Pipetting 4000, 6000 µL** | No, even after 72 hours | - | - |

**Table 5.7.** *Physical appearance and texture analysis of A1-D2 films*

| Formulation Code | Film formation | Transparency | Stickiness |
|---|---|---|---|
| **A1, A2, A4, A5** | Yes | Transparent | Not sticky |
| **A3** | No | - | - |
| **A6** | Yes | Not transparent | Sticky |
| **B1, B2, B4, B5** | Yes | Transparent | Not sticky |
| **B3** | No | - | - |
| **B6** | Yes | Not transparent | Sticky |
| **C1, C2, C4, C5** | Yes | Transparent | Not sticky |
| **C3** | No | - | - |
| **C6** | Yes | Not transparent | Sticky |
| **D1, D2** | Yes | Transparent | Not sticky |

Accordingly, A3, B3, and C3 formulations were excluded from any further studies for not forming a film at all. A6, B6, and C6 formulations were also excluded from any further studies because of the stickiness of formed films that makes them hard to handle. A3, B3, C3, A6, B6, and C6 contain PG as a plasticizer and this indicates its poor plasticizing properties comparing to PEG 400 and Gly. Figure 5.4 shows a non-sticky transparent film right after separating it from the petri dish and after cutting it into 2×2 cm film.

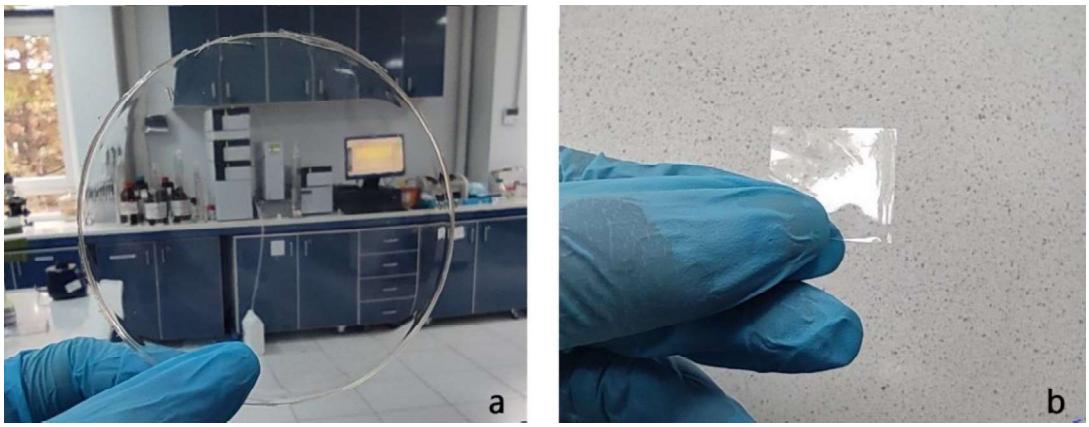


**Figure 5.4.** a: *Non-sticky transparent film separated from petri dish,* b: *Film of desired size (2x2 cm)*

Approximately 0.5 cm of the film formed on the side surface of the petri dish as shown in Figure 5.5. and that's why the amount of added DSL was 88 mg.

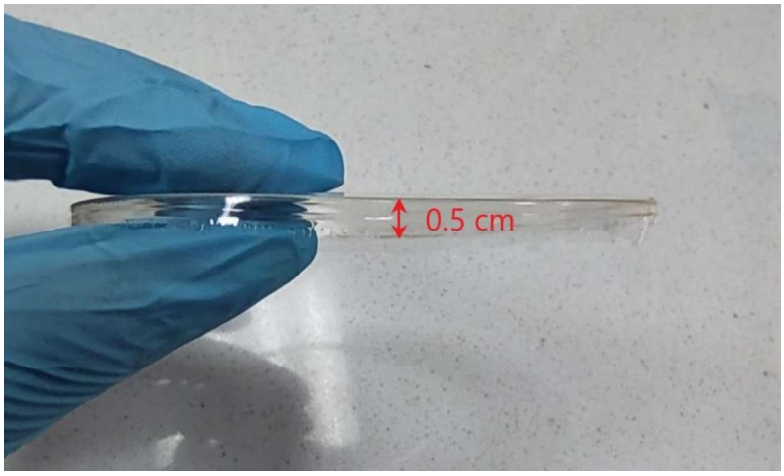


**Figure 5.5.** *Film formed on the side surface of petri dish*

### 5.3. Characterization of DSL Oral Film

No specified requirements for the evaluation process of these films are explained in the pharmacopeias such as in Ph. Eur. due to the newness of this dosage form. The only mentioned requirements in the Ph. Eur. are having good mechanical properties to endure handling without breakage with fast disintegration of the films (Speer et al., 2018). In literature, optimum ODFs are reported to have low disintegration time with a transparent appearance (Kulkarni et al., 2010). It's important to mention that among the selected formulation in our study based on the previous section, transparent with no visible roughness films were subjected to the characterization tests. Other films, especially those near to the edges or with visible roughness or imperfections were excluded from any study (Abdelbary et al., 2014).

#### 5.3.1. Disintegration time

Many disintegration test methods are reported in the literature such as the petri dish method and slide frame method. In the petri dish method, the film is placed on the top of known volume fluid in a petri dish or glass vessel. The volume of the fluid is varied in the literature between 2, 4, 10, 15, and 25 mL to mimic the small volume of the saliva. The petri dish could be swirled at defined time intervals to simulate the rinse conditions over the film's surface in the mouth medium (Speer et al., 2018). In a lot of studies, the time required for the film to start breaking is defined as disintegration time. In other studies, the time required for complete dissolving is defined as a disintegration time. However, other studies define the time required for complete dissolving as dissolving time, not disintegration time (Hoffmann et al., 2011; Parejiya et al., 2013). In the slide frame method, the film is assembled to a slide over a petri dish and a defined fluid volume is poured to the center of the film. The time required for the film to form a hole or for the fall down of the first drop of the fluid through the film into the petri dish beneath is defined as the disintegration time. (Hoffmann et al., 2011; Speer et al., 2018). Accordingly, the disintegration test using petri dish method in a media of 10 mL with swirling every 10 sec while the time required for the film to break was considered as the disintegration time has been done in our study.

All F1-F6 formulations started to disintegrate after more than 1 min which does not meet the requirements of ODFs as these films typically disintegrate in the range of 5 to 30 sec (Hoffmann et al., 2011). This was the first main reason to exclude these formulations from further studies.

Table 5.8. shows the disintegration time of selected formulations among the first batch of A1-C2 formulas with no citric acid.

**Table 5.8.** *Disintegration time of A1-C2 films*

| Film code | Disintegration time (Sec) | Film code | Disintegration time (Sec) |
|---|---|---|---|
| **A1** | 10 | **A4** | 62 |
| **A2** | 9 | **A5** | 70 |
| **B1** | 4 | **B4** | 25 |
| **B2** | 6 | **B5** | 33 |
| **C1** | 13 | **C4** | 28 |
| **C2** | 8 | **C5** | 40 |

Investigation of paracetamol oral films made of HPMC using solvent casting method showed that it takes 3.5 minutes for the strip with the lowest concentration of HPMC to disintegrate completely while 4 minutes was needed for the formulation with the higher amount of HPMC (Upret et al., 2014). Similar conclusion of prolonged disintegration time related to the increase of HPMC concentration has been noted extensively in literature (Liew et al., 2014). Loratadine oral films were prepared using HPMC E3, HPMC E6 and HPMC E15 with different concentrations (300,600 and 900 mg). As the concentration increased the disintegration time was longer with ranges of (25-29, 29-46, and 41-64) sec for HPMC E3, HPMC E6 and HPMC E15 films respectively (Raju et al., 2013). Decreasing the HPMC concentration produced films with rapid disintegration (Liew et al., 2014). In our study, it was obvious that increasing the amount of the polymer increases the time needed for the film to disintegrate. Formulas A4, A5, B4, B5, C4, and C5 contain the double quantity of

HPMC (600 g) with disintegration time ranges from 25 to 70 sec comparing to formulas A1, A2, B1, B2, C1, and C2 that have 300 mg HPMC with disintegration time ranges from 4 to 13 sec.

Increase in PEG 400 and Gly concentrations produced ODF with shorter disintegration time (Liew et al., 2014). Any decrease or increase in the plasticizer concentration should be done carefully. High amounts form sticky films and low amounts form films with poor flexibility as reported in literature (Chaudhary et al., 2013). In our study, increasing the amount of plasticizer decreases the disintegration time significantly in the formulas of high polymer concentration (600 mg) as noted in formulas B4 and B5 that contain higher amount of plasticizer comparing to A4 and A5. The same conclusion applies to C4 and C5 which have the double amount of the plasticizer comparing to formulas A4 and A5. However, this decline in disintegration time was not very clear in formulations of low polymer concentration (300 mg). Plus, B formulations have the lowest disintegration time even though they don't contain the highest amount of plasticizer. Equal amounts of PEG 400 and Gly noted to have almost the same effect on the disintegration time in low polymer concentration films. However, PEG 400 resulted in lower disintegration time in high polymer concentration films.

