“DESIGN, DEVELOPMENT AND CHARACTERIZATION OF S-SMEDDS OF BUDESONIDE FOR THE TREATMENT OF EOSINOPHILIC ESOPHAGITIS”

A Thesis Submitted to

NIRMA UNIVERSITY

in Partial Fulfillment for the Award of the Degree of

MASTER OF PHARMACY

IN

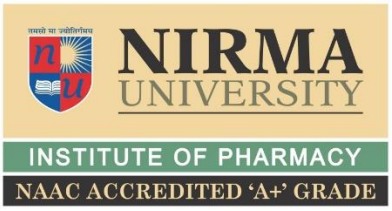
PHARMACEUTICS

BY

MUSKAN JOSHI (21MPH121), M. PHARM.

Under the guidance of

Dr. Tejal Mehta – GUIDE
Professor, Department of Pharmaceutics



Department of Pharmaceutics
Institute of Pharmacy
Nirma University
Ahmedabad-382481
Gujarat, India.

May 2023

CERTIFICATE

This is to certify that the dissertation work entitled "Design, development and characterization of S-SMEDDS of budesonide for the treatment of eosinophilic esophagitis" submitted by Muskan Joshi (21MPH121)in partial fulfillment for the award of Master of Pharmacy in "Name of a Department" is a bonafide research work carried out by the candidate at the Department of Pharmaceutics, Institute of Pharmacy, Nirma University under my/our guidance. This work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

Guide

Dr. Tejal Mehta
M. Pharm., Ph.D.,
Designation,
Department of Pharmaceutics,
Institute of Pharmacy,
Nirma University

Prof. Tejal A. Mehta
M. Pharm., Ph.D.
Director
Institute of Pharmacy,
Nirma University

13, May, 2023

CERTIFICATE FROM INDUSTRY (IF APPLICABLE)

This is to certify that the dissertation work entitled "Design, development and characterization of S-SMEDDS of budesonide for the treatment of eosinophilic esophagitis" submitted by Muskan Joshi (21MPH121) in partial fulfillment for the award of Master of Pharmacy in "Pharmaceutics" is a bonafide research work carried out by the candidate at Nanz Pharma under my/our guidance from 01/09/2022 to 01/5/2023. Muskan Joshi was regular in her research work carried out during this tenure. The work was found to be satisfactory as per expectations.

Laxminarayan Joshi
B. Pharm,
Nanz Pharma
Canada

13, May, 2023

CERTIFICATE OF ORIGINALITY OF WORK

This is to undertake that the dissertation work entitled "Design, development and characterization of S-SMEDDS of budesonide for the treatment of eosinophilic esophagitis" submitted by Muskan Joshi (21MPH121)" Submitted by Muskan Joshi (21MPH121) in partial fulfillment for the award of Master of Pharmacy in "Pharmaceutics" is a bonafide research work carried out by me at the "Name of Department", Institute of Pharmacy, Nirma University under the guidance of "Dr.Tejal Mehta". I am aware about the rules and regulations of Plagiarism policy of Nirma University, Ahmedabad. According to that, this work is original and not reported anywhere as per best of my Knowledge.

Ms. Muskan Joshi (21MPH121.)
Department of Pharmaceutics,
Institute of Pharmacy,
Nirma University

Guide

Dr. Tejal Mehta
M. Pharm., Ph.D.,
Director,
Department of Pharmaceutics,
Institute of Pharmacy,
Nirma University

13, May, 2023

DECLARATION

I hereby declare that the dissertation entitled "Design, development and characterization of S-SMEDDS of budesonide for the treatment of eosinophilic esophagitis", is based on the original work carried out by me under the guidance of Dr. Tejal Mehta, Director, under the Department of Pharmaceutics, Institute of Pharmacy, Nirma University. I also affirm that this work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

Ms. Muskan Joshi (21MPH121)
Department of Pharmaceutics
Institute of Pharmacy,
Nirma University,
Sarkhej - Gandhinagar Highway,
Ahmedabad-382481,
Gujarat, India

13, May, 2023

ACKNOWLEDGEMENTS

I would like to thank my parents for providing me with the opportunities, love and care to be able to complete my Masters of Pharmacy. I would like to thank my father, Laxminarayan Joshi, for being a constant source of inspiration.

I would like to thank my guide Prof. Tejal Mehta for her all of her support in my journey of completing my Masters.

The completion of this thesis and Masters would not have been possible with Dr. Pragna Shehlat and my father. Thank you for guiding me through my research and being a constant support. Thank you, Dr. Shiv Prakash Ratnam and Dr. Hetal Patel, for all your support.

I would like to thank Krishna Patel and the Puri family for their kindness and providing me support as I complete my Masters.

Last but not least, I would like to thank my loved ones for providing me with words of encouragement and listening to me as I complained about this journey. Thank you, Simran Joshi, Ishan Sevak, Crystal Dobson, Riddhi Jadiya, Vishal Tahiliani, Siddarth Nankani and Hemali Dadhania. A huge thank you to Riddhi Jadiya for being a great friend and helping me with everything.

For my Father,

who has been my greatest inspiration,

I aspire to be half the scientist you are.

List of Abbreviations

EoE	Eosinophilic Esophagitis
Th-2	T-helper-2
GERD	Gastrointestinal Reflux Disease
IL-3	Interleukin-3
MBC	Major Basic Protein
Hpf	High-power Field
PPI	Proton Pump Inhibitor
PPI-REE	Proton-pump Inhibitor-responsive Esophageal Eosinophilia
BCS	Biopharmaceutical Classification System
GR	Glucocorticoid Receptors
CBP	cAMP-response-lement-inding-protein-binding protein
TNF	Tumour Necrosis Factor
GRE	Glucocorticoid Response Elements
OBV	Oral Viscous Budesonide
SMEDDS	Self-microemulsifying Drug Delivery System
GI	Gastrointestinal
GIT	Gastrointestinal Tract
ODT	Orodispersible Tablet
API	Active Pharmaceutical Ingredient
SSG	Sodium Starch Glycolate
SNEDDS	Self-nanoemulsifying Drug Delivery System
FTIR	Fourier Transform Infrared

DSC	Differential Scanning Calorimetry
DCM	Dichloromethane
Kbr	Sodium bromide
UV	Ultra violet
PDI	Polydispersity Index
SSDC1	solid-SMEDDS direct compression 1
SSDC2	solid-SMEDDS direct compression 2
SSWG1	solid-SMEDDS wet granulation 1
SSWG2	solid-SMEDDS wet granulation 2
HPMC	Hydroxy propyl methyl cellulose
HPC	Hydroxy propyl cellulose

List of Figures

24	A 3D surface plot of the polydispersity index (PDI) of optimized liquid SMEDDS.
25	The overlay plot of all three responses.
26	Particle size distribution curve and mean size and PI values.
27	Data of zeta potential of optimized liquid-SMEDDS.
28	Disintegration of orodispersible tablets. A: Disintegration at 11 seconds. B: Disintegration at 35 seconds. C: Disintegration at 1:05 minutes.

List of Tables

17	Composition of F6 using SSDC1 for the direct compression of budesonide orodispersible tablets.
18	Composition of F7 using SSDC1 for the direct compression of budesonide orodispersible tablets.
19	Composition of F8 using SSDC1 for the direct compression of budesonide orodispersible tablets.
20	Composition of F9 using SSDC1 for the direct compression of budesonide orodispersible tablets.
21	Composition of F10 using SSDC2 for the direct compression of budesonide orodispersible tablets.
23	Composition of F11 using SSDC2 for the direct compression of budesonide orodispersible tablets.
24	Composition of F12-F16 using SSWG1 for the compression of orodispersible tablets of budesonide.
25	Composition of F17-F21 using SSWG1 for the compression of orodispersible tablets of budesonide.
26	Composition of F22 using SSWG1 for the compression of orodispersible tablets of budesonide.
27	Micromeritics of budesonide tablet blend.
28	Tablet hardness for 10 orodispersible tablets of budesonide reported in kg/cm^2.
28	Weight variation of 20 orodispersble tables of budesonide.
29	Drug content of 10 orodispersible tablets of budesonide in mg/ml.
30	Dissolution of 6 orodispersible tablets of budesonide.

Table of Contents

Abstract

Eosinophilic Esophagitis (EoE) is a chronic gastrointestinal disease which is cause by a Th2-mediated response to allergen sensitization, which leads to the activation and infiltration of eosinophils in the esophageal mucosa. Current therapies for EoE include off-label drugs for which patients often have to prepare their own formulations or inhaled budesonide and fluticasone, which can cause unwanted systemic side effects. The aim of this project is to develop, characterize and evaluate orodispersible tablets of budesonide as an effective treatment for EoE. Orodispersible tablets of budesonide were formulated by preparing liquid-SMEDDS which is proposed to increase the solubility of the budesonide. The prepared liquid-SMEDDS of budesonide showed high stability, monodispersed and small particle size. The optimized liquid-SMEDDS had a mean size of 125 nm, a PDI of 0.347 and a zeta potential of -53.6 mV. The liquid-SMEDDS were adsorbed onto a carrier to form solid-SMEDDS that can be compressed into orodispersible tablets to increase patience compliance. The solubility of the solid-SMEDDS was compared to the solubility of pure budesonide in 6.8 pH phosphate buffer. The results indicated that incorporating budesonide into liquid-SMEDDS significantly improved its solubility in 6.8 pH buffer. The formulated orodispersible tablets of budesonide had an average drug release of 81.1% and an average drug content of 96.1%. The incorporation of budesonide into liquid-SMEDDS and formulation into solid oral dosage form increased its solubility and allowed for fast disintegration and a high dissolution rate.

INTRODUCTION

1. Introduction

Eosinophilic esophagitis (EoE) once considered rare, has now become an increasingly common disorder in today's population (Hirano and Dellon, 2021). Eosinophilic esophagitis is a chronic gastrointestinal disorder which is driven by T-helper 2 antigens (Gonsalves and Aceves, 2020). The condition known as eosinophilic esophagitis (EoE) exhibits the presence of eosinophils in the esophageal region, but not in the GIT. The symptoms of EoE include vomiting, regurgitation, pain, difficulty swallowing, and the sensation of food getting stuck in the esophagus. These symptoms resemble symptoms of gastrointestinal reflux disease (GERD), but EoE patients do not respond to GERD treatment. In children, EoE may present with symptoms resembling GERD or food refusal, while adults may experience dysphagia, food impaction, and strictures. Patients with EoE usually have other allergies, such as high levels of immunoglobulin E (IgE), peripheral eosinophilia, asthma, or atopic dermatitis. EoE is caused by an allergic response to food antigens and is more likely to occur in individuals with a genetic susceptibility to the condition. (Spergel, 2007; Molina-Infante et al., 2018).

1.1 Pathophysiology of Eosinophilic Esophagitis

Eosinophils are normally present in all locations of the gastrointestinal tract, except for the esophagus, which concludes that eosinophils in the esophageal mucosa is abnormal. Murine and human data implies that eosinophil infiltration and activation is caused by a Th2-mediated response to allergen sensitization. Specifically, IL-13 results in the production of Eotaxin-3. Eotaxin-3 is a potent chemokine which is observed to be present 50-fold in patients with EoE in comparison to controls. Once eosinophils are activated, they degranulate and release major factors such as major basic protein (MBC). Major basic proteins can disrupt the esophageal epithelium and their presence is increased in patients with EoE. The Th2-mediated response also leads to the infiltration of mast cells via IL-9. In EoE, there is an increased number of mast cells, as well as an upregulation of mast cell-associated genes (Fig. 1). Mast cells are important mediators of esophageal remodelling and fibrosis, which leads to esophageal strictures in EoE (clinical trial).

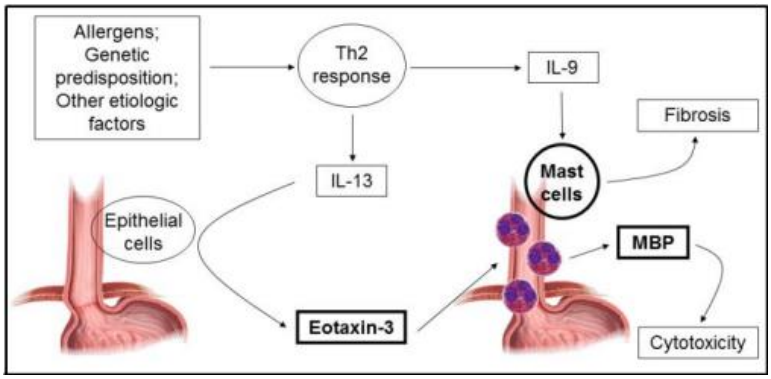


Figure 1. Proposed pathogenic pathway for eosinophilic esophagitis (clinical trial).

1.2 Diagnosis of Eosinophilic Esophagitis

Currently, there are no diagnostic tests that can be used for the diagnosis of EoE. The diagnosis of this disease primarily depends on clinical and pathologic data. Multiple methods have been proposed which may aid in the diagnosis (Rothenberg, 2009)

Normally, eosinophils can be found throughout the gastrointestinal tract, with the exception of the esophagus. To diagnose eosinophilic esophagitis, the existence of eosinophils specifically in the esophagus is used as a diagnostic method. A concentration of 20 eosinophils per high-power field is considered to indicate EoE, and multiple biopsies are typically needed to confirm the diagnosis. However, diagnosing patients that have an intermediate amount of eosinophils (7-15/hpf) can be challenging for several reasons. Firstly, there is no established threshold for the exact number of eosinophils required to diagnose EoE. Secondly, the diagnosis may depend on how many biopsy samples are taken, and the maximum amoutn of eosinophils in those samples can vary. (Rothenberg, 2009).

Some patients with EoE may also have severe basal cell hyperplasia. There are other conditions that can cause the migration of eosinophils in the esophagus, like GERD and allergic rhinitis. However, in these conditions, only 0-5 eosinophils per high-power field are found (Spergel, 2007). Previously, proton pump inhibitors (PPI) were administered to patients to differentiate between EoE and GERD. In one study, a subset of patients with EoE had resolved symptoms after taking PPI in the absence of GERD. This study introduced more confusion than clarity,

which led to the conclusion that PPI response should not be used for diagnosis of EoE. Eosinophilic esophagitis is caused by food allergies; therefore, it is important to identify certain food allergens. Currently, the only way to identify food allergens is by diet restriction.

1.2.1 Endoscopic Findings

Signs of EoE that can be observed during an endoscopy include linear concentric rings, white exudates and linear furrows reduced blood vessels, strictures in the esophagus, and a narrower diameter of the esophagus. Endoscopy and biopsies are critical tests that should be performed for the diagnosis of EoE, therefore, endoscopists should be familiar with the images shown in Figure 2 & 3 (Abe et al., 2017).

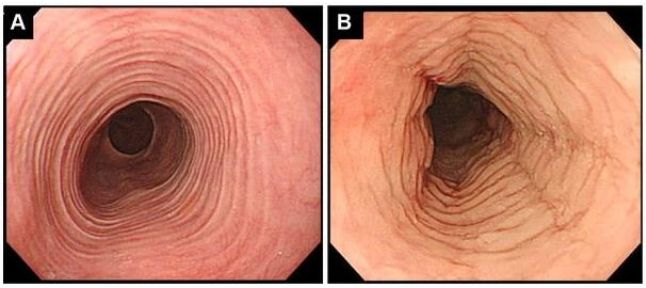


Figure 2. Concentric rings observed along horizontal axis on the esophagus (Abe et al., 2017).

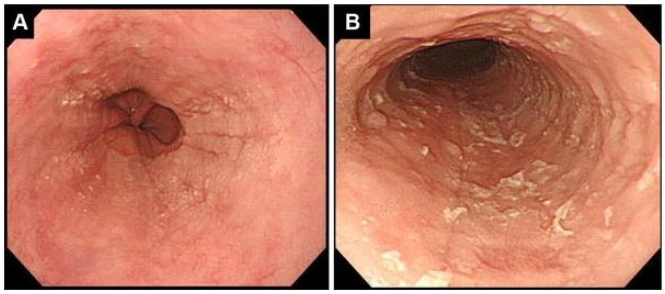


Figure 3. Granular white exudates observed in the lower esophagus (Abe et al., 2017).

1.3 Treatment

The best course of treatment for EoE is still unknown nearly three decades after it was originally recognized as a unique disorder (Laserna-Mendieta et al., 2020). The current therapeutic approaches consist of a “3D” concept which includes Diet, Drugs and Dilation

(Abe et al., 2017). As a specific food allergy that is primarily caused by food antigens, many dietary therapy approaches have shown efficacy in sustaining remission of EoE. Many studies have also shown that topical steroids are successful in inducing EoE remission. Additionally, half of patients who receive proton pump inhibitors (PPI) experience histologic and symptomatic remission. Finally, Esophageal dilation relieves symptoms in up to 95% of patients. It is a treatment that should be explored if patient experiences symptoms despite receiving effective anti-inflammatory treatment (Laserna-Mendieta et al., 2020).

1.3.1 Diet Restriction

Dietary restrictions for EoE may involve several approaches, such as eliminating specific allergenic foods, using an elemental formula that contains amino acids exclusively, following a diet based on food allergy testing, or using an empiric elimination diet.

Research has shown that eliminating certain food allergens from the diet has improved symptoms and esophageal histology of 98% of patients with EoE (Rothenberg, 2009). A study published in 1995 suggested that food allergens are the primary antigenic trigger of EoE. In this study, eight children who had refractory esophageal eosinophilia experienced a complete reversal of their symptoms after being fed an amino acid-based formula exclusively for six weeks. Dietary restriction therapy is a potential non-pharmacologic treatment option for EoE that involves avoiding certain foods in the long term (Molina-Infante & Lucendo, 2018).

Although dietary restriction therapy is an effective treatment for EoE, patient compliance can be low due to the difficulty of avoiding multiple food groups, both common and uncommon. Additionally, the skin prick test is not a reliable method for identifying which foods should be removed from the diet (Rothenberg, 2009). Elemental amino acid formula is effective, however, it can be challenging for patients to tolerate due to the requirement for a feeding tube, which can also be expensive (Rothenberg, 2009). There is conflicting data on how dietary restriction impacts anthropometric profiles and growth in individuals with EoE, so it is important to assess weight loss and growth rates before initiating any elimination diet and to closely monitor these factors during treatment. In addition, regular monitoring of

macronutrient intake, particularly calcium, vitamin D, and iodine in milk, wheat, and egg-free diets, is important. It should also be considered that eliminating milk, wheat, and legumes may impact the intestinal microbiota due to the reduction of prebiotic carbohydrates reaching the gut (Molina-Infante & Lucendo, 2018).

1.3.2 Drugs

1.3.2.1 Proton-Pump Inhibitors (PPIs)

Many studies show that proton pump inhibitors (PPIs) can result in complete symptom remission for EoE patients. It is possible that eosinophilic inflammation may be triggered by reflux disease, and some retrospective and prospective studies have shown that 30-70% of adult EoE patients have experienced improvement in both symptoms and histologic changes due to PPI therapy. There are two proposed mechanisms of action for PPI therapy: (1) PPI can prevent allergen penetration from the esophageal surface by treating acidic damage, and (2) PPI may reduce eosinophilic inflammation by inhibiting the expression of Th2-associated genes or cytokines (Abe et al., 2017).

Eosinophil infiltration in the esophagus is not specific to EoE, but is also observed in PPI-REE and GERD. Patients with PPI-REE exhibit similar clinical and histologic characteristics as those with EoE, but they achieve complete symptom remission with PPIs. It is unclear whether PPI-REE is a distinct disease or a subset of EoE patients who respond well to PPI therapy. Therefore, it is uncertain if PPI therapy is effective in treating EoE or if it is treating a subset of the disease, namely PPI-REE (Swathi and Evan S, 2015).

1.3.2.2 Steroid Therapy

When proton pump inhibitors fail to provide relief, steroid therapy is used as an alternative. Inhaled corticosteroids are preferred over systemic corticosteroids due to their effectiveness with fewer side effects. Fluticasone is often used because it reduces the infiltration of eosinophils, mast cells, and lymphocytes in the esophagus. Topical corticosteroids can improve the esophageal diameter, distensibility, and food impaction. Budesonide is preferred as it delivers the drug uniformly and reliably to the entire esophageal mucosa. Patients should rinse

their mouth after swallowing the drug to prevent oral candidiasis and should not eat or drink for 30 minutes to an hour to prevent the drug from being diluted. Previous studies show that topical steroid therapy induces histological and symptomatic remission in patients, but the remission rate varies due to multiple factors such as dosage form, dose, patient age, sample size, treatment duration, and definition of remission. In one study, the effectiveness of topical steroids was observed only in patients who had previously taken PPI therapy, indicating the usefulness of taking PPIs before starting steroid therapy. Topical steroids can be used for maintenance therapy to manage clinical symptoms or eosinophilic inflammation. (Abe et al., 2017).

Topical steroid therapy for EoE has some drawbacks, including a high relapse rate after discontinuation of medication. However, the adverse effects associated with topical therapy are less severe than those associated with systemic steroid therapy. Up to 10% of patients may develop oral candidiasis from topical steroids. From the survey of different studies, it was evident that around 10% children develops adrenal shortage as they are given topical steroids for not for 1 month but > 6 months, though it has not been that much evident in adult human being,s long-term monitoring of patients receiving topical steroids is important. Low-dose budesonide is reported to be effective for maintenance therapy, and dose reduction should be considered when administering budesonide for this purpose (Abe et al., 2017).

1.3.2.3 Dilation

Medical therapy may not always effectively treat esophageal strictures or narrowing, leading to the use of dilation therapy. This procedure is more commonly performed on adults, as long-term inflammation can cause esophageal remodeling that makes dilation necessary. There are three types of dilation procedures. TTS dilation is preferred as it allows for more extended dilation without significant complications like pain, bleeding, or perforation.

During dilation therapy, it is crucial to proceed gently and gradually, as the fragile esophageal mucosa can tear or cause chest pain. Esophageal perforation is a rare but critical complication that can occur in 0.1% of patients. Young patients who have numerous dilation in the upper

esophagus and have difficulty to pass even endoscope are more prone to develop infection. Although most patients experience improvement in symptoms after dilation therapy, its long-term effectiveness is still uncertain (Abe et al., 2017).

1.4 Budesonide as the Choice of Treatment for Eosinophilic Esophagitis

1.4.1 Characteristics of Budesonide

Budesonide is a powerful glucocorticoid that has potent anti-inflammatory properties and is a BCS class II drug. Its solubility in water is low (0.045mg/ml) and oral bioavailability is also low (6-8%). Despite this, budesonide has been used to treat other medical conditions such as asthma, and IBD. In addition to EoE. Budesonide has high level of systemic activity due to first-pass metabolism in the various organ such as liver when compared with local action. (Ryfeldt et al., 1982; Bodas and Ige, 2019).

Budesonide is a steroid that is a mixture of two epimers, 22R and 22S, in a 1:1 ratio. Both epimers have similar half-lives of around 2.7 hours and are biologically active. However, the 22R epimer has more potency in terms of its anti-inflammatory activity, and it has a higher distribution volume and clearance compared to the 22S epimer. This may be due to the 22R epimer having a greater affinity for glucocorticoid receptors. Budesonide has low systemic bioavailability because it is rapidly cleared through first-pass metabolism, which reduces its potential side effects.

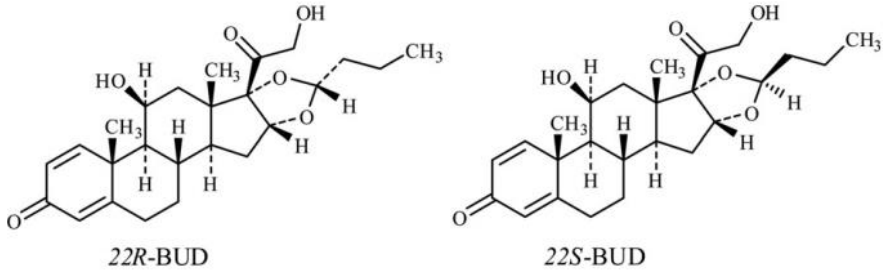


Figure 4. Structures of budesonide epimers (Youming et al., 2013).

1.4.2 Mechanism of Action

Budesonide is a type of glucocorticoid that functions by binding and activating glucocorticoid receptors. Upon binding, the budesonide-GR complex migrates and binds to HDCS2 and

cAMP-response-element-binding-protein-binding protein (CBP) (HAT). By doing so, this complex suppresses the expression of genes that may cause bronchoconstriction (Kolala and Ambati, 2023).

Budesonide, when it binds and activates glucocorticoid receptors (GR), can suppress the activation of inflammatory cells. It can also induce apoptosis and prevent the activation of eosinophils. Through this action, the budesonide-GR complex can inhibit the production of inflammatory cytokines such as ILs and TNF. As a result, airway inflammation and hyperreactivity are reduced, leading to a decrease in bronchospasms, wheezing, and coughing. (Kolala and Ambati, 2023).

Budesonide is used to treat EoE by blocking the secretion of inflammatory molecules in the esophageal epithelium that are triggered by antigens. This results in a substantial reduction in the number of eosinophils in the esophageal epithelium (as stated in the Jorveza patent).

The process by which budesonide achieves its anti-inflammatory effects is shown in Figure 4. Budesonide binds to glucocorticoid receptors within the cell, which then move from the cytoplasm to the nucleus. Glucocorticoid receptor bind to GREs located in the steroid-sensitive genes that produce anti-inflammatory proteins. However, glucocorticoid receptor may also bind to negative GREs to suppress genes, leading to some of the unwanted effects of corticosteroids (NF)-κB (Barnes, 2006).