The disintegration time limit of 30 seconds or less for orally disintegrating tablets (ODTs) described in the Center for Drug Evaluation and Research (CDER) guidance can be applied to ODFs (Bhyan et al., 2011). According to the previous results, formulas A4, A5, B4, B5, C4, and C5 were excluded from further studies for not meeting the requirements of rapidly dissolved oral films as in A4, A5, B5, and C5 films or for their relatively prolonged disintegration time value which were close to the highest accepted value (30 sec) as in B4 and C4.

CA has been added to the second batch of A1, A2, B1, B2, C1, and C2 formulas. However, films of formulas A1, A2, B1, B2 were easy to break and hard to handle as the amount of the plasticizer was not enough to plasticize the films (Galgatte et al., 2013). This result led us to exclude them and include formulations D1 and D2 with higher amount of plasticizer into our study. The disintegration test repeated for formulas C1 and C2 and their results alongside the results of D1 and D2 are represented in Table 5.9.

**Table 5.9.** *Disintegration time of C1, C2, D1, and D2 films*

| Film code | Disintegration time (Sec) | | | | |
|---|---|---|---|---|---|
| | **Film 1** | **Film 2** | **Film 3** | **Film 4** | **Mean ± SD** |
| **C1** | 11 | 11 | 12 | 11 | 11.25 ± 0.5000 |
| **C2** | 13 | 14 | 13 | 13 | 13.25 ± 0.5000 |
| **D1** | 9 | 9 | 8 | 8 | 8.50 ± 0.5773 |
| **D2** | 10 | 8 | 8 | 9 | 8.75 ± 0.9574 |

These results confirmed our claim of the effect of decreasing the disintegration time by increasing the plasticizer concentration as D formulations that have higher amount of the plasticizer disintegrate within 8.5-8.75 sec comparing to C formulations that disintegrate within 11.25-13.25 sec.

In our study films of PEG 400 as plasticizer tend to disintegrate slightly faster than those of Gly films in contrary to what has been reported in literature where Gly was reported to form films that disintegrate faster than those of PEG 400 (Galgatte et al., 2013; Kulkarni et al., 2010). However, the disintegration time values of both formulations (C and D) are accepted since they are less than 30 sec. Figure 5.6 shows a film after it started to disintegrate.

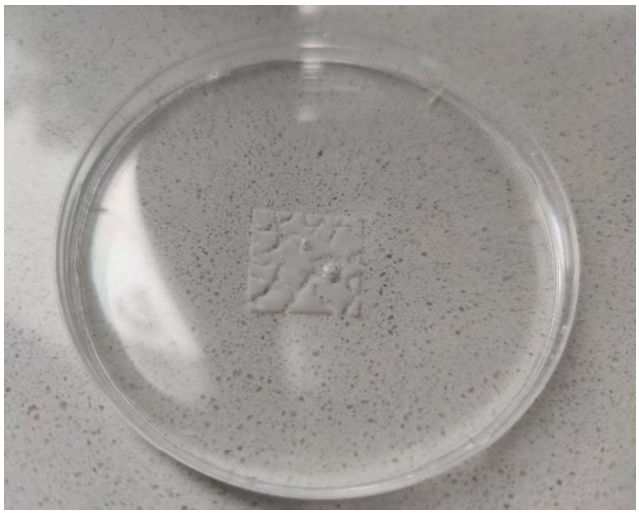

**Figure 5.6.** *Disintegrating of 2×2 cm film after placing it in a petri dish containing 10 mL of distilled water*

### 5.3.2. Mechanical properties evaluation

The mechanical properties of the films are very significant among their characteristics to be taken into consideration when the plan of film preparation is designed (Takeuchi et al., 2020).

The folding endurance test is the most proper indicator for the actual strength, ease of handling and other mechanical characteristics of the film during the manufacturing and dose administration. The folding endurance value can be obtained by determine how many times the film is able to be folded at the same point until it breaks. This test can be done manually as it has been done widely in most studies. However, a recent study has studied the ability to run it automatically in which the folding conditions are controllable. The strip was folded at the same point and at constant angle and speed. The value of folding until the film breaks was automatically recorded (Takeuchi et al., 2020).

The tensile test is another important test to evaluate the mechanical properties of the films that has been widely used. The tensile test provides information about strength, elasticity and toughness of the films. Tensile test equipment provides us with data needed to generate the stress-strain profile represented in Figure 5.7 (Felton et al., 2008). Generally, the stress- strain profile has at its initial part a linear region which represents the elastic deformation of the film followed by loss of linearity as the behavior shifted from elastic to plastic deformation. When reaching the maximum stress the film breaks (Franceschini et al., 2016).

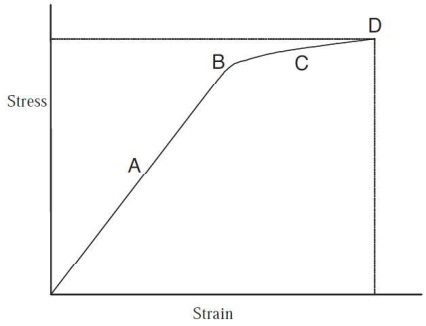


**Figure 5.7.** *Example of a stress–strain curve developed from tensile test. (A) Region of elastic deformation, (B) yield point, (C) region of plastic deformation, (D) film breaks (Felton et al., 2008)*

Based on this profile different mechanical parameters, namely, tensile strength, elongation, work of failure, and Young's modulus, are calculated. Tensile strength is the highest stress load applied to a point when the film raptures. Although, calculating the tensile strength alone is not helpful to evaluate the mechanical characteristics of the films, its high values are good indicator of film's abrasion resistance. It can be calculated by dividing the load at break over the cross-sectional area of the film as described in equation 5.1 (Felton et al., 2008).

$$\text{Tensile strength} = \frac{Load\ at\ failure}{Film\ thickness\ \times\ Film\ width} \tag{5.1}$$

A film elongates under applied stress, percent elongation can be calculated by dividing the increase in length of the film at the point of break over the initial length of the film multiplied by 100 as described in equation 5.2 (Franceschini et al., 2016).

$$\text{Percent elongation} = \frac{Increase\ in\ length\ of\ film}{Original\ length\ of\ film} \times 100 \tag{5.2}$$

Work of failure is the energy or work required to get the film raptured. It provides information about the toughness of the film. Work of failure can be calculated using three parameters; area under the curve, cross-head speed and the cross-sectional area of the film as described in equation 5.3 (Felton et al., 2008).

$$\text{Work of failure} = \frac{Area\ under\ curve\ \times\ Cross-head\ speed}{Film\ thickness\ \times\ Film\ width} \tag{5.3}$$

Young's modulus, also referred to as elastic modulus, is a measure of the stiffness of the film. It can be calculated using three parameters; the slope of the linear part of the stress-strain curve, film thickness and cross-head speed as described in equation 5.4 (Felton et al., 2008).

$$\text{Young's modulus} = \frac{Slope}{Film\ thickness\ \times Cross-head\ speed} \tag{5.4}$$

High values of tensile strength and Young's modulus with low elongation value indicate brittle and hard film. In contrast, tough and soft film resulted from low tensile strength and Young's modulus with high elongation value (Felton et al., 2008). An optimal

oral film should have moderate-high tensile strength, high elongation and low elastic modulus values (Hoffmann et al., 2011; Morales & McConville, 2011).

Accordingly, folding endurance test was performed in our study for intensive use in literature. High folding endurance value indicates good mechanical properties. Despite the fact that there is no specific range of folding endurance determined for good mechanical characteristics yet, a value more than 100 was believed to be good enough for handling (Takeuchi et al., 2020). A value of 300 times is sometimes reported as the maximum limit to the test (Morales & McConville, 2011). In our study, the film with folding endurance value ≥ 100 was considered to owe good mechanical properties.

Folding endurance values of F1-F6 formulations were less than 70 and that mostly resulted from the high polymer concentration (1250 mg of HPMC) in the formulations. This was the second main reason to exclude these formulations from further studies for not meeting the requirements of good mechanical properties. Folding endurance values of C1, C2, D1, and D2 films are represented in Table 5.10.