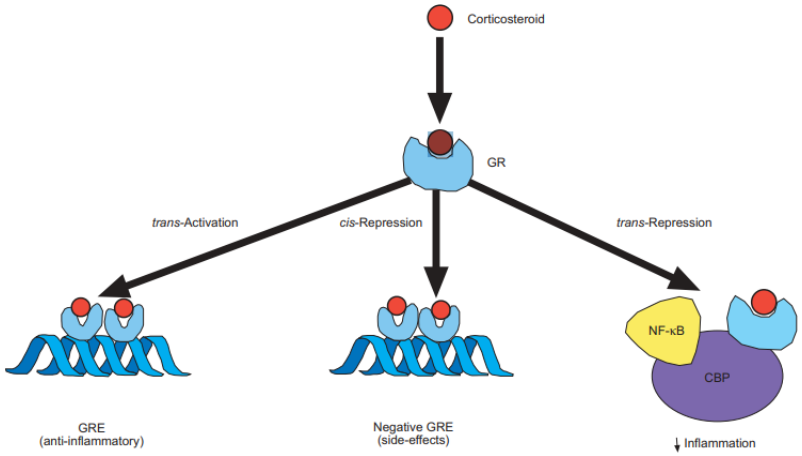


Figure 5. Pathway by which corticosteroids elicit their inflammatory effects (Barnes, 2009).

1.4.3 Treating EoE with Budesonide

Back in 2007, a retrospective study was performed on 20 children, where they were given oral viscous budesonide (OVB), which resulted in a histological response in 80% of the patients. The study also improved symptoms and endoscopic findings, without any recorded adverse effects. Since then, there have been 9 randomized clinical trials and 7 placebo-controlled studies conducted to evaluate the effectiveness of budesonide for EoE (Nennstiel and Schlag, 2020).

The initial study involved 36 patients aged 15 years and older who were administered either a budesonide suspension (1 mg) or placebo for 15 days. Results showed that 72% of the patients who received budesonide achieved histological remission compared to only 11% in the placebo group. Furthermore, budesonide-treated patients reported improvement in symptoms and endoscopic findings (Nennstiel and Schlag, 2020).

Research has shown that a viscous preparation of budesonide is more effective than a nebulized preparation due to longer mucosal contact time. In a multicenter phase II trial, two esophagus targeted budesonide formulations were studied: an orodispersible tablet and a viscous preparation, which induced remission in 94.7-100% of patients with no adverse events reported. Approximately 80% of patients preferred orodispersible tablets, and a phase III trial using the orodispersible tablet resulted in histological remission and symptom resolution in 57.6% of patients. The 1 mg orodispersible budesonide tablet (Jorveza®) was approved for sale in Europe in 2018.

1.4.4 Marketed Product

Jorveza® is a 1 mg orodispersible budesonide tablet that is approved for the induction of clinico-pathological remission of eosinophilic esophagitis in adults. It is not recommended for use in children or elderly patients, as there is insufficient evidence for its safety and efficacy

in these populations. The tablet should be placed on the tongue and allowed to dissolve for approximately 2 minutes. Effervescence occurs when saliva comes in contact with the tablet, which dissolves the tablet and produces more saliva. The dissolved tablet is then swallowed slowly as it disintegrates (Jorveza patent).

1.4.5 Drawbacks of Budesonide

Budesonide is classified as a BCS class II drug, which is known for its low solubility in water (0.045 mg/ml) and poor oral bioavailability (6-8%). Despite its low water solubility, budesonide is able to enter cells due to its log P value of 3.2, which is common among corticosteroids. However, its low oral bioavailability limits its effectiveness as a therapeutic agent, a common problem shared by other corticosteroids (Bodas and Ige, 2019).

1.4.6 Adverse reactions

When using inhaled budesonide, there is a risk of localized infections of the oral cavity and pharynx caused by the fungus candida. To avoid systemic absorption, patients are advised to rinse their mouth with water and spit it out after inhaling the drug. If oral candidiasis develops, the infection should be treated with an antifungal agent simultaneously with budesonide treatment, and in some cases, the budesonide treatment may be temporarily stopped. Patients using inhaled budesonide should be monitored for any signs or symptoms of oropharyngeal fungal infections (Kalola and Ambati, 2023).

Budesonide is an immunosuppressive medication, making individuals who have compromised immune systems more susceptible to infections than those who are healthy. Women may develop vulvovaginal candidiasis due to an overgrowth of Candida albicans in their genital area. Budesonide treatment is cautiously prescribed to patients who have active bacterial, viral, fungal, and parasitic infections, as well as tuberculosis and oral herpes simplex.

Patients receiving budesonide treatment are at risk of developing hypersensitivity reactions, which can manifest as a range of allergic reactions such as anaphylaxis, bronchospasm, rash, urticaria, angioedema, contact dermatitis, among others. If such symptoms occur, the use of budesonide should be ceased without delay (Kalola and Ambati, 2023).

1.5 Enhancing Bioavailability of Budesonide

1.5.1 Self-microemulsifying Drug Delivery System (SMEDDS)

Budesonide's limited therapeutic potential due to its low water solubility and bioavailability necessitates new formulations to harness its pharmacological properties. Self-microemulsifying drug delivery systems (SMEDDS) are a type of mixture that consists of lipids and surface coating emulsion and are isotropic and optically clear. They have a small globule size (<250 nm) and high thermodynamic stability. After being taken orally, SMEDDS creates microemulsions consisting of oil, water, surfactant, and co-surfactant. Emulsifiers help maintain an ultra-low interfacial tension that drives microemulsion formation. There are three types of emulsions: oil-in-water, water-in-oil, and multiple emulsions. Pharmaceutical applications typically use oil-in-water emulsions that require a more water-soluble emulsifying agent. Water-in-oil formulations are stabilized by surfactants that are stable in the oil phase (Dokania and Joshi, 2014; Gaikwad et al., 2017).

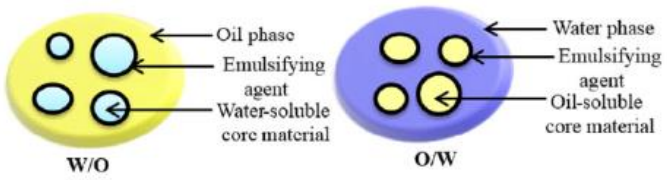


Figure 6. Illustration of emulsion systems (w/o, o/w) (Bakry et al., 2016).

The use of SMEDDS can enhance the effectiveness of drugs by speeding up the rate of absorption into biological membranes. Upon contact with water, SMEDDS quickly create emulsions that trap the poorly soluble drug within a lipid-soluble core. The small droplets in the emulsion provide a larger surface area, thereby facilitating more efficient drug transfer

across the membrane, leading to an overall increase in bioavailability. Incorporating budesonide into a SMEDDS formulation can improve the solubility and permeability of the drug, which can lead to an increase in its bioavailability (Gaikwad et al., 2017).

To prepare SMEDDS, it is necessary to ensure that the oil concentration is below 20% and that the surfactant's HLB value is less than 12. In addition, factors such as the drug's lipophilicity and dosage should be considered when developing a SMEDDS formulation. It is recommended that the drug has a low dose and a log P value greater than or equal to 2. Furthermore, the drug should have sufficient solubility in pharmaceutical liquids, surfactants, and co-solvents (Dokania and Joshi, 2014).

1.5.2 Advantages of SMEDDS Over Other Emulsions

Table 1. Summary of the several advantages of SMEDDS over other emulsions (Dokania and Joshi, 2014).

Storage: SMEDDS have similar advantages as emulsions when increasing the solubility of hydrophobic drugs. Over time, macroemulsions will undergo creaming. However, SMEDDS are thermodynamically stable, and they can be stored easily.	**Stability:** In comparison to microemulsion or nano emulsions, SMEDDS do not contain water, which allows them to have higher physical and chemical stability when stored long-term.
Compliance: SMEDDS formulations can be prepared in the form of capsules or tablets, which have smaller size and are more convenient for administration, thus improving patient adherence (Dokania and Joshi, 2014).	**Palatability:** SMEDDS formulations can be prepared in capsule dosage forms, which eliminates the taste-related problems associated with lipid-based formulations.

Effect of Food: SMEDDS formulations are not affected by food intake and may even benefit from the presence of a high-fat meal, as the lipophilic components of the meal can enhance drug absorption (reworded).	**Quick Onset of Action:** SMEDDS enable fast oral absorption of the medication, resulting in a rapid onset of action.
Ease to Manufacture and Scale up: SMEDDS can be easily manufactured on a large scale as it only requires simple and cost-effective manufacturing facilities, such as mixers with agitators and liquid filling equipment.	

1.5.3 Limitations of SMEDDS

SMEDDS formulations have multiple advantages, however they do have disadvantages that may limit their applications (Table 2).

Figure 7. Challenges associated with SMEDDS formulations (Dokania and Joshi, 2014).

Table 2. Summary of the limitations associated with SMEDDS formulations (Dokania and Joshi, 2014).

Drug Precipitation on Dilution: When SMEDDS are diluted in gastrointestinal fluid, the drug may precipitate out of the system, which cancels out the benefits of using a lipid-based formulation. Therefore, it is crucial to maintain the drug in a solubilized state in the gastrointestinal tract.	**Encapsulation in Soft Gelatin Capsules:** Soft gelatin capsules are commonly used to market SMEDDS formulations, but they have certain disadvantages such as high manufacturing costs, concerns regarding transmissible spongiform encephalopathy (TSE), and issues related to consumer preference and religious beliefs regarding animal gelatin. In addition, volatile co-solvents used in SMEDDS may migrate into the gelatin shell, potentially causing drug precipitation in lipophilic drugs.
Storage and Handling: Difficulties in handling, storing and stability are observed for liquid-SMEDDS.	**Lack of good in vitro models:** There is a lack of good predicative in vitro models for SMEDDS. Traditional dissolution methods cannot be used for these formulations.
Oxidation and polymorphism of Lipids: The use of unsaturated fatty acid-containing lipids in the formulation may result in lipid oxidation, and it is important to add lipid-soluble antioxidants to the formulation. Thermos-softening lipid excipients are known to be associated with polymorphism.	

1.5.4 Solid-Self-microemulsifying Drug Delivery System (Solid-SMEDDS)

In recent years, self-microemulsifying drug delivery systems (SMEDDS) have been widely used to enhance the solubility and oral bioavailability of drugs that have poor water solubility. However, SMEDDS have some limitations such as limited dosage form options, low manageability and portability, limited shelf-life, and the risk of leakage when used in hard gelatin capsules. Storage at lower temperatures may lead to drug or excipient precipitation, which requires redissolving the materials upon warming to room temperature to ensure drug solubility. The effectiveness of SMEDDS is mostly dependent on a moist environment. To address these issues, incorporating liquid-SMEDDS into solid dosage forms can combine the benefits of both liquid-SMEDDS and solid formulations (Oh et al., 2011).

Solid-SMEDDS are formed by solidifying liquid excipients into powders, which improves the solubility and bioavailability of drugs that are poorly soluble in water. By combining the advantages of liquid-SMEDDS with solid dosage forms, solid-SMEDDS offer greater stability, reproducibility, and compliance for patients. When agitated in aqueous media, solid-SMEDDS form microemulsions with droplets smaller than 200 nm. This increases the surface area available for drug absorption, leading to improved and consistent bioavailability.

The process of turning liquid-SMEDDS into solid-SMEDDS can be accomplished through various solidification techniques such as spray drying, spray cooling, adsorption onto solid carriers, melt extrusion, and microencapsulation. These techniques result in the formation of dry microemulsions, which address stability and microbiological concerns that arise during storage of standard microemulsions (Katja et al., 2014).

1.5.5 Orodispersible Tablets (ODT)

Oral drug delivery is a widely used and favored method of administration for liquid and solid dosage forms. Solid dosage forms are preferred for their ease of administration, precise dosing, self-medication, pain avoidance, and high patient compliance. Tablets and capsules are commonly used, but some individuals, such as pediatric, geriatric, and mentally challenged patients, may experience difficulty swallowing them, known as dysphagia. Therefore, it is

essential to explore alternative dosage forms to overcome this issue and improve patient compliance and therapeutic outcomes (Dey and Maiti, 2010).

Orodispersible tablets (ODT) are a type of tablet that dissolve within seconds to one minute when placed on the tongue, and then swallowed. They are also known as orally disintegrating, mouth-dissolving, rapid-dissolving, fast-disintegrating, or fast-dissolving tablets. These tablets contain super disintegrants that allow them to dissolve rapidly in saliva. They have many advantages, including easy administration, accurate dosing, good stability, and no need for water. The super disintegrants facilitate rapid absorption and onset of action, leading to increased bioavailability of the drug. The drug is absorbed through the mouth, pharynx, and esophagus, which avoids first-pass metabolism and allows for dose reduction and fewer side-effects. Orodispersible tablets are a promising alternative to conventional tablets, especially for patients who have difficulty swallowing (Bandari et al., 2008).