**Table 5.10.** *Folding endurance of C1, C2, D1, and D2 films*

| Film code | Folding endurance value | | | | |
|---|---|---|---|---|---|
| | **Film 1** | **Film 2** | **Film 3** | **Film 4** | **Mean ± SD** |
| **C1** | 60 | 58 | 64 | 67 | 62.25 ± 4.0311 |
| **C2** | 98 | 105 | 110 | 102 | 103.75 ± 5.0579 |
| **D1** | 97 | 93 | 100 | 95 | 96.25 ± 2.9861 |
| **D2** | 305 | 300 | 315 | 325 | 311.25 ± 11.0867 |

As a value ≥ 100 was set to determine the films of good mechanical properties, C2 and D2 films with a value of ≈ 104 and 311 respectively were noted to pass this test successfully. D1 films could be considered to owe good mechanical characteristics as their endurance values were very close to 100.

It was stated in literature that the incorporation of PEG 400 and Gly as plasticizers increased the elasticity of the films (Liew et al., 2014; Takeuchi et al., 2020) D1 films that

contain higher amount of PEG 400 than C1 films, provide almost 34 increase in folding endurance value, whereas D2 films that contain higher amount of Gly than C2 films provide very significant higher folding endurance value and it was noted to be the highest value among all the formulations (almost 310). It's obvious that increasing the amount of the plasticizer result in increasing the folding endurance value and therefore improving the mechanical properties of the film. It's important to pay attention to the plasticizer concentration in the formulation while considering the mechanical properties of the films. The plasticizer amount should be adjusted to avoid forming brittle film. However, high concentrations of plasticizer could result in agglomeration or sticking of the films during storage, which will affect the drug release from the dosage form (Felton et al., 2008).

It was stated that increasing the concentration of Gly has been found to provide higher elasticity (Liew et al., 2014). Significant difference in folding endurance value was reported in literature when equal amounts of PEG 400 and Gly were used; Gly and PEG 400 provided films with values equals to 275 and 135 respectively (Galgatte et al., 2013). Comparing C formulations that contain PEG 400 with D formulations that contain Gly in our study led us to consider Gly as better plasticizer. Different plasticizer with the same amount as in (C2, D2) and (C1, D1) result in nearly 207 and 34 disparities in the folding endurance values respectively.

### 5.3.3. Surface pH

Any variation in the pH of the oral cavity is a cause of concern. The normal range pH of the oral cavity is within 6.4-6.8. Irritation in the oral cavity can be resulted because of minor alterations in the pH of the oral cavity. This might cause the patient to spit out the oral dosage form. Therefore, it's important for the oral films to not cause significant alteration in the pH of the oral cavity after they come into contact with the oral mucosa (Singh et al., 2013). At the pH of saliva, ODFs tend to disintegrate faster to release the drug available for the absorption inside the oral cavity. In our study, all F1-F6 formulations recorded an acidic pH witch most probably resulted from the 50 mg of CA that used as saliva stimulating agent. It was possible to bring the pH values to the normal level by using NaOH solution. 4500 µL 0.1 M NaOH was enough to bring the pH values to the normal level (Sheikh et al., 2020). However, half of the amount of CA (25 mg) was used in C1, C2,

D1 and D2 films in order to get rid of adding NaOH step to adjust the pH. Surface pH values of C1, C2, D1, and D2 films are represented in Table 5.11.

**Table 5.11.** *Surface pH values of C1, C2, D1, and D2 films*

| Film code | Surface pH value | | | |
|---|---|---|---|---|
| | **Film 1** | **Film 2** | **Film 3** | **Mean ± SD** |
| **C1** | 6.39 | 6.43 | 6.44 | 6.42 ± 0.0265 |
| **C2** | 6.59 | 6.58 | 6.60 | 6.59 ± 0.0100 |
| **D1** | 6.48 | 6.46 | 6.50 | 6.48 ± 0.0200 |
| **D2** | 6.60 | 6.62 | 6.57 | 6.60 ± 0.0252 |

In literature, the surface pH values of ODFs were mostly in the range of 6.4-6.8 not to cause irritation to the oral mucosa (Raghavendra & Kumar, 2017; Bharti et al., 2019). Some studies recorded lower values such as 4.7-5.9 (Garcia et al., 2018), while others recoded higher values up to 7.1 (Sjöholm & Sandler, 2019). All prepared films (C and D formulations) recorded surface pH values between 6.39-6.62 which were within the normal range of oral cavity's pH. This ensures no significant change of the pH will result after the film come into contact with the oral mucosa. The prepared films are suitable for oral consumption.

### 5.3.4. Weight variation

Low weight variation is required to ensure the uniformity of the drug content in the films. A large variation might indicate inefficiency of the method employed (Nair et al., 2013). The weights of C1, C2, D1, and D2 films are represented in Table 5.12. Mean of weights, SD, and % of weight variation were calculated in order to give a proper judgment.

**Table 5.12.** *Weight and % weight variation of C1, C2, D1, and D2 films*

| n=10 | Weight (mg) | | | | % Weight variation | | | |
|---|---|---|---|---|---|---|---|---|
| | C1 | C2 | D1 | D2 | C1 | C2 | D1 | D2 |
| **Film 1** | 18.81 | 17.66 | 18.11 | 18.60 | 3.76 | -1.45 | -9.52 | -2.59 |
| **Film 2** | 17.43 | 17.63 | 20.26 | 19.46 | -3.85 | -1.61 | 1.22 | 1.91 |
| **Film 3** | 20.48 | 17.89 | 18.75 | 19.82 | 12.97 | -0.16 | -6.32 | 3.80 |
| **Film 4** | 18.19 | 17.41 | 18.46 | 20.44 | 0.34 | -2.84 | -7.77 | 7.04 |
| **Film 5** | 19.51 | 17.08 | 21.52 | 18.70 | 7.62 | -4.68 | 7.51 | -2.07 |
| **Film 6** | 17.70 | 17.82 | 22.19 | 18.74 | -2.36 | -0.55 | 10.86 | -1.86 |
| **Film 7** | 17.31 | 17.86 | 20.42 | 18.64 | -4..51 | -0.33 | 2.02 | -2.38 |
| **Film 8** | 16.99 | 18.61 | 21.41 | 17.55 | -6.28 | 3.86 | 6.96 | -8.09 |
| **Film 9** | 17.27 | 18.59 | 19.44 | 19.13 | -4.73 | 3.74 | -2.88 | 0.18 |
| **Film 10** | 17.59 | 18.64 | 19.60 | 19.87 | -2.97 | 4.02 | -2.08 | 4.06 |
| **Mean** | 18.13 | 17.91 | 20.02 | 19.10 | - | - | - | - |
| **SD** | 1.13 | 0.53 | 1.39 | 0.83 | 6.25 | 2.99 | 6.93 | 4.34 |

It was stated in literature that the SD of average % weight variation should not be more than ±7.5% and the % weight variation should not be more than ±15% for an individual film (Dharmasthala et al., 2018; Mushtaque et al., 2020). Accordingly, there was no weight variation reported in C1, C2, D1, and D2 films as the SD values of average % weight variation (2.99, 4.34, 6.25, and 6.93) were lower than 7.5% and the weight of each individual film didn't deviate more than 15%. It's unlikely that drug content uniformity could be affected by the weights of our film since no significant variation in their weights was recorded (Borges et al., 2015).

### 5.3.5. Thickness

Measuring the thickness of the film is fundamental to ensure the uniformity of film thickness as it's one of the major factors that affect the dose of the drug in the film; thus the

drug content uniformity. There are many options to measure the thickness of a film include: digital screw gauge, digital vernier caliper and scanning electron microscope (SEM) images (Nair et al., 2013). Digital vernier caliper was used in our study. The thickness of C1, C2, D1, and D2 films are represented in Tables 5.13, 5.14, 5.15, and 5.16 respectively. Mean of thicknesses and RSD were calculated in order to give a proper judgment.

**Table 5.13.** *Thickness of C1 films*

| C1 (n=6) | Thickness (µm) | | | | | |
|---|---|---|---|---|---|---|
| | Corner 1 | Corner 2 | Corner 3 | Corner 4 | Center | Mean ± SD |
| **Film 1** | 50 | 50 | 50 | 50 | 50 | 50 ± 0.0000 |
| **Film 2** | 50 | 50 | 60 | 50 | 50 | 52 ±4.4721 |
| **Film 3** | 60 | 50 | 50 | 50 | 50 | 52 ±4.4721 |
| **Film 4** | 50 | 50 | 50 | 50 | 50 | 50 ± 0.0000 |
| **Film 5** | 50 | 50 | 50 | 50 | 50 | 50 ± 0.0000 |
| **Film 6** | 50 | 50 | 50 | 50 | 50 | 50 ± 0.0000 |
| **Mean ± RSD of the 6 films =** 50.6667 ± 2.0384 | | | | | | |

**Table 5.14.** *Thickness of C2 films*

| C2 (n=6) | Thickness (µm) | | | | | |
|---|---|---|---|---|---|---|
| | Corner 1 | Corner 2 | Corner 3 | Corner 4 | Center | Mean ± SD |
| **Film 1** | 50 | 50 | 50 | 50 | 50 | 50 ± 0.0000 |
| **Film 2** | 50 | 50 | 50 | 60 | 50 | 52 ± 4.4721 |
| **Film 3** | 50 | 50 | 50 | 50 | 50 | 50 ± 0.0000 |
| **Film 4** | 50 | 50 | 60 | 50 | 50 | 52 ± 4.4721 |
| **Film 5** | 60 | 50 | 50 | 50 | 50 | 52 ± 4.4721 |
| **Film 6** | 50 | 50 | 60 | 50 | 50 | 52 ± 4.4721 |
| **Mean ± RSD of the 6 films =** 51.3333 ± 2.01194 | | | | | | |

**Table 5.15.** *Thickness of D1 films*

| D1 (n=6) | Thickness (µm) | | | | | |
|---|---|---|---|---|---|---|
| | Corner 1 | Corner 2 | Corner 3 | Corner 4 | Center | Mean ± SD |
| **Film 1** | 50 | 60 | 50 | 50 | 50 | 52 ± 4.4721 |
| **Film 2** | 50 | 60 | 60 | 50 | 50 | 54 ± 5.4772 |
| **Film 3** | 60 | 60 | 50 | 50 | 50 | 54 ± 5.4772 |
| **Film 4** | 60 | 50 | 50 | 60 | 50 | 54 ± 5.4772 |
| **Film 5** | 50 | 50 | 50 | 50 | 60 | 52 ± 4.4721 |
| **Film 6** | 60 | 50 | 50 | 50 | 60 | 54 ± 5.4772 |
| **Mean ± RSD of the 6 films =** 53.3333 ± 1.9365 | | | | | | |

**Table 5.16.** *Thickness of D2 films*

| D2 (n=6) | Thickness (µm) | | | | | |
|---|---|---|---|---|---|---|
| | Corner 1 | Corner 2 | Corner 3 | Corner 4 | Center | Mean ± SD |
| **Film 1** | 60 | 60 | 50 | 50 | 50 | 54 ± 5.4772 |
| **Film 2** | 50 | 60 | 50 | 50 | 50 | 52 ± 4.4721 |
| **Film 3** | 50 | 50 | 50 | 60 | 50 | 52 ± 4.4721 |
| **Film 4** | 50 | 50 | 60 | 50 | 50 | 52 ± 4.4721 |
| **Film 5** | 50 | 60 | 60 | 50 | 50 | 54 ± 5.4772 |
| **Film 6** | 50 | 50 | 50 | 60 | 50 | 52 ± 4.4721 |
| **Mean ± RSD of the 6 films =** 52.6667 ± 1.9610 | | | | | | |

While we measured the thickness at 5 locations of the film including the center point as many studies have done (Thakur & Narwal, 2012; Castro et al., 2018), measuring thickness using 3 or 6 different locations was also reported in literature (Patil et al., 2013; Vuddanda et al., 2017)

The thickness's mean of all our films ranges between 50 to 53 µm. In literature, lower values ranges between 37 to 53 µm were reported (Garcia et al., 2018) while in others higher

values were recorded;  81 to 96 µm (Vuddanda et al., 2017) and 69 to 72 µm (Sharma & Agarwal, 2021). Generally, it was suggested that an oral film should have a thickness of 50 to1000 µm while others suggested a range of 5 to 200 µm. As our films' thickness values were within these both suggested ranges and within the values found in literature, our ODFs were considered to have a suitable thickness. There was no significant thickness variation reported in our formulations. No effect on drug content uniformity is expected to be resulted from thickness variation (Sjöholm & Sandler, 2019).

### 5.3.6. Scanning electron microscopy

In addition to the surface morphology that can be evaluated using SEM, this test has been reported to be used as a tool to evaluate the lower and upper surfaces of the film. The difference in roughness between the lower and upper surfaces must be taken into consideration for further characterization like mucoadhesion properties of the films and their surface pH. However, these suppositions need further investigations (Garsuch & Breitkreutz, 2009). Therefore,  absence of pores and surface uniformity are believed to represent  a film with good quality (Sharma & Agarwal, 2021).

SEM images of the 2 films of the excluded ones because of their visible roughness on one side are shown in Figure 5.8 where the upper and lower sides were imaged. The visible roughness in these films appeared on the upper surface of the film (not the side in the direct contact with the petri dish).

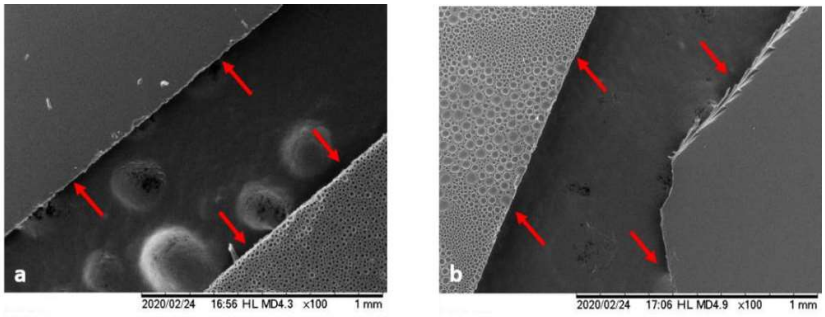


**Figure 5.8.** *SEM images of 2 films of the excluded ones at 100 X magnification where the red arrows show the edges of the film.* **a:** *Excluded C1 film where the right side shows the upper surface and the left side shows the lower surface,* **b:** *Excluded D1 film where the right side shows the lower surface and the left side shows the upper surface*

The upper side of the excluded films have a lot of pores and similar SEM images have been reported in literature related to films of poor quality. However, their lower surfaces were smooth with no pores (Alhayali et al., 2019). The SEM images of the porous surfaces of the excluded films with 200 X, 500 X and 1.2 K X magnifications are shown in Figure 5.9. Although we excluded such films with visible roughness from any study, we included them in this test an indicator to provide us with a reference of smooth and rough surfaces when the selected films of the selected formulations are subjected to SEM test.

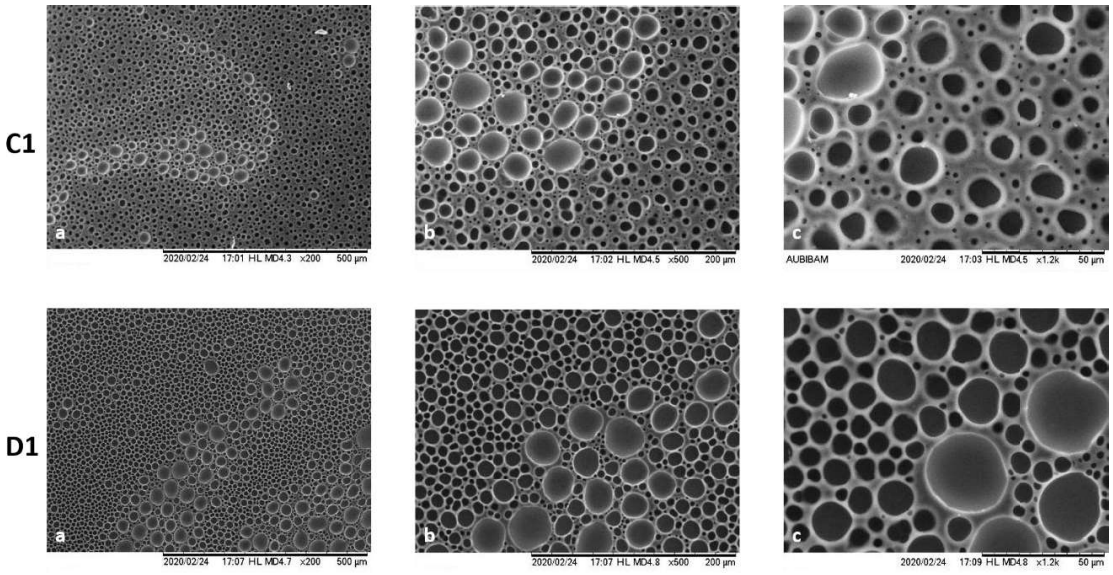


**Figure 5.9.** *SEM images of excluded C1 and D1 films at different magnifications as an indicator of film roughness/smoothness*, **a:** *200 X,* **b:** *500 X,* **c:** *1.2 K X*

The SEM images of the selected C1, C2, D1, and D2 films that show their surface morphology at 1.2 K, 2.5 K and 5.0 K magnification are shown in Figures 5.10, 5.11, 5.12, and 5.13 respectively.