Some of the challenges in developing orodispersible tablets are (Bandari et al., 2008):

- Rapid disintegration of the tablet must be ensured to improve bioavailability.
- Tablet size should not be increased to aid in easy swallowing.
- The tablet must have sufficient mechanical strength to avoid breakage or chipping during handling and transport.
- There should be little to no residue in the mouth after the tablet has been dissolved and swallowed.
- The tablet must be protected from moisture to ensure stability.
- Good packaging design should be implemented to maintain product integrity.
- Compatibility with taste masking technology is essential for improving patient acceptability.
- Drug properties should not be affected by the tablet formulation.

1.5.6 Formulation of Orodispersible Tablets (ODT)

Various tablet properties need to be considered when formulating ODTs (Bandari et al., 2008). Properties such as:

- The mechanical strength of the tablet should be sufficient.
- The taste and mouth feel of the tablet should be pleasant to ensure patient compliance.
- Patients should not experience difficulty swallowing.
- Ensure adequate dissolution of the drug in saliva.
- The bioavailability of the drug.
- The stability of the drug and overall formulation.

Several techniques are employed to develop ODTs, such as freeze-drying, cotton candy process, molding, spray drying, mass extrusion, compaction and direct compression. Direct compression is the simplest and most economical approach for making tablets, as it utilizes common ingredients and equipment. To create an ODT formulation, the active pharmaceutical ingredient (API) and excipients blend should have suitable flow properties and cohere under pressure. Sugar-based excipients are preferred as diluents in ODTs because of their high solubility, sweetness, taste masking abilities, and pleasant mouthfeel. The use of a disintegrant is crucial in ODTs as it facilitates rapid tablet disintegration into smaller particles for speedy dissolution. Examples of commonly used synthetic disintegrants include crospovidone, croscarmellose, and sodium starch glycolate (SSG). Natural disintegrants such as karaya, modified starch, and agar are also employed (Pawar et al., 2014)

Literature Review

2.0 Literature Review on Treatments for Eosinophilic Esophagitis

Rationale	Inference	Reference
L. Kia et al. investigated the effectiveness of orally administering fluticasone in a powder formulation as an alternative to using off-label topical steroids to treat EoE, which are not approved by US FDA.	• Fluticasone powder (500 to 1000 mcg) was administered to the patients for treatment. • After the treatment, a significant difference in eosinophilia levels ($P<0.0001$) was observed in comparison to before the treatment. • About 75% of the patients showed peak densities of less than 15 eosinophils/hpf, and the dysphagia symptoms and endoscopic findings of furrows and exudates also improved.	• L. Kia et al. Disease of the Esophagus. 31(12), 1-6. 2018.
Mingzhuo Cao et al. developed oral isoliquiritigenin (ILQ) loaded SNEDDS to increase the solubility of the poorly water-soluble drug ILQ, for the treatment of EoE.	• ILQ-SNEDDS resulted in the formation of spherical droplets with an average size of 33.4 ± 2.46 nanometers, a polydispersity index (PDI) of 0.10 ± 0.05, and a zeta potential of -10.05 ± 3.23 millivolts. • Tests conducted on the absorption of SNEDDS in the intestines showed that the drug delivery system was able to increase the apparent permeability coefficient of ILQ	• Mingzhuo Cao et al. Pharmaceuticals.15(12), 1587. 2022.

Alka Prasher et al. developed two drug delivery devices; a fluticasone eluting string and a fluticasone eluting 3D printed ring as an alternative treatment to topical corticosteroids, which yield suboptimal results to treat EoE.	• The eluting string demonstrated a controlled release of 1mg/day of fluticasone in vitro. • Porcine esophageal tissue showed a high accumulation of fluticasone. • In vitro drug release of the 3D printed rings showed release of fluticasone at a constant rate for 1 month. • High levels of drug were accumulated in porcine esophageal tissue from the rings.	• Alka Prasher et al. Polymers. 13(4), 557. 2021.
Juluis Krause et al. have introduced a novel drug delivery system named EsoCap, that is designed to administer drugs specifically to the esophagus and maintain their effects for an extended period. The development of this drug delivery system is crucial as there is currently no locally targeted therapy available for the treatment of EoE.	• EsoCap consists of a rolled-up film which contains desired API. The EsoCap is administered using a retainer device which ensures the film rolls open in the esophagus. • In vitro studies indicate that 80% of drug is released from the film after 25 mins. • In vivo studies in 12 subjects show that patients were able to take EsoCap easily without any negative effects. The film was able to roll out 100% in the esophagus.	• Julius Krause et al. Journal of Controlled Release. 327, 1-7. 2020.

Evan S. Dellon et al. conducted a RCT to evaluate the safety and efficacy of fluticasone propionate oral disintegrating tablet since there lacks an US FDA approved drug to treat EoE.	• Histologic response results were 80% and placebo was 0% for 3 mg twice daily tablet of fluticasone. • By the end of the 12th week, the severity of symptoms such as edema, ring, exudates, furrows, and strictures had decreased from a score of 4.5 to 2.3 for the 3 mg tablet. • Dysphagia frequency also improved over 14 days. The safety and tolerability of the fluticasone tablet were found to be satisfactory. However, an increased risk of candidiasis was observed with higher twice-daily doses.	• Evan S. Dellon. Clinical Gastroenterology and Hepatology. 20(11), 2485-2494. 2022.
Erin Phillips Syverson et al. prepared a viscous preparation of mometasone for the treatment of EoE due to mometasone's ability to have higher deposition in the mucosa than fluticasone or budesonide.	• Around 76% of patients showed a histologic response to mometasone treatment, and approximately 68% of patients achieved complete remission. • All patients except for 1 experienced a decrease in eos/HPF. Patients who did not respond well to steroid treatment in the past achieved a histologic response rate of 72%, and 56% of these patients achieved complete remission.	• Erin Phillips Syverson et al. The Journal of Allergy and Clinical Immunology. 8(3), 1107-1109. 2020.

Corey J. Ketchem and his team conducted research on the efficacy of a standardized compounded fluticasone suspension as there is no FDA-approved medication available for treating EoE, leading patients to resort to off-label drugs and self-formulation.	• A retrospective cohort study was performed where compounded fluticasone was prescribed to patients. • Majority of the patients used dietary elimination or topical corticosteroids but did not have much of a response. • After taking fluticasone, their symptoms and endoscopic findings improved. The highest number of eosinophils seen decreased from 52 to 37 eosinophils per high-power field (hpf), and approximately 35% of patients had eosinophil counts lower than 15 per hpf.	• Corey J. Ketchem et al. Diseases of the Esophagus. 34(7). 2021.

2.1 Literature Review on Budesonide-based Drug Delivery Systems

Rationale	Inference	Reference
Sahar Khoshyari and Reza Mahjub created a self-nanoemulsifying drug delivery system (SNEDDS) to improve the limited solubility of budesonide and enable its oral delivery.	• The SNEDDS underwent characterization, and their properties, including size, polydispersity index, zeta potential, and entrapment efficiency, were analyzed. The results indicated that the SNEDDS had a size of 146±37 nm, a polydispersity index of 0.211±0.06, a zeta potential of +3.6±0.84 mV, and an entrapment efficiency of 94.3±6.58%	Sahar Khoshyari and Reza Mahjub. Avicenna J Pharm Res. 1(1) : 24-32. 2020.

	• The in vitro drug release was 33.81±1.67% in simulated intestinal fluid during 360 minutes, showing a sustained drug release.	
K.L. Prasad and K. Hari developed a solid self-nanoemulsifying drug delivery system (DDS) to enhance the solubility and dissolution rate of budesonide for the treatment of inflammatory bowel disease (IBD).	• The self-nanoemulsifying drug delivery system (SNEDDS) in its liquid form has been optimized to contain 20% oil and 80% surfactant/co-surfactant. • The size of the globules in the formulation was 82.4 nanometers, the polydispersity index (PDI) was 0.349, and the zeta potential was -28.6 millivolts. • The solid-SNEDDS formulation was characterized with DSC, FTIR and XRD and no incompatibility was found. • The formulation release 100% drug in 20 minutes in comparison to pure drug release which was 47% in 60 minutes.	K.L Prasad and K. Hari. Research Journal of Pharmacology and Technology. 14(11):5755-5763. 2021.
Yasin Turanli and Fusun Acarturk created nanofibers containing budesonide (BUD) that are specific to the colon to treat inflammatory bowel disease (IBD) because the current BUD formulations are not optimal for treating the entire colon in IBD.	• The aim was to prepare controlled release nanofibers using pH-sensitive Eudrajit S100 (ES100) and Eudrajit RL 100. • The researchers examined the surface characteristics, drug release profile, water contact angle, swelling index, and mucoadhesive properties of the colon-specific nanofibers loaded with budesonide.	Turanli and Acarturk. 63, 1773-2247. 2021.

	• The formulation containing ES100:ERL 100 exhibited the most significant drug release, with a minimal release at pH 1.2 and 6.8 and a significant release at pH 7.4.	
Muhammad Arif et al. developed reducible sodium alginate budesonide loaded nanoparticles to improve the side effects that result from current conventional formulations to treat IBD.	• The nanoparticles prepared were 430 nm in size, observed by TEM image. • DLC indicated high stability and narrow size-distribution. • Cytotoxic studies show that no cell inhibition is observed between the nanoparticles. • The nanoparticles loaded with budesonide showed a high rate of drug release in a buffer with a pH of 7.4, suggesting their potential use for targeted drug delivery to the colon.	Muhammad Arif et al. 18, 229-2317. 2020.
Yun Liu et al. developed a micellar DDS to which is based on lipid-DNA to maximize the efficacy of budesonide and reduce its adverse effects for the treatment of asthma.	• UU11mer lipid DNAA was used to enhance the water solubility of budesonide while achieving a high loading capacity. • The drug delivery system (DDS) displays inhibitory activity based on the inhibition of interleukin-8 release.	Yun Liu et al. 130, 123-127. 2018.

Yun Liu et al. developed a micellar DDS to which is based on lipid-DNA to maximize the efficacy of budesonide and reduce its adverse effects for the treatment of asthma.	• Budesonide was made water-soluble and had a high loading capacity by using lipid DNAA (UU11mer). • The drug delivery system (DDS) showed inhibitory activity, as evidenced by the inhibition of interleukin-8 release.	Yun Liu et al. 130, 123-127. 2018.
Sunil Pattanaik et al. developed a hydrogel film with a cyclodextrin complex of budesonide and quaternary surfactants to improve the drug's ability to pass through mucosal barriers.	• FTIR analysis showed that there was hydrogen bonding between the drug and the polymer. • The drug was determined to be in an amorphous state through the use of SEM, DSC, and XRD techniques. • The hydrogel film, which contains benzalkonium and hydroxypropyl beta-cyclodextrin, showed the highest in vitro dissolution and mucosal permeation rates, with values of 87.2 and 95.8, respectively. • The mucoadhesive properties of the polymer enhanced mucosal tissue residence time. • The inflammation in a rabbit's eye was effectively managed within three hours.	Sunil Pattanaik et al. Revista de Chimie. 71 (6). 332-345. 2020.

Rayane S.C.M.Q Antonio et al. developed a mucoadhesive gellifying formulation of budesonide using a thermoreversible polymer, PF127, to obtain prolonged retention of drug at the site of action which conventional formulations lack.	• The polymeric micelles were analyzed using X-ray diffraction and transmission electron microscopy (TEM) images, indicating that budesonide was completely dissolved in them. • In vitro studies showed that the gels had a mucoadhesive force of 5-15g. • The formulation was found to stick to the mucosa in ex vivo studies. • The prepared budesonide formulation resolved inflammatory injury in intestinal mucosa in a murine model.	Rayane S.C.M.Q Antonino et al. Journal of Controlled Release. 303, 12-23. 2019.
Lan Zhang et al. developed chitosan-based swellable microparticles of budesonide to increase drug targeting to improve and overcome unwanted side effects of current therapies for lung diseases.	• The allergic asthma animal model was treated with budesonide microparticles, and the therapeutic effect was linked to the in vitro release pattern, which lasted for 12 to 18 hours. • The eosinophil count was reduced, and the mRNA expression of IL-4 and IL-5 was considerably suppressed after seven days of treatment. • The microparticles permitted a longer administration interval of two days and lowered the dose by 50%.	Lan Zhang et al. Journal of Controlled Release. 283, 163-174. 2018.