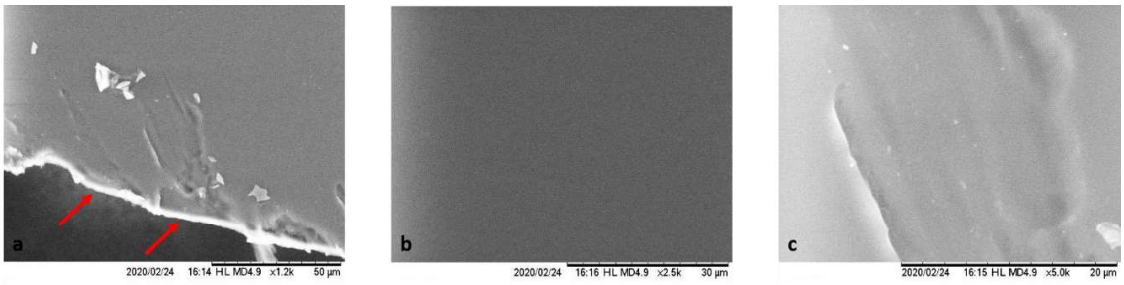


**Figure 5.10.** *SEM images of C1 film at different magnifications* **a:** *1.2 K X (The red arrows show the edge of the film),* **b:** *2.5 K X,* **c:** *5.0 K X*

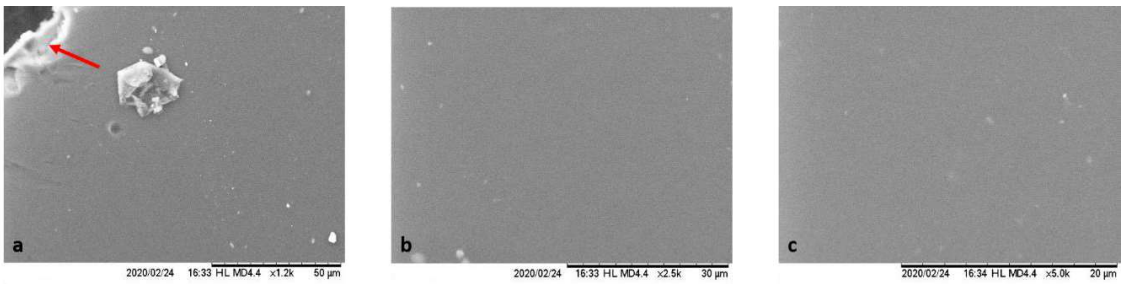


**Figure 5.11.** *SEM images of C2 film at different magnifications* **a:** *1.2 K X (The red arrow shows the edge of the film),* **b:** *2.5 K X,* **c:** *5.0 K X*


**Figure 5.12.** *SEM images of D1 film at different magnifications* **a:** *1.2 K X (The red arrows show the edge of the film),* **b:** *2.5 K X,* **c:** *5.0 K X*

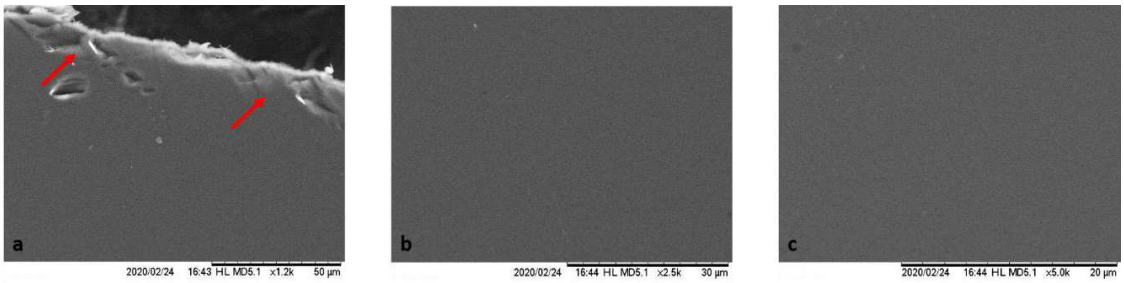


**Figure 5.13.** *SEM images of D2 film at different magnifications* **a:** *1.2 K X (The red arrows show the edge of the film),* **b:** *2.5 K X,* **c:** *5.0 K X*

The surface morphology of C1, C2, D1, and D2 films showed smooth surface with no reported pores. Similar SEM images have been reported in literature related to films of good quality (Pimparade et al., 2017; Alhayali et al., 2019). This affirmed the smooth texture of film surface in our formulations and its uniformity and indicate good distribution and complete solubility of the drug particles in the polymeric film matrix. (Al-Mogherah et al., 2020).

### 5.3.7. Drug content and content uniformity

Drug content is worked out to determine the drug content in each film as described by the standard assay specified for individual drug in the pharmacopoeias. Content uniformity is determined by estimating the drug content in individual strip (Sharma & Agarwal, 2021).

Drug content of C1, C2, D1, and D2 films were calculated and represented in Table 5.17 alongside with their mean and SD values.

Drug content of the films ranges between 4.5534 mg in the third film of C1 and 5.6027 mg in the first film of C2. % Drug content values were calculated using equation 4.3 to characterize the content uniformity knowing that each film of 2×2 cm is claimed to contain 5.00 mg of DSL. % Drug content of C1, C2, D1, and D2 films are represented in Tables 5.18-5.21. Mean, SD and RSD were calculated.

**Table 5.17.** *Drug content of C1, C2, D1, and D2 films*

| Film code | (n=3) | Drug content (mg) | | | Mean ± SD |
|---|---|---|---|---|---|
| | | Sample 1 | Sample 2 | Sample 3 | |
| C1 | Film 1 | 5.1065 | 4.9871 | 4.8963 | 4.9967 ± 0.1054 |
| | Film 2 | 5.0852 | 5.0118 | 5.0067 | 5.0485 ± 0.0439 |
| | Film 3 | 4.7077 | 4.7331 | 4.7025 | 4.7144 ± 0.0164 |
| C2 | Film 1 | 5.6650 | 5.6021 | 5.5409 | 5.6027 ± 0.0621 |
| | Film 2 | 4.9424 | 4.2656 | 4.4523 | 4.5534 ± 0.3496 |
| | Film 3 | 5.5228 | 5.5404 | 5.4762 | 5.5131 ± 0.0332 |
| D1 | Film 1 | 5.4193 | 5.2656 | 5.3462 | 5.3437 ± 0.0769 |
| | Film 2 | 4.9451 | 5.1569 | 5.0456 | 5.0492 ± 0.1059 |
| | Film 3 | 4.9575 | 4.9089 | 5.0786 | 4.9817 ± 0.0874 |
| D2 | Film 1 | 4.8579 | 4.6908 | 5.2730 | 4.9406 ± 0.2998 |
| | Film 2 | 5.2179 | 5.1393 | 5.1528 | 5.1700 ± 0.0421 |
| | Film 3 | 5.0687 | 5.2354 | 5.1839 | 5.1627 ± 0.0853 |

**Table 5.18.** *% Drug content of C1 films*

| C1 (n=3) | % Drug content | | | Mean ± SD |
|---|---|---|---|---|
| | Sample 1 | Sample 2 | Sample 3 | |
| Film 1 | 102.1301 | 99.7428 | 97.9264 | 99.9331 ± 2.1083 |
| Film 2 | 101.7044 | 100.2360 | 100.1341 | 100.6915 ± 0.8787 |
| Film 3 | 94.1535 | 94.6619 | 94.0507 | 94.2887 ± 0.3273 |
| **Mean ± RSD of the 3 films =** 98.3044 ± 3.5587 | | | | |

**Table 5.19.** *% Drug content of C2 films*

| C2 (n=3) | % Drug content | | | Mean ± SD |
|---|---|---|---|---|
| | Sample 1 | Sample 2 | Sample 3 | |
| **Film 1** | 113.3007 | 112.0425 | 110.8173 | 112.0535 ± 1.2418 |
| **Film 2** | 98.8486 | 85.3124 | 89.0451 | 91.0687 ± 6.9913 |
| **Film 3** | 110.4558 | 110.8089 | 109.5237 | 110.2629 ± 0.6639 |
| **Mean ± RSD of the 3 films =** 104.4616 ± 11.1363 | | | | |

**Table 5.20.** *% Drug content of D1 films*

| D1 (n=3) | % Drug content | | | Mean ± SD |
|---|---|---|---|---|
| | Sample 1 | Sample 2 | Sample 3 | |
| **Film 1** | 108.3858 | 105.3125 | 106.9230 | 106.8738 ± 1.5373 |
| **Film 2** | 98.9013 | 103.1386 | 100.9128 | 100.9842 ± 2.1196 |
| **Film 3** | 99.1507 | 98.1783 | 101.5717 | 99.6336 ± 1.7475 |
| **Mean ± RSD of the 3 films =** 102.4972 ± 3.7561 | | | | |

**Table 5.21.** *% Drug content of D2 films*

| D2 (n=3) | % Drug content | | | Mean ± SD |
|---|---|---|---|---|
| | Sample 1 | Sample 2 | Sample 3 | |
| **Film 1** | 97.1589 | 93.8153 | 105.4608 | 98.8117 ± 5.9961 |
| **Film 2** | 104.3589 | 102.7857 | 103.0559 | 103.4002 ± 0.8412 |
| **Film 3** | 101.3738 | 104.7071 | 103.6782 | 103.2530 ± 1.7068 |
| **Mean ± RSD of the 3 films =** 101.8216 ± 2.5611 | | | | |

According to the United States Pharmacopeia 27 (USP 27), the requirements of content uniformity are met if the drug content is within the range of 85 to 115% of claimed drug content with RSD ≤ 6% (Sharma & Agarwal, 2021).

% Drug content of C1, D1, and D2 films ranges between nearly 94-106 % with RSD values of 3.5587, 3.7561, and 2.5611 respectively. Accordingly, C1, D1 and D2 formulations met the pharmacopoeia requirements of content uniformity as their % drug content values were within the range of 85-115% and the RSD values were less than 6. On the other hand, content uniformity of C2 films was not achieved as RSD value was equals to 11.1363 even though their % drug content which ranges between nearly 91-112% was within the accepted range.

One of the major challenges during film preparation is meeting the requirements of content uniformity as it's affected by many factors. Insufficient content uniformity could lead to batch-to-batch variations. This insufficiency might be resulted because of improper viscosity, entrapped air bubbles and by any other problem connected to poor mass spreadability during casting (Centkowska et al., 2020).

### 5.3.8. Moisture loss and uptake

Moisture loss describes the moisture transmitted out of the unit area of the film in unit time. Moisture loss test's importance develops from its ability to evaluate the film capability to maintain its physicochemical properties under normal conditions (Dharmasthala et al., 2018).

Initial weights of C1, C2, D1, and D2 films and their final weight after 3 days are shown in Table 5.22 alongside their % moisture loss which were calculated using equation 4.4. Mean and SD of % moisture loss are shown in the same table.

In literature, low moisture loss value indicates good physical stability and integrity of the film. The final formulation of ODFs of different API showed a moisture loss in the range of 0.97-1.78% when the films were kept inside the desiccator containing anhydrous calcium chloride for three days. Moisture loss was calculated as a percentage of weight loss (Bharti et al., 2019). Under the same conditions, relatively higher value ranges have been also reported in literature; 4.5-6.5% (Reddy & Ramana Murthy, 2018), 4-6.5% (Reddy et al., 2016), and 0.66-5.69% (Al-Mogherah et al., 2020) while the moisture loss has been calculated as a percentage of weight loss as well. In our study, no significant % moisture loss reported in all formulations according to low weight loss values which were in the range

of 0.27-2.40%. These values were within or less than the values found in literature. This indicates that the films had good integrity and were dry enough to handle after keeping them wrapped in aluminum foil inside the desiccator at room temperature.

**Table 5.22.** *% Moisture loss of C1, C2, D1, and D2 films*

| Film code | n=3 | Initial weight (mg) | Final weight (mg) | % Moisture loss |
|---|---|---|---|---|
| C1 | **Film 1** | 18.81 | 18.62 | 1.01 |
| | **Film 2** | 17.43 | 17.21 | 1.26 |
| | **Film 3** | 16.64 | 16.52 | 0.72 |
| | **Mean ± SD of % moisture loss =** 0.9978 ± 0.2707 | | | |
| C2 | **Film 1** | 17.89 | 17.46 | 2.40 |
| | **Film 2** | 17.41 | 17.10 | 1.78 |
| | **Film 3** | 17.08 | 16.77 | 1.81 |
| | **Mean ± SD of % moisture loss =** 1.9997 ± 0.3501 | | | |
| D1 | **Film 1** | 18.11 | 18.06 | 0.27 |
| | **Film 2** | 18.46 | 18.37 | 0.49 |
| | **Film 3** | 18.75 | 18.70 | 0.27 |
| | **Mean ± SD of % moisture loss =** 0.3434 ± 0.1249 | | | |
| D2 | **Film 1** | 18.70 | 18.41 | 1.55 |
| | **Film 2** | 18.60 | 18.27 | 1.77 |
| | **Film 3** | 18.74 | 18.43 | 1.65 |
| | **Mean ± SD of % moisture loss =** 1.6597 ± 0.1118 | | | |

Initial weights of C1, C2, D1, and D2 films and their final weight after 3 days are shown in Table 5.23 alongside their % moisture uptake which were calculated using equation 4.5. Mean and SD of % moisture uptake are shown in the same table.

**Table 5.23.** *% Moisture uptake of C1, C2, D1, and D2 films*

| Film code | n=3 | Final weight (mg) | Initial weight (mg) | % Moisture uptake |
|---|---|---|---|---|
| C1 | **Film 1** | 18.37 | 18.19 | 0.98 |
| | **Film 2** | 20.51 | 20.46 | 0.24 |
| | **Film 3** | 19.68 | 19.51 | 0.86 |
| | **Mean ± SD of % moisture uptake =** 0.6958 ± 0.3958 | | | |
| C2 | **Film 1** | 16.13 | 16.53 | -2.48 |
| | **Film 2** | 17.42 | 17.63 | -1.21 |
| | **Film 3** | 17.36 | 17.66 | -1.73 |
| | **Mean ± SD of % moisture uptake =** -1.8045 ± 0.6406 | | | |
| D1 | **Film 1** | 20.34 | 20.26 | 0.83 |
| | **Film 2** | 22.36 | 22.19 | 0.76 |
| | **Film 3** | 21.57 | 21.52 | 0.23 |
| | **Mean ± SD of % moisture uptake =** 0.6081 ± 0.3278 | | | |
| D2 | **Film 1** | 17.40 | 17.55 | -0.86 |
| | **Film 2** | 19.20 | 19.46 | -1.35 |
| | **Film 3** | 19.70 | 19.82 | -0.61 |
| | **Mean ± SD of % moisture uptake =** -0.9418 ± 0.3789 | | | |

It has been reported that increasing the amount of Gly concentration led to an increase in the moisture uptake by the film (Al-Mogherah et al., 2020). In literature, moisture uptake ranges of 6.5-9.5% have been reported when films have been kept for three days at room temperature in an environment of relative humidity equals to 75%. Moisture uptake has been calculated as a percentage of weight gain (Reddy et al., 2016; Reddy & Ramana Murthy, 2018). Under the same conditions, moisture uptake range of 1.06-7.51 has been reported in literature (Sheikh et al., 2020). C1 and D1 films that contain PEG 400 as a plasticizer showed no significant weight gain according to their very low % moisture uptake values which were in the range of 0.23-0.98%. Unexpectedly, C2 and D2 films that contain Gly as plasticizer showed negative % moisture uptake values. This indicates a loss in their

weight. It's expected that C2 and D2 films had higher hygroscopic properties as their films absorbed moisture to a point at which their surface started to dissolve since a part of the film was noticed to be stuck on the aluminum foil as shown in Figure 5.14.

**Figure 5.14.** *Part of the film stuck on the aluminum foil because of moisture uptake*

This explains the loss in their weights after 3 days of keeping them wrapped in aluminum foil at room temperature under 75% relative humidity conditions. Decreasing the plasticizer amount might be considered to solve this problem as higher amount of plasticizer is reported to increase the % moisture uptake (Singh et al., 2013). Proper packaging is required to protect the films from humidity and to maintain their physicochemical properties (Sheikh et al., 2020).

### 5.3.9. Differential scanning calorimetry

DSC test was carried out to investigate the compatibility of the pure substances (drug and polymer) and any possible interactions between the components after the film formation. DSC shows any changes in the enthalpies of a reaction in the shape of shift of melting endothermic or exothermic peaks and/or variations in them (Abdelbary et al., 2014). Figure 4.15 shows DSC thermograms of pure DSL, DSL+HPMC, and (C1, C2, D1, and D2) films.