1.3 Literature Review of Budesonide-based Drug Delivery Systems Used for the Treatment of Eosinophilic Esophagitis

Rationale	Inference	Reference
Antonella Casiraghi et al. suggested a uniform budesonide formulation to enhance the duration of budesonide on the esophageal mucosa as a substitute for the current unapproved topical steroid treatments for EoE.	• Drug-loaded and placebo formulations were prepared with different amounts of xanthum gum and guar gum. • Results indicated that the gums added allowed for a prolonged residence time. • It is important to rationalize the concentration of the mucoadhesive to allow for syringeability of the formulation.	Antello Casiraghi et al. Pharmaceutics. 12(3): 829. 2020.
Valentino Laquintana et al. prepared mucoadhesive thiolated oral formulation of budesonide as an alternative to aerosol therapy to increase contact time with the esophageal mucosa.	• They synthesized a mucoadhesive thiolated HP-βCD to improve water solubility of budesonide. • Mucoadhesive studies of this complex were performed on porcine esophagus mucosa, which proved the mucoadhesive properties. • The researchers were successful in enhancing the amount of time that budesonide remains on the mucosa of the esophagus,	Valentino Laquintana et al. International Journal of Pharmaceutics. 572. 2019.

	which could lead to an increase in the drug's bioavailability.	
Warzecha and colleagues created a new thick formulation because there was no readily available topical steroid drug that could be used to treat EoE in children.	• They developed a viscous formulation which contained polysaccharides and oily excipients. • The formulation showed 64% effectiveness for histological remission. • The mean EREFS score decreased from 3.1 points to 1.6 points after treatment with the viscous formulation. • The proprietary solvent used in the formulation was well-accepted by both adults and children.	Warcezha et al. J. Clin. Med. 11(22): 6730. 2022.
Chen and Xiaofei conducted a study to evaluate and compare the effectiveness of budesonide oral suspension and placebo in treating patients with EoE.	• The efficacy and safety outcomes were similar for adults and children administered 2mg twice daily oral suspension of budesonide. • There were improvements seen in histologic, symptomatic and endoscopic outcomes over 13 weeks.	Chen and Xiaofei. Clincal Gastroenterology and Hepatology. 20(5) : 1188-1189. 2021.

	• Adults experienced more improvement in dysphagia symptoms.	
Reed et al. conducted a study to evaluate the effectiveness of a standardized compounded suspension of budesonide as there are no approved medications available for treating EoE and patients often resort to using off-label drugs or self-made formulations.	• A retrospective cohort study was conducted. • After a follow-up of 17 months, a significant decrease was observed in symptoms of dysphagia, improvements in heartburn, and global symptom release. • The eosinophil count was observed to reduce from 55 to 20 eos/hpf. • Esophageal candiasis was rare (6%).	Reed et al. J. Gastroenterol. Hepatol. Res. 7(1) : 2509-2515. 2018.

1.4 Literature Review on Self-microemulsifying Drug Delivery Systems

Rationale	Inference	Reference
Zhu and colleagues created a self-microemulsifying drug delivery system (SMEDDS) loaded with licochalcone A (LCA) to improve the effectiveness of the drug for treating hyperuricemia, as current treatments can cause negative side effects when used for extended periods.	• Sprague-Dawley rats were given LCA-SMEDDS and free LCA orally to observe their bioavailability. • The particle size of the formulation was 25.68±0.79 nm, the PDI was 0.074±0.024, and the zeta potential was -14.37±2.17 mV. • The bioavailability of LCA via oral administration was found to be 2.36 times higher when using this particular formulation as compared to using free LCA. • The LCA-SMEDDS formulation reduced uric acid levels by 60.08%.	Zhu et al. Journal of Microencapsulation. 38(7-8) : 459-471. 2020.
Kovacevic et al. studied the potential of various mesoporous carriers to enhance the solubility of carvedilol through the adsorption of liquid-SMEDDS.	• Wet granulation and high shear granulator (HSG) were used to prepare granules. • The granules with the greatest quantity of SMEDDS were produced using Syloid 244FP and	Kovacevic et al. Pharmceutics. 14(10) :2077. 2022.

	Neusilin US2 as mesoporous carriers. • SMEDDS made from HSG had superior powder flow properties. • All the granules had a rapid in vitro release, with Syloid 244FP releasing 93% of carvedilol within 5 minutes.	
Sharma et al. created a drug delivery system called SMEDDS, which contains sertraline hydrochloride, in order to enhance the solubility and oral bioavailability of the drug, as it has limited effectiveness due to extensive metabolism and poor oral bioavailability.	• The SMEDDS formulation was composed of isopropyl myristate, tween 80 and propylene glycol. • The optimized formulation demonstrated no indications of phase separation or precipitation. • The formulation possessed a particle size of 101 nm, a PDI of 0.319, a drug content of 99.14±0.35%, a viscosity of 10.71±0.02 mPa, and a drug release rate of 98.25±0.22%.	Sharma et al. Pat. Nanotechnol. 17(4) :2212-4020. 2022.
Lee and Lee developed a self-microemulsifying drug delivery system (SMEDDS) that contains tolvaptan to improve the drug's oral bioavailability	• The SMEDDS was made up of Capryol 90, Tween 20, and Transcutol as its components. • The best formulation had a composition of 10% Capryol 90, 70% Tween 20, and 20% Transcutol.	Lee and Lee. Pharmaceutics. 14(2) : 415. 2022.

and expand its potential use.	• The formulation had small droplet size and a dissolution rate of 95% in 15 minutes. • The formulation showed stability for 3 months under accelerated conditions. • In a rat model, the bioavailability of the formulation was 22-23 times higher than the standard formulation.	

AIM, RATIONALE AND OBJECTIVE

3 Aim, Rational and Objective

Aim:

The aim of this project is to develop and characterize orodispersible tablets of budesonide using solid-SMEDDS technology for the treatment of eosinophilic esophagitis.

Rationale:

Current therapies for the treatment of eosinophilic esophagitis include off-label drugs for which patients have to prepare their own suspensions to treat EoE. Additionally, budesonide and fluticasone that are administered through inhalation have variable drug delivery. Drugs administered through inhalation result in systemic drug delivery, which can cause undesired side effects. Considering the drawbacks of the current therapies for EoE, there is interest in developing a drug delivery system alternative to current therapies.

Budesonide is a poorly water-soluble drug for which novel formulations are required to exploit it medicinal effectiveness. It is proposed that formulation of budesonide into liquid-SMEDDS will increase the solubility of the poorly water-soluble drug. Additionally, incorporation of liquid SMEDDS into solid dosage forms can combine the advantages of SMEDDS and of solid formulations to overcome the listed drawbacks.

Objective:

Poor water solubility of budesonide affects its therapeutic effect (oral BA is 18-36%) and also it shows variable bioavailability. Therefore, in the present work, attempt is made to improve solubility of budesonide through formulation of a self-microemulsifying drug delivery system. The proposed strength of the tablet would be 1mg per tablet. To support the scientific experimental work, the following objectives are:

- Formulation of liquid-SMEDDS
- Formulation of solid-SMEDDS
- Formulation of orodispersible tablets
- Characterization of Solid-SMEDDS and Orodispersible table.

MATERIALS AND METHOD

4 MATERIALS

4.1 Drug Profile

Drug	Budesonide
Indication	Glucocorticosteroid
BCS Class	II
Physical Appearance	White crystalline powder
Solubility	Practically insoluble in water, soluble in ethanol, methanol and DMSO.
Log P	2.73
Half Life	2-3.6 hours

4.2 List of Materials

Material	**Company Name**
Peceol	Gatte Fosse Canada
Maisine	Gatte Fosse Canada
Transcutol	Gatte Fosse Canada
Labrasol ALF	Gatte Fosse Canada
Labrafil 2125	Gatte Fosse Canada
Prosolv SMCC	JRS Pharma
Celny	Nisso America
Magnesium Stearate	Sigma Aldrich
Neotame	Sigma Aldrich
Crospovidone	Sigma Aldrich
Galen IQ	BASF
Cellactose 80	MEGGLE Pharma
Ludipress	BASF
Pharmaburst 500	SPI Pharma
Ultraburst	SPI Pharma

MCC	Sigma Aldrich
Disintequik MCC 25	Azelis Canada
Optify	McCormick Flavor Solutions
Fujicalin	Pharma Excipients
Fujisil	Pharma Excipients
Neusilin US2	Pharma Excipients

4.3 List of Equipment

Equipment	**Company Name**
Analytical Balance	Mettler Toledo MS1602TS
Hot Plate and Stirrer	IKA C-MAG HS7
Digital pH Meter	Mettler Toledo S400
Centrifuge	Thermo Scientific
UV-Spectrophotometer	Shimadzu UV-1800
Incu-Shaker	Benchmark
Tablet Press	Manesty
Friabilator	Vankel 45-2100
FT-IR	Jasco
DSC	Hitachi DSC-7020
Particle Size Analyzer	Horiba SZ-100
Viscometer	Brookfield Engineering Laboratories
Hardness	ERWEKA
Mechanical Stirrer	REMI
Oven	EIE-101

CHAPTER FIVE

5 Drug Authentication Studies

5.1 Methods

Fourier Transform Infrared Spectroscopy (FTIR):

The mortar and pestle and pellet dies were thoroughly cleaned with dichloromethane (DCM) The mortar and pestle and pellet dies were thoroughly cleaned with dichloromethane (DCM) prior to mixing sample. A small sample of budesonide was triturated in sodium bromide (KBr) using a mortar and pestle. This mixture was filled into the pellet die and compressed to the bottom of the pellet die. The pellet die was placed into the FTIR instrument for analysis of budesonide.

Differential Scanning Calorimetry (DSC):

The cooling unit was turned on to allow the sample to cool at appropriate times. A small sample of budesonide was placed in a sample pan and covered with a lid. The sample pan and lid were crimped together to enclose the sample using a sample press. The pressed sample pan was placed inside the DSC instrument using forceps. The sample pan was placed in the right slot and a reference pan was placed in the left slot. The reference pan was used for comparison during DSC analysis. The weight of the sample was entered into the DSC software as well as heating and cooling temperatures. The temperature range selected was 50°C to 300°C. A heating and cooling rate of 10°C per minute was selected. After the sample run was completed, the instrument was allowed to cool down completely before turning it off.

5.2 Results

Fourier Transform Infrared Spectroscopy (FTIR):

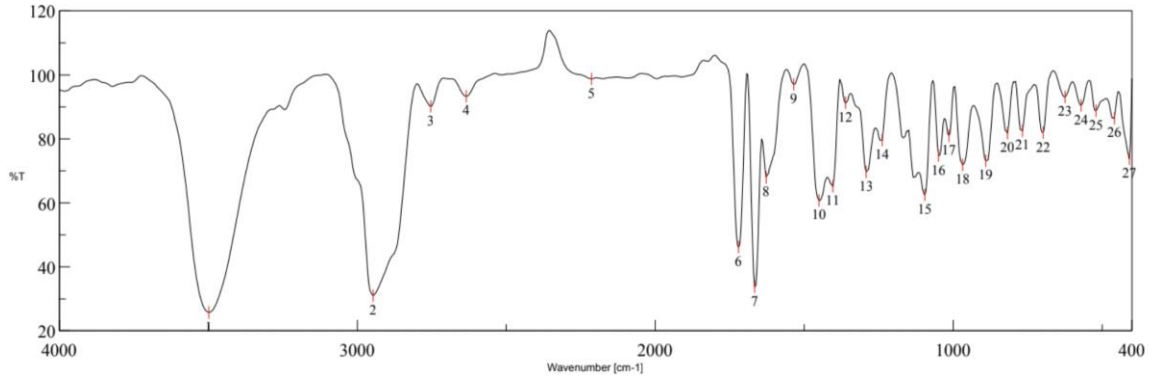


Figure 8. FTIR of pure budesonide.

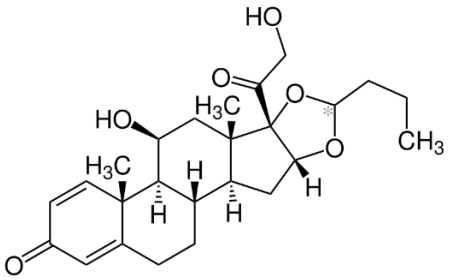


Figure 9. Chemical structure of budesonide

Table 3. IR stretching frequencies of functional groups in budesonide.

Peak Number	Functional Group	IR Stretching (cm^{-1})
1	O-H	3498.24
6	C=O (unsaturated ring)	1720.19
7	C=O	1666.2
8	C=C	1627.63

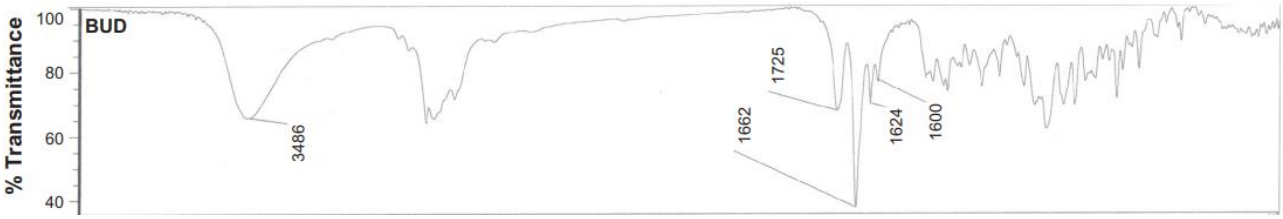


Figure 10. Literature FTIR spectra of pure budesonide (Sahib et al., 2011).