It has been stated in literature that the lack of any significant change in the peak (melting point) of the drug in the DSC thermogram compared to the peak obtained when a sample of a physical mixture of the drug and the polymer is analyzed indicates no possible interaction between them. The DSC thermograph of ropinirole hydrochloride showed an endothermic peak at ≈ 246°C (melting point) while the drug+polymer mixtures showed endothermic peaks in the range of 240- 255°C which indicated weak interaction between drug and polymer (Panchal et al., 2012). In our study DSL thermogram exhibited an endothermic peak corresponding to its melting point at ≈ 160°C (Figure 5.15a). Similar endothermic peak at the same temperature was obtained when a sample of DSL+HPMC (Figure 5.15b) was analyzed which indicates no physical or chemical interaction has been occurred between DSL and the polymer used and proved their compatibility with each other.

In literature, decrease in the melting point and the intensity of the peak of the drug when the film is formed has been reported indicating the transformation of the drug state from crystalline to amorphous state. It could be also resulted due to the dissolution of drug in the carrier agent at a temperature below its melting point (Raghavendra & Kumar, 2017). However, complete disappearance of the drug peak after film formation has been reported in many studies as well. The studies concluded that this loss of the peak might be an indication of the homogenous dispersion of the drug in the film and its presence in amorphous state (Bala et al., 2014; Al-Mogherah et al., 2020). In our study, the characteristic peak of pure DSL disappeared completely in all drug loaded films; C1, C2, D1, and D2 films (Figure 5.15c-f). This indicates that DSL is uniformly dispersed and present in an amorphous state in the polymeric matrix with no interactions with the other excipients.

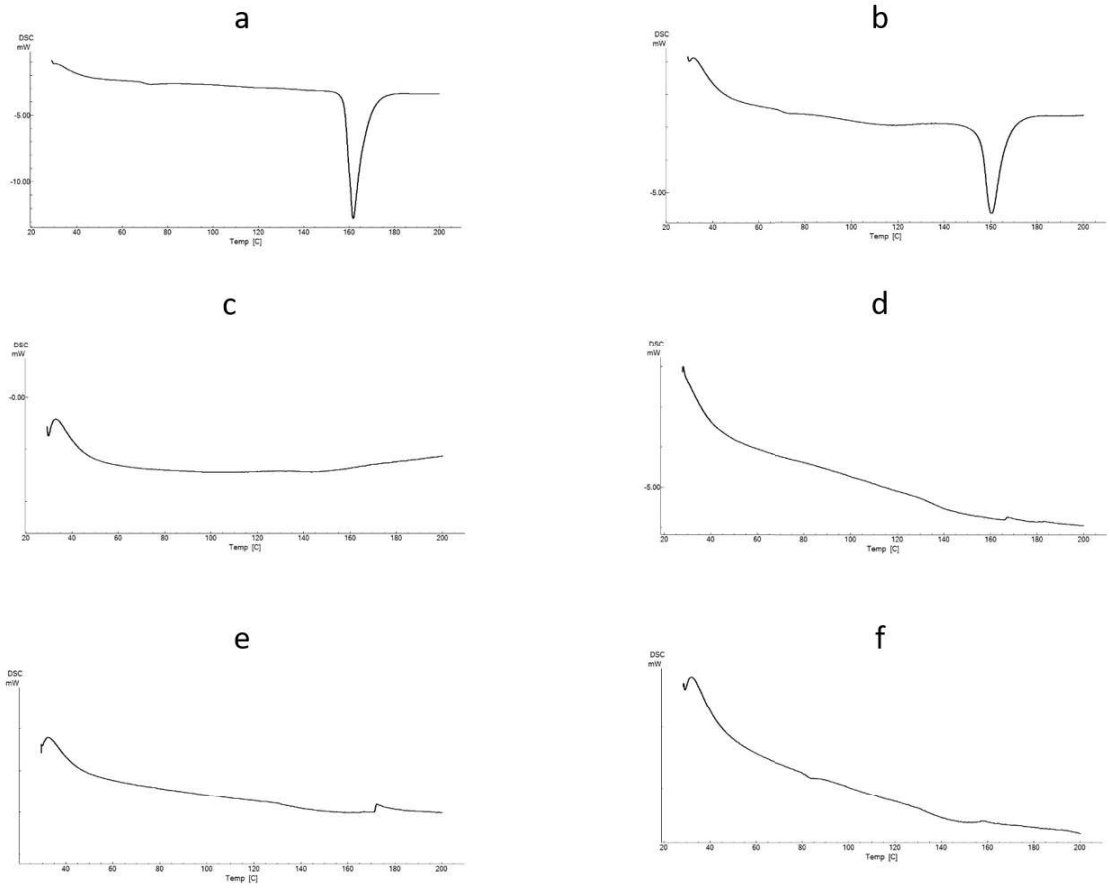


**Figure 5.15.** *DSC thermograms of: a: DSL, b: DSL+HPMC, c: C1, d: C2, e: D1, f: D2*

### 5.3.10. Fourier transform infrared spectroscopy

FT-IR test was carried out to investigate any possible interactions between the pure drug and the polymer and with the components after the film formation. The FT-IR spectra are compared with each other to detect any changes in the drug spectrum in terms of variation in its characteristic peaks, new peaks, or loss of any peak (Dharmasthala et al., 2018). The studies concluded that the drug is compatible with the polymer and has no interactions with the other excipients in the film when the characteristic peaks of the drug are obtained with no significant changes in the spectrum of its physical mixture with the polymer and in the spectrum of drug-loaded film (Panchal et al., 2012; Bala et al., 2014; Raghavendra & Kumar, 2017). FT-IR spectra DSL, DSL+HPMC, and DSL loaded film are shown in Figure 5.16.

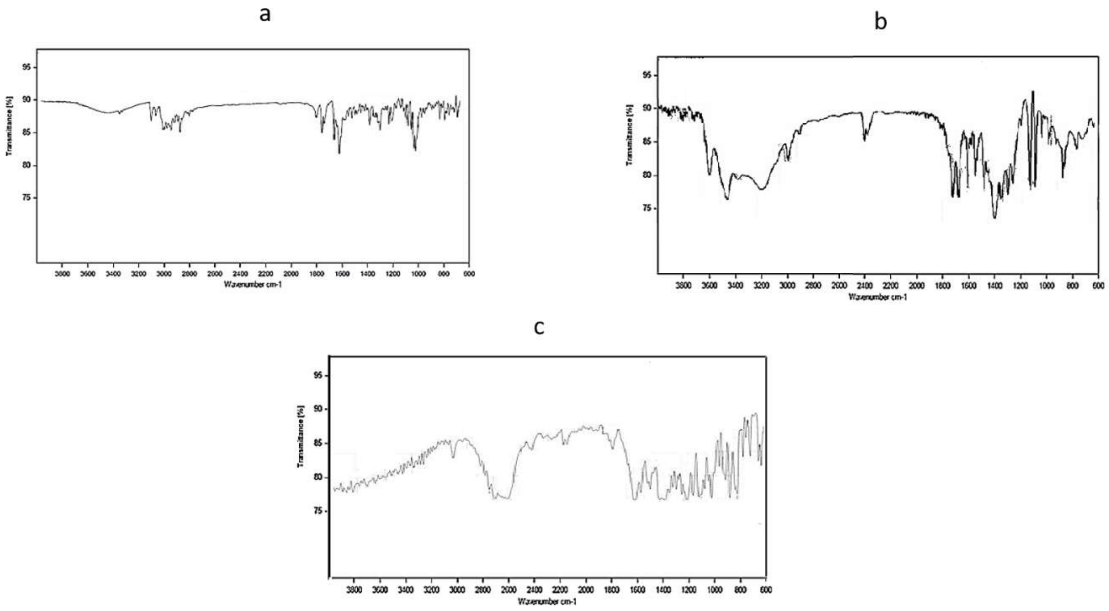


**Figure 5.16.** *FT-IR spectra of: a: DSL, b: DSL+HPMC, c: DSL loaded film*

The spectra of the physical mixture of DSL+ HPMC and DSL loaded film exhibited the characteristic peaks of DSL in its spectrum indicating the compatibility of DSL with polymer used and no interactions with the other excipients in the film after its formation.

### 5.3.11. Dissolution test

Although in-vitro dissolution test is one of the most frequently test in the pharmaceutical production to evaluate the drug release profile, no standard dissolution test has been approved to use for the ODFs in any of the available pharmacopeias or regulatory bodies worldwide can be found up to now. As these films are considered solid dosage forms, the available standard dissolution tests of the oral solid dosage forms such as basket apparatus (USP 1), paddle apparatus (USP 2) and the flow-through cell (USP 4) have been used extensively in literature. However, these methods have many drawbacks to use resulted in incorrect drug release profiles for oral films. These drawbacks include the following: high dissolution rates strongly dependent on agitation speeds and film positioning, large hold-up volumes, low residence times, and floating and adherence of films to components of the

conventional equipment causes poor reproducibility of the experimental data (Adrover et al., 2015; Speer et al., 2019).

USP 1 was used in our study to carry out the dissolution test. Drug release profiles of C1 and C2 films are shown in Figures 5.17 and 5.18 and the mean of their calculated cumulative % drug release corresponding to time are listed in Table 5.24.

**Table 5.24.** *Mean of cumulative % drug release of C1 and C2 films*

| Time (min) | Cumulative % drug release | |
|---|---|---|
| | C1 (n=3) | C2 (n=3) |
| 0.25 | 60.71 | 60.02 |
| 0.5 | 68.17 | 58.41 |
| 1 | 71.14 | 62.90 |
| 2 | 76.09 | 75.38 |
| 4 | 87.92 | 88.11 |
| 8 | 91.34 | 98.42 |
| 16 | 92.42 | 100.78 |
| 30 | 95.56 | 100.07 |

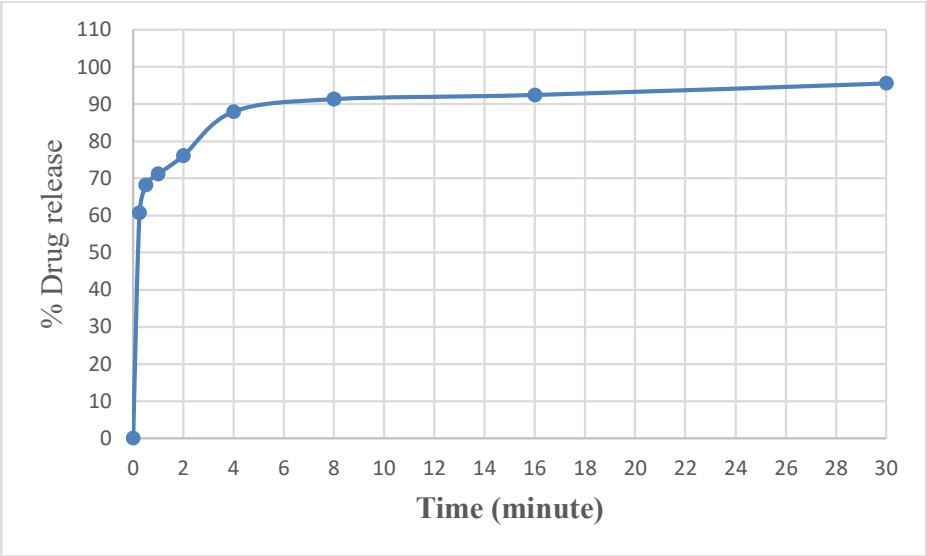


**Figure 5.17.** *% Drug release profile of C1 films*

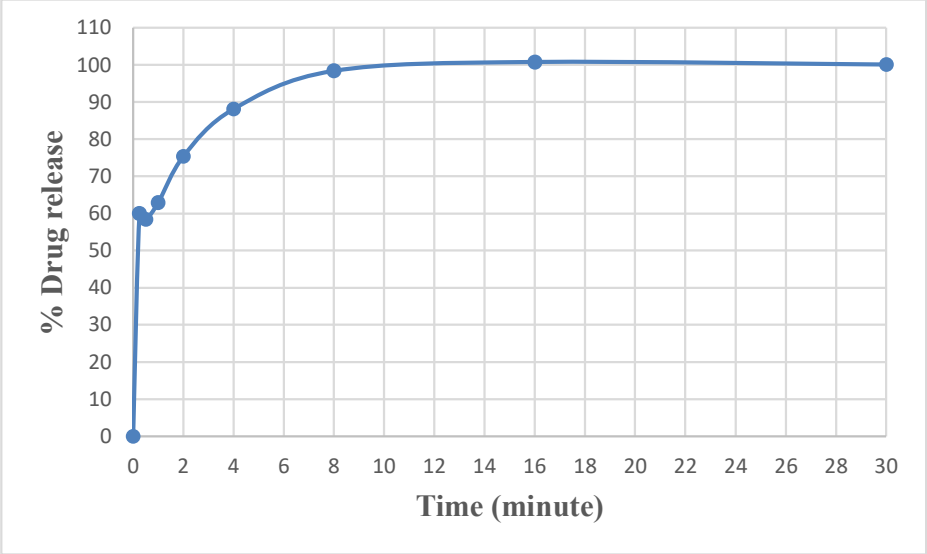


**Figure 5.18.** *% Drug release profile of C2 films*

Since ODF is a fast disintegrating dosage form, its complete release of the drug will be within minutes. Accordingly, the drug release at 4 minutes was considered to be a measurement for the analysis. Low drug release values in the range of 23-67% have been reported in literature where DSL films were prepared for pediatric use. Gly containing films were reported to dissolute faster than those of PEG 400 (Singh et al., 2013). Higher values

were reported in our formulations. About 60% of the drug released after just 15 seconds while more than 87% of the drug was released by the 4$^{th}$ minute in our formulations. No significant difference was reported between Gly and PEG 400 at the 4$^{th}$ minute. However, Gly containing films exhibited higher drug release values at the 8$^{th}$ minute and at the end of period time of our study.

Despite the original goal and preparations to maintain the sink- conditions, our data was collected under non-sink conditions. It was hard to replace the taken sample by an equal blank solution since the sampling time intervals are very small especially in the first-minute interval that has 3 sampling points (15,30, and 60 sec). The different pharmacopeias (Ph. Eur. and USP) suggest the use of sink-conditions to run a dissolution test. However, when a medium fails to provide sink conditions, non-sink conditions may be acceptable if supported by a suitable justification (Adrover et al., 2015). In fact, there are few studies that carried out the dissolution test of oral films under non-sink conditions (Vuddanda et al., 2017). Therefore, we didn't run the dissolution test for the rest of the formulations (D1 and D2).

We believe that conventional USP dissolution apparatuses are unable to characterize the drug release profile of oral films since they don't simulate the physiology of the oral cavity; such as the small saliva volume, saliva flow rate and the force applied by the tongue. Customized methods are needed to mimic these conditions (Adrover et al., 2015; Speer et al., 2019). Automatic rather than manual sampling is suggested since the drug release is a matter of seconds in these films. In our study, this requires complicated instrumental setup and complex manual operations which prevented us from running the standard test using USP 1 apparatus for the rest of the formulations (D1 and D2) as well.

## 6. CONCLUSION

Orodispersible films are novel dosage form that has been a subject of interest in the previous years. Preparation of 5 mg DSL transparent and flexible film that disintegrates in seconds using solvent casting method was our goal in this study. HPMC was the best film forming agent among the used polymers (HPMC, PVA, and Eudragit RS 100) in terms of film forming ability, transparency, and lack of stickiness. A lower concentration of HPMC resulted in lower disintegration time. We were able to prepare DSL films that started to disintegrate in less than 14 seconds. Increasing the amount of the PEG 400 and Gly (as plasticizers) has a significant effect on the mechanical properties of the film which was reported as the folding endurance values increased by the increase of the plasticizer concentration. In the films of higher plasticizer concentration, Gly was reported to be better than PEG 400 as it resulted in films with higher folding endurance with more than 200 disparities in value compared to PEG 400. In the films of lower plasticizer concentration, Gly was reported to better than PEG 400 with less variance in folding endurance values.

There was no variation between films in terms of thickness and weight. The data obtained from DSC and FT-IR studies revealed no interaction between the drug and the other excipients. Smooth surface morphology of the films with no reported pores obtained by SEM proved that the DSL was homogeneously dispersed in the film matrix.

No moisture loss was reported in all formulations under the specified conditions. On the other hand, significant moisture uptake was reported in films that contain Gly since a part of these films got stuck on the packaging material indicating partial dissolving of them by absorption water under 75% humidity conditions.

In terms of drug release, the dissolution test was carried out for 2 of our formulations using USP 1, and more than 87% of DSL was released by the $4^{th}$ minute. Gly containing films exhibited higher drug release values at the $8^{th}$ minute and at the end of period time of our study. However, we didn't run the test for all the selected formulations for the following reasons: sink conditions couldn't be achieved because of the difficulty of manual sampling as the drug release is a matter of seconds in this dosage form and for believing that conventional USP dissolution apparatuses are unable to characterize the drug release profile of oral films since they don't simulate the physiology of the oral cavity. Customized methods are needed.

Approximately 5 mg of DSL was obtained in most of our formulations with a pH within the range of normal pH of the oral cavity and this indicates the suitability of this dosage form and the successful of solvent casting method in preparing 5 mg DSL films for oral consumption as an alternative to conventional dosage forms with higher patient compliance and convenience to treat allergic symptoms in geriatric patients.

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