Differential Scanning Calorimetry (DSC):

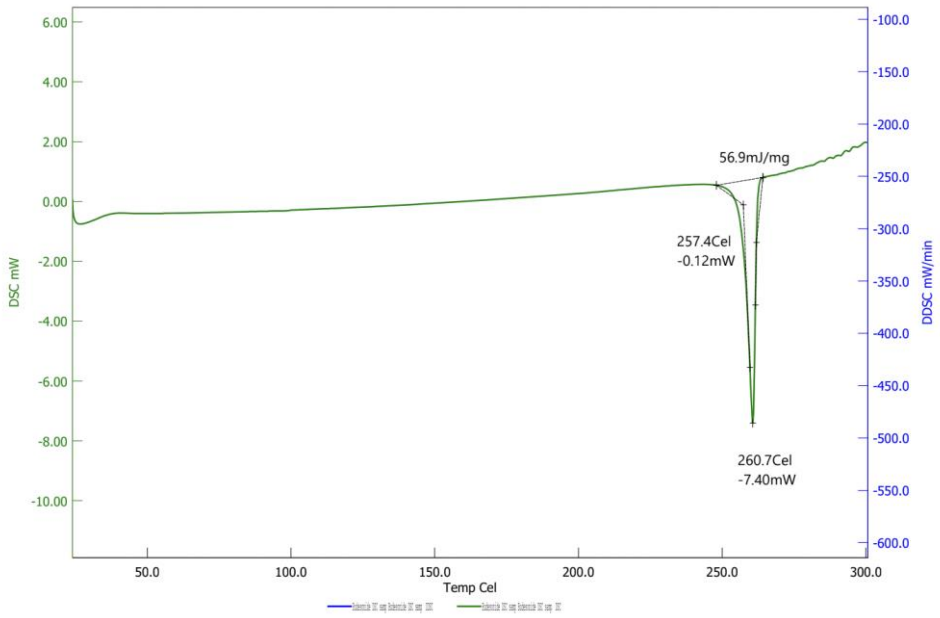


Figure 11. DSC of pure budesonide.

Table 4. Comparison of theoretical, experimental and DSC melting point of budesonide.

Theoretical Melting Point	Experimental Melting Point	DSC Melting Point
261.58°C	260.0°C	260.7°C

Figure 12. Literature DSC spectrum of pure budesonide with a reported melting point of 261.58°C (Sahib et al., 2011).

5.3 Discussion

The FTIR results indicate peaks at certain functional groups which can be attributed to the functional groups that make up the chemical structure of budesonide. Peak 1 (3498.24 cm^{-1}) can be attributed to the hydroxyl (OH) that belongs to the carboxylic acid group in budesonide. Peak 6 (1720.19 cm^{-1}) can be attributed to the ketone group (C=O) in the unsaturated ring of the structure. Peak 8 (1627.63 cm^{-1}) can be attributed to the carbon double bonds in the unsaturated ring. The FTIR spectrum of the experimental sample of budesonide is similar to the literature spectrum, with a few minor peaks seen in the 3500 cm^{-1} to 2000 cm^{-1} region of the experimental spectra. The similarities between the experimental and literature spectrum allows for the conclusion that the experimental drug being studied is budesonide.

The experimental DSC spectrum indicates that the melting point of budesonide is 260.7°C. The spectrum and melting point peak are similar to the literature spectrum, which shows a melting point of 261.58°C for pure budesonide. The similarities allow for the conclusion that the experimental budesonide sample is pure without any major impurities.

6 Analytical Studies

6.1 Calibration Curve of Budesonide

6.1.1 Methods

Preparation of Standard Stock Solution:

A standard stock solution of budesonide in methanol was prepared by dissolving 10mg of the drug in 100mL of distilled water in a volumetric flask. The flask was inverted 20-25 times to ensure thorough mixing. The resulting concentration of the standard stock solution was 100 ug/mL.

In order to make a stock solution of phosphate buffer with pH 6.8, budesonide was weighed accurately, 11 mg in this case, and dissolved in 100 mL volumetric flask filled with distilled water. The mixture was well mixed by inverting the flask 20-25 times. The concentration of the resulting stock solution was 110 μg/mL.

Selection of Wavelength for Analysis of Budesonide:

A diluted solution with a concentration of 1ug/mL was created by taking 0.25 mL of the standard stock solution and adding distilled water to a total volume of 25 mL. This diluted solution was then subjected to UV analysis within the range of 200 nm to 500 nm. The resulting UV spectrum of budesonide exhibited the highest absorption at 245 nm, indicating its λ_{max}.

Validation of the Method:

The identification analytical method was confirmed for its linearity. Different concentrations of budesonide (1,5,10,15,20,25 ug/mL) were prepared and analyzed using a UV Spectrophotometer in the range of 200-500 nm, after which a methanol calibration curve was plotted. The absorbance values obtained were plotted against their corresponding concentrations, resulting in a calibration plot shown in the figure. The process was repeated to create a calibration curve for a 6.8 pH phosphate buffer. The same was repeated for a 6.8 pH phosphate buffer calibration curve.

6.1.2 Results

Linearity Study:

Medium: Methanol

Table 5. Range of concentrations and their respective absorbance values.

Concentration (ug/mL)	Absorbance
1	0.024
5	0.186
10	0.340
15	0.513
20	0.689
25	0.864

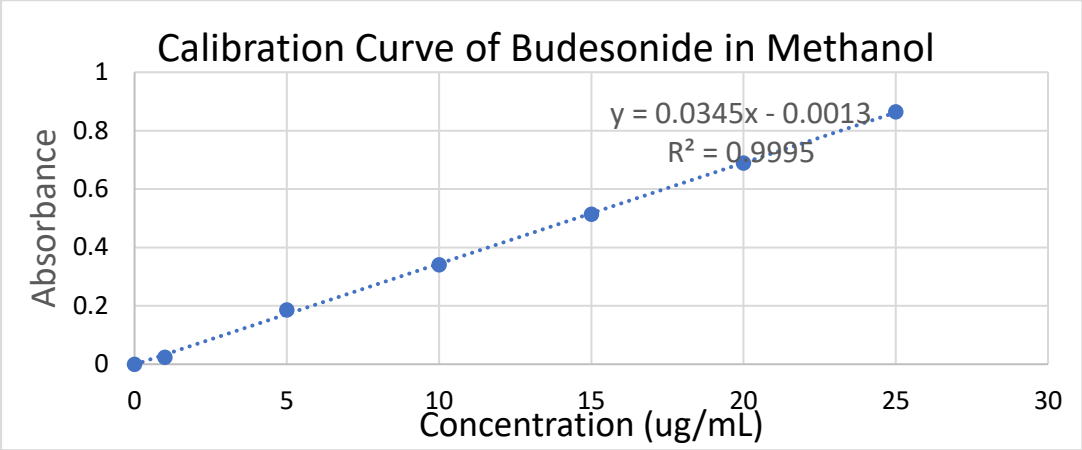


Figure 13. Calibration curve of budesonide in methanol showing a linear relationship between absorbance and concentration.

Medium: Phosphate Buffer 6.8 pH

Table 6. Absorbances of budesonide at varying concentrations in 6.8 pH phosphate buffer.

Concentration (ug/mL)	Absorbance
1.1	0.0331
5.5	0.1714
11	0.3332
15.4	0.4819
22	0.6940
25.3	0.8160

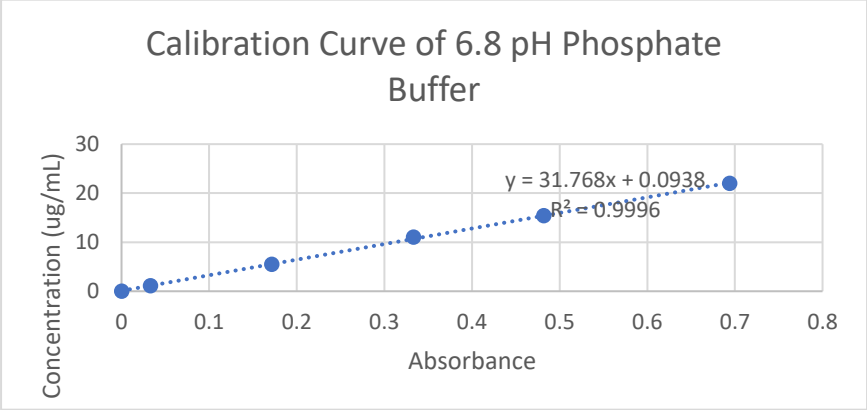


Figure 14. Calibration curve of budesonide in 6.8 pH phosphate buffer showing a linear relationship between absorbance and concentration.

6.1.3 Discussion

The λ_{max} of budesonide was determined to be at 245 nm by UV analysis. Gouda et al. reported the λ_{max} of budesonide at 246 nm (Gouda et al., 2011). It can be concluded that the identification studies were successful, and the sample budesonide can be used for further studies. The quality of an analytical method depends on the linearity of the calibration curve (Moosavi and Ghassabian, 2017). The calibration curve obtained for methanol indicates a linear relationship between the concentration and absorbance values. This is a positive indication of the assay performance in a validated range. Additionally, the correlation coefficient (R^2=0.9993) is close to unity, which can be used to conclude that the calibration curve is linear (Moosavi and Ghassabian, 2017). The calibration curve obtained for 6.8 pH phosphate buffer indicates a linear relationship between the concentration and absorbance values. This is a positive indication of the assay performance in a validated range.

7 Drug Excipient Compatibility

7.1 Methods

Fourier-transform Infrared Spectroscopy (FTIR):

The mortar and pestle and pellet dies were thoroughly cleaned with dichloromethane (DCM) prior to mixing sample. A small sample of the tablet blend was triturated in sodium bromide (KBr) using a mortar and pestle. This mixture was filled into the pellet die and compressed to the bottom of the pellet die. The pellet die was placed into the FTIR instrument for analysis of the tablet blend.

Differential Scanning Calorimetry (DSC):

The cooling unit was turned on to allow the sample to cool at appropriate times. A small sample of budesonide was placed in a sample pan and covered with a lid. The sample pan and lid were crimped together to enclose the sample using a sample press. The pressed sample pan was placed inside the DSC instrument using forceps. The sample pan was placed in the right slot

and a reference pan was placed in the left slot. The reference pan was used for comparison during DSC analysis. The weight of the tablet blend was entered into the DSC software as well as heating and cooling temperatures. The temperature range selected was 50°C to 300°C. A heating and cooling rate of 10°C per minute was selected. After the sample run was completed, the instrument was allowed to cool down completely before turning it off.

Physical Compatibility Study:

A mixture of solid-SMEDDS containing budesonide and other excipients was stored away from light and was observed for any physical changes for up to 20 days at room temperature and at 40ºC ± 2ºand 75% RH± 2% according to ICH guidelines.

7.2 Results

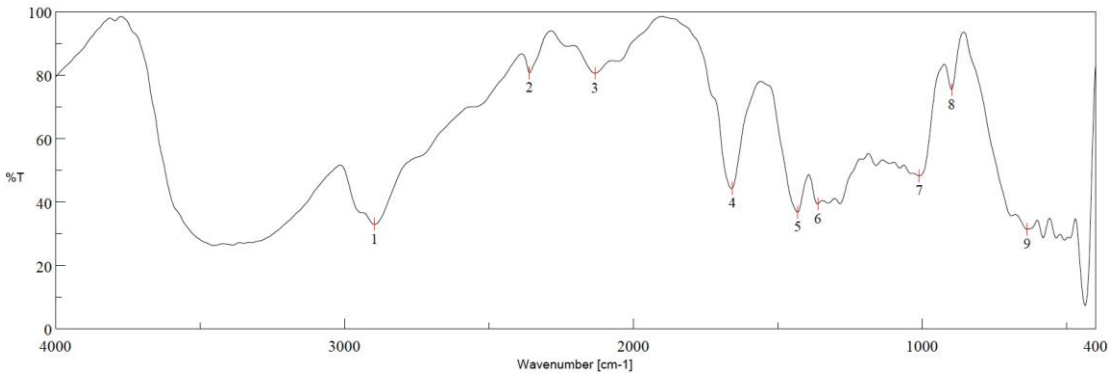


Figure 15. FTIR spectrum of tablet blend containing budesonide.

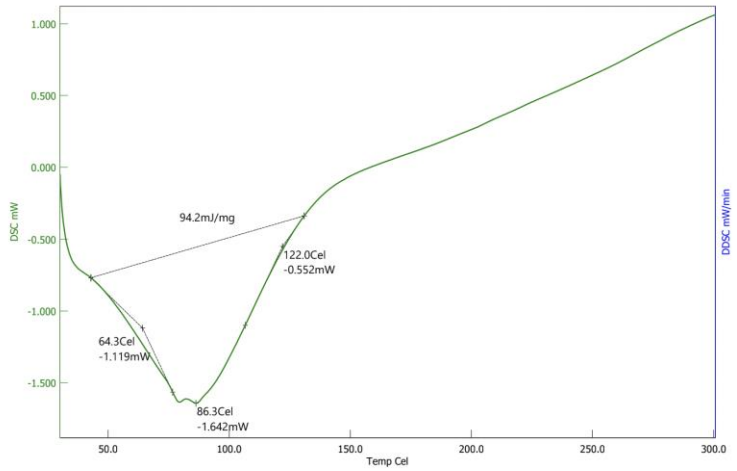


Figure 16. DSC Spectrum of tablet blend containing budesonide and tablet excipients.

Table 7. Physical compatibility of tablet blend observed over 20 days at room temperature and 40ºC ± 2ºand 75% RH± 2%.

Days	Observation at Room Temperature	Observation at 40°C ± 2° and 75% RH± 2%
1	No change in appearance	No change in appearance
10	No change in appearance	No change in appearance
20	No change in appearance	No change in appearance

7.3 Discussion

The FTIR spectrum of the tablet blend containing budesonide indicates that budesonide has been completely encapsulated within granules. The peaks of the drug in the fingerprint region have broadened in comparison to the pure drug spectrum, which shows encapsulation of the drug. The DSC spectrum shows the disappearance of the drug peak and broad peak of the excipients in the blend. The physical compatibility of the tablet blend was observed at room temperature and 0°C ± 2° and 75% RH± 2% for 20 days. The initial observation at day 0 was a white powder. There was no change in the appearance observed at room temperature or 40°C ± 2°C and 75% RH ± 2%. This indicated that there was no instability or chemical interaction observed between budesonide and the tablet excipients which included prosolv (SMCC 90), HPC, crospovidone, magnesium stearate and flavourants.

EXPERIMENTAL WORK II

8 Preparation and Evaluation of Solid-SMEDDS of Budesonide

8.1 Prescreening of Excipients

8.1.1 Methods

Saturated Solubility Studies:

Various oils, surfactants, and co-surfactants were screened to find the most suitable vehicles that enhance the solubility of budesonide. The shake-flask method was employed to determine the solubility of each vehicle. Specifically, 500 mg of budesonide was added to 4 ml of each vehicle in a centrifuge tube. The tubes were shaken at 37±0.1°C for 48 hours to promote budesonide solubility. After 48 hours, the tubes were centrifuged to separate excess drug at the bottom. The supernatant was decanted, diluted, and analyzed using a UV-Spectrophotometer to calculate the solubility of budesonide.

Solubility of Budesonide in Water:

The shake-flask method was employed to determine the solubility of budesonide in distilled water. To an excess amount of budesonide (500 mg) added to 4 ml of distilled water in a centrifuge tube, the tube was shaken at 37±0.1°C for 48 hours to facilitate the solubility of budesonide. After 48 hours, the tube was centrifuged to ensure excess drug is settled at the bottom of the tube. The supernatant from the centrifuge was decanted, diluted to an appropriate concentration, and analyzed using a UV-Spectrophotometer to determine the solubility.

8.1.2 Results

Table 8. Solubility of budesonide in various oils, surfactants and co-surfactants.

Oils (mg/mL)		**Surfactants (mg/mL)**		**Co-surfactants (mg/mL)**	
Olive oil	8.801	Labrafil 2125	52.052	Transcutol	222.746
Maisine	72.948	Labrafil 1944	47.179	Lauroglycol fcc	5.688
Peceol	102.142	Tween 80	6.345	PEG 400	8.649
Sesame oil	16.048	Labrasol ALF	71.477		
Soybean oil	13.484				

Labrafac 1349	7.139				

Table 9. Solubility of budesonide in distilled water.

Drug	**Solubility in Water**
Budesonide	0.041 mg/ml

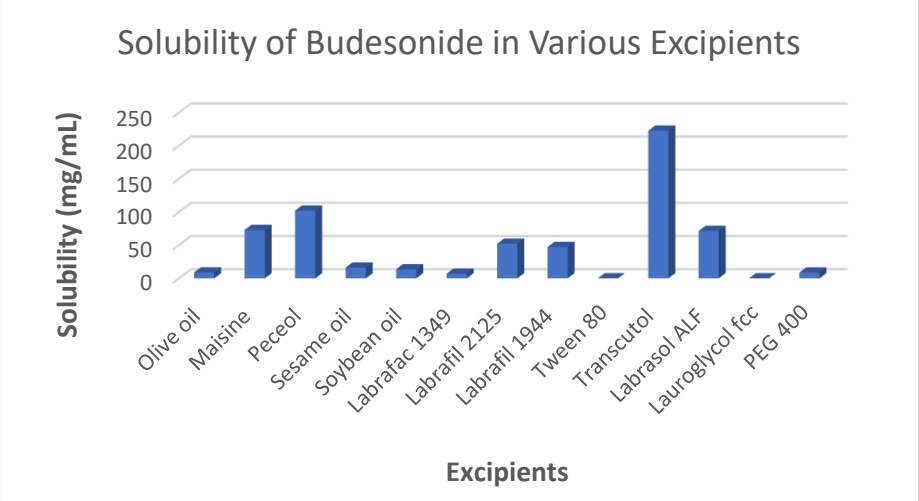


Figure 17. Solubility of budesonide in various oils, surfactants and co-surfactants, presented in a histogram.

8.1.3 Discussion

The aim of the preliminary screening studies is to identify the vehicles that would offer the highest solubility for budesonide in the formulation of liquid-SMEDDS. The results of the saturated solubility studies showed that Peceol, Labrasol ALF, and Transcutol had the highest solubility of budesonide, at 102.142 mg/ml, 71.477 mg/ml, and 222.746 mg/ml, respectively. Based on these findings, a pseudo ternary diagram was constructed to facilitate the further development of liquid-SMEDDS.

8.2 Preparation of Liquid-SMEDDS and Construction of a Pseudo Ternary Phase Diagram

8.2.1 Methods

Preparation of Liquid-SMEDDS:

For the preparation of liquid SMEDDS, three surfactant and co-surfactant (Smix) ratios were selected for screening. Peceol as an oil, Labrasol as a surfactant and Transcutol as a co-surfactant were selected for the composition of liquid-SMEDDS based on the solubility study results. Smix ratios of 1:1, 1:2 and 2:1 were screened. Liquid-SMEDDS were prepared by varying concentrations of oil and Smix (1:9, 2:8, 3:7…9:1) (Table 10) For an Smix ratio of 1:1, a stock solution of 50 mL composed of 25 mL of Labrasol and 25 mL of Transcutol was prepared. In a 150-mL beaker, 1 mL of Peceol was pipetted, followed by 9 mL of Smix. Aqueous titration method was used by titrating the oil and Smix mixture drop-by-drop with distilled water using a burette, while the solution was stirred at 400 rpm. The samples were classified as microemulsion that appear as clear liquids with a blue tint. This was repeated for each Smix ratio with varying concentrations of oil and Smix.

Construction of a Pseudo Ternary Phase Diagram:

Chemix School was utilized to generate a pseudo ternary phase diagram. The composition of oil, Smix, and water for each Smix ratio was calculated and inputted into the software to produce three separate phase diagrams.

8.2.2 Results

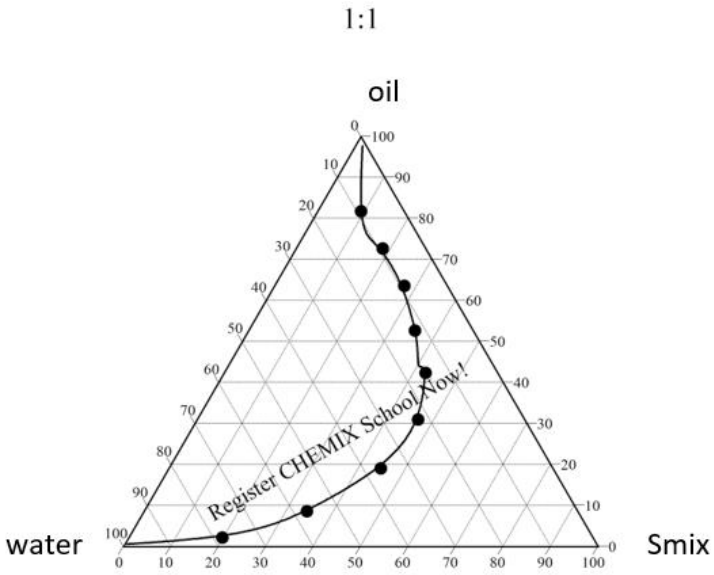


Figure 18. Pseudo ternary phase diagram of Smix ratio 1:1 (labrasol:transcutol).

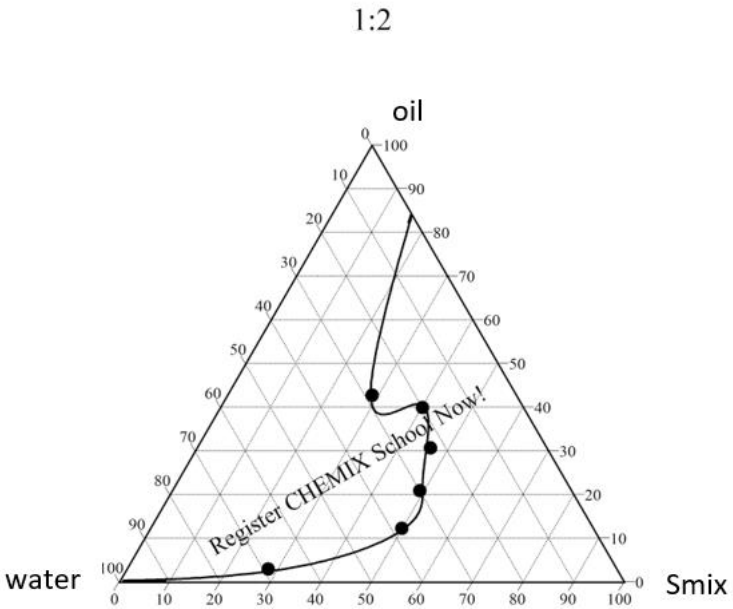


Figure 19. Pseudo ternary phase diagram of Smix ratio 1:2 (labrasol:transcutol).

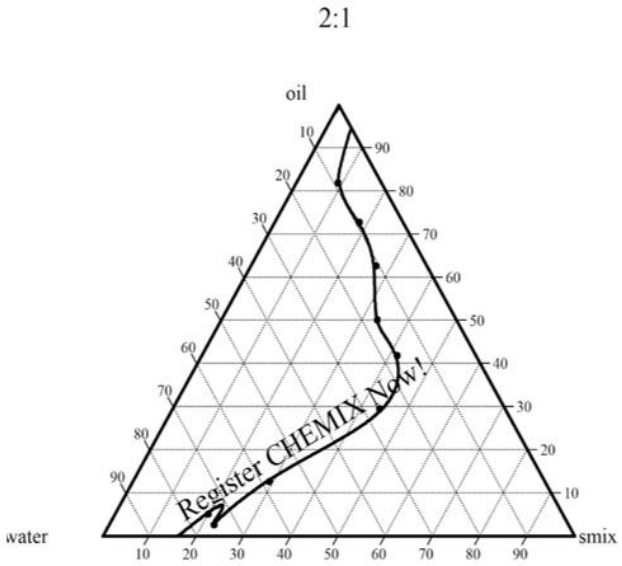


Figure 20. Pseudo ternary phase diagram of Smix ratio 2:1 (labrasol:transcutol).

8.2.3 Discussion

Pseudo-ternary phase diagrams are used to determine regions of microemulsion existence. These diagrams summarize the effect of Smix ratios on the stability of microemulsions and a region of microemulsions can be identified. The phase diagrams obtained indicate that an Smix ratio 1:1 gives the greatest region of microemulsion existence. The microemulsion region increases as Smix percentage increases. Smix ratio of 1:1 was used for the optimization of the liquid-SMEDDS composition.

8.3 Optimization of Liquid-SMEDDS

8.3.1 Design of Experiment

8.3.1.1 Methods

To obtain the optimal formulation for liquid-SMEDDS, Design Expert software was employed. The optimization was done using a mixture design, where the concentrations of oil (1-4%), Smix (19-45%), and water (38-76%) were analyzed. Based on the results from the pseudo ternary phase diagrams, 11 formulations were created using Design Expert software (as shown in the figure). These 11 formulations were prepared by adding required amounts of oil and Smix in a 100 mL beaker. Next, aqueous titration method was used to titrate the mixture with

the volume of distilled water specified in table x under stirring at 400 rpm. Each formulation was evaluated for percentage transmittance (UV-Spectrophotometer at 628 nm), particle size (particle size analyzer), polydispersity index (particle size analyzer) and zeta potential (particle size analyzer). The results obtained from the characterization of the formulations were inputted into Design Expert to yield 3D surface plots of the evaluation parameters (Table 11). A final optimized formulation was obtained from Design Expert.

The final optimized formulation was prepared with 2.38% oil, 35.66 Smix and 61.94% water.

8.3.1.2 Results

Optimization of Liquid-SMEDDS

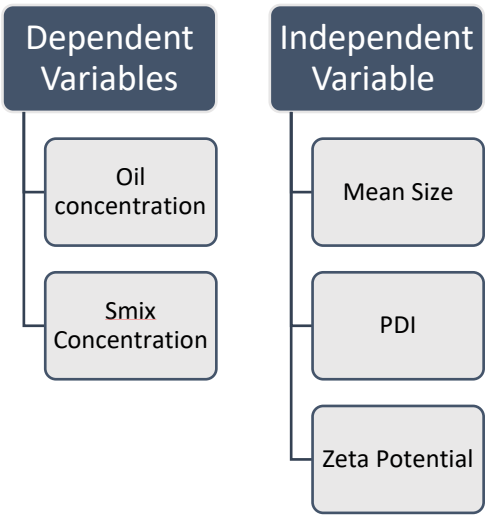


Figure 21. The dependent and independent variables that are evaluated for the optimization of liquid-SMEDDS.

Table 10. Formulations F1-F11 obtained from Design Expert for the optimization of liquid-SMEDDS.

Formulation	Oil (%)	Smix (%)	Water (%)
F1	4.000	33.080	62.919
F2	3.759	27.159	69.080
F3	2.523	21.476	76.000
F4	1.045	22.954	76.000
F5	3.997	40.745	55.256
F6	1.000	39.570	59.429
F7	1.252	45.000	53.747
F8	3.997	45.000	51.002
F9	1.917	25.468	72.614
F10	1.000	31.599	67.400
F11	4.000	20.033	75.966

Table 11. Evaluation parameters of F1-F11 including percent transmittance, mean size, zeta potential and polydispersity index (PDI).

Formulations	% Transmittance	Mean size (nm)	Zeta potential (mV)	PDI
F1	98.8	1272.8	-64.8	0.671
F2	82.3	739.5	-64.4	1.1
F3	97.9	130.4	-47.5	0.356
F4	99.5	150.7	-56	0.272
F5	95.4	463.9	-60.7	0.737
F6	98.6	146.5	-44.9	0.232
F7	99.1	139.3	-43.6	0.199
F8	98.9	173.6	-56.7	0.351
F9	97.4	165.6	-50.7	0.253
F10	99.4	162.6	-54.8	0.284

F11	82.3	739.5	-64.4	1.1

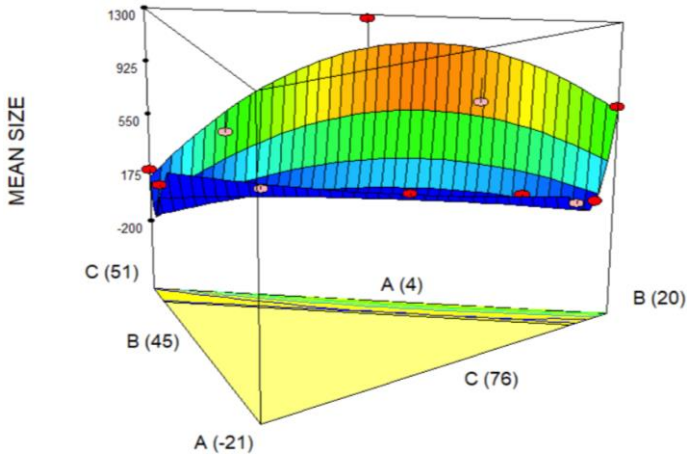


Figure 22. A 3D surface plot of the mean size of optimized liquid SMEDDS.

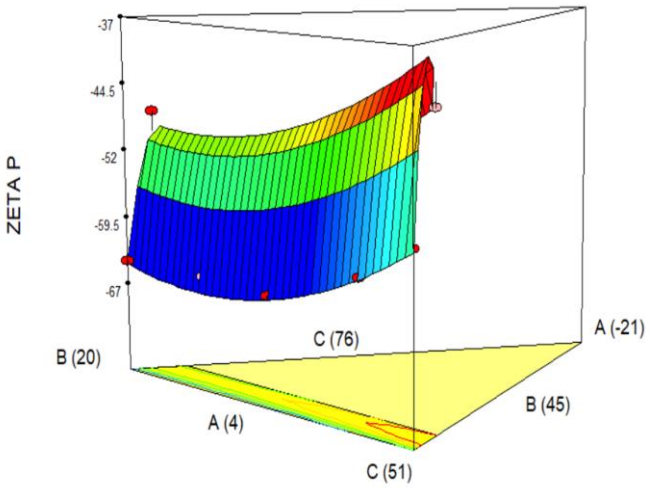


Figure 23. A 3D surface plot of the zeta potential of optimized liquid SMEDDS.

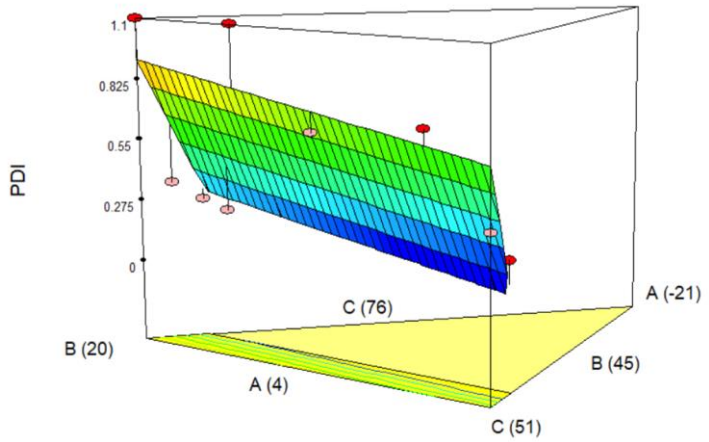


Figure 24. A 3D surface plot of the polydispersity index (PDI) of optimized liquid SMEDDS.

Table 12.

RESPONSES	MODEL	SD	R^2	ADJUSTED R^2	PREDICTED R^2
Y2(**Mean size (nm)**)	Linear	299.45	0.4965	0.3706	0.0783
	Special Cubic	153.58	0.9338	0.8345	-0.0419
Y3(**Zeta potential (mV)**)	Quadratic	2.63	0.9438	0.8877	0.6817
Y4(**PDI**)	Linear	0.21	0.6929	0.6162	0.4137

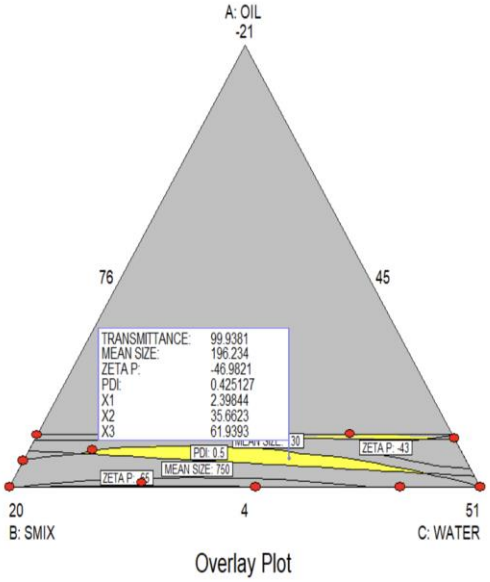


Figure 25. The overlay plot of all three responses.

8.3.1.3 Discussion:

D-optimal mixture design was chosen since it is the most appropriate design for a three-component system as it has the maximum prediction power. The dependent variables in the design are oil and Smix concentration and the independent variables are PDI, zeta potential and mean size (Fig. 21). Formulations F1-F11 obtained from Design Expert for the optimization of liquid-SMEDDS were evaluated for mean size, percent transmittance, zeta potential and polydispersity index (PDI). The results from table 11 indicate that as the oil percentage increases in the formulation, percentage transmittance decreases. The increase in oil negatively impacts the percentage transmittance as it is crucial to obtain clear microemulsions with a percentage transmittance close to 100%. The increase in oil percentage also impacts the mean size negatively because there is an increase in the mean size of the microemulsion. The mean size of the microemulsion should ideally be between 100-200 nm to ensure smaller size and larger surface area which will allow for better penetration of the drug within the microemulsion, resulting in better bioavailability. The increase in oil percentage negatively impacts the zeta potential and polydispersity index (PDI). As the oil percentage increases, zeta potential becomes more negative, which indicates that the

formulation is more stable. The PDI also increases as oil increases which indicates that the formulation is a highly polydisperse sample with multiple particle sizes. It is crucial for the PDI value to be close to 0 to ensure uniformity within the sample in regards to particle size. The increase of Smix percentage and decrease of oil percentage has a positive impact on all evaluation parameters, however it decreases the value of the zeta potential. As Smix concentration increases, zeta potential decreases from -60 mV to -50 to -40 mV. This indicates that the stability of the formulation is decreasing. Additonally, as Smix increases, the mean size of the microemulsion decreases, percentage transmittance increases and PDI decreases, approaching closer to 0. The overlay plot of all three responses indicates a region in which any composition within the region will yield SMEDDS of with ideal response values. This plot was used to formulate the optimized formulation for which the composition was 2.38% oil, 35.66 Smix and 61.94% water.

8.4 Characterization of Optimized Liquid-SMEDDS

8.4.1 Methods

Centrifugation:

10 mL of liquid-SMEDDS were added to a centrifuge and centrifuged for 30 minutes at 3000 RPM. The formulation was checked for phase separation.

Viscosity:

The viscosity of the liquid-SMEDDS was determined using Brookfield Viscometer. Spindle S18 water employed with a small sample adapter at 100 RPM and 19.8% torque.

pH:

The pH of the liquid-SMEDDS was determined using a Mettler Toledo pH Meter. The pH meter was calibrated prior to testing the sample. The pH probe was inserted into a 50-mL beaker of liquid-SMEDDS and the value of the pH was recorded.

Robustness:

The robustness of liquid-SMEDDS was determined by adding 1-mL of the liquid-SMEDDS into 250 mL of distilled water. This solution was stored for 24 hours to observe any signs of phase separation or drug precipitation.

Percentage Transmittance:

The percentage transmittance of the liquid-SMEDDS was determined using a UV-Spectrophotometer. Liquid-SMEDDS were poured into a cuvette and analyzed at 628 nm.

Mean Size:

The mean particle size of microemulsions formed from the optimized liquid-SMEDDS were determined using Horiba Scientific Nano Particle Analyzer. A drop of liquid-SMEDDS was diluted with double distilled water and inserted into the particle size analyzer using a cuvette to determine the particle size.

Zeta Potential:

The zeta potential of the microemulsions formed from liquid-SMEDDS were determined using Horiba Scientific Nano Particle Analyzer. A drop of liquid-SMEDDS was diluted with double distilled water and inserted into the particle size analyzer using a cuvette to determine the zeta potential.

PDI:

The PDI of the microemulsions formed from liquid-SMEDDS were determined using Horiba Scientific Nano Particle Analyzer. A drop of liquid-SMEDDS was diluted with double distilled water and inserted into the particle size analyzer using a cuvette to determine the PDI.

8.4.2 Results

Centrifugation:

There was no phase separation observed after centrifugation of liquid-SMEDDS.

Robustness:

After 24 hours, there were no signs of phase separation or drug precipitation.

Table 12. Evaluation of liquid-SMEDDS; pH, viscosity and percentage transmittance.

Evaluation	**Results**
pH	3.37
Viscosity	5.76 cP
Percentage Transmittance	98.4%
Mean size	125 nm
PDI	0.347
Zeta Potential	-53.6 mV

Particle size and PDI:

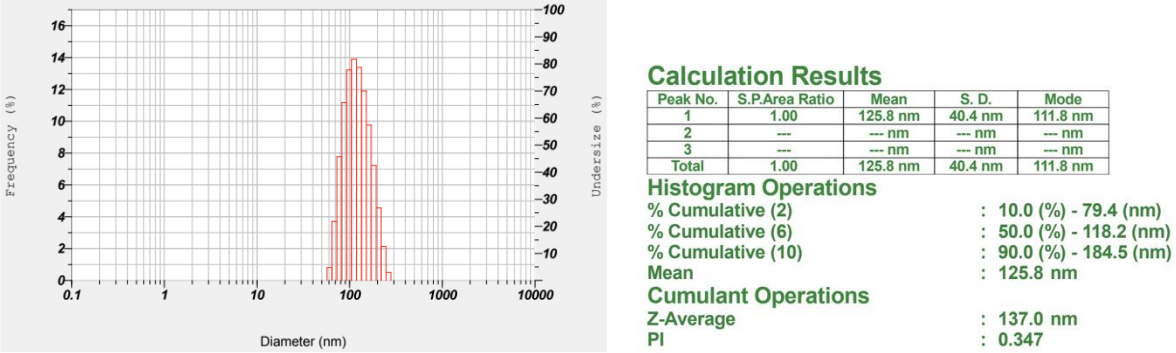
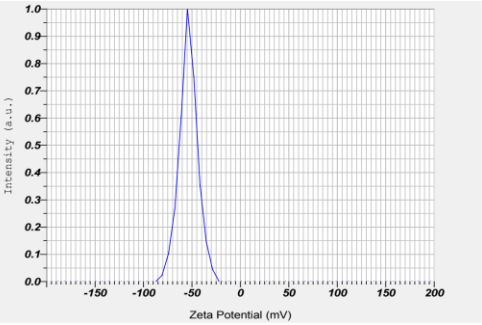


Figure 26. Particle size distribution curve and mean size and PI values.

Zeta Potential:



Calculation Results

Peak No.	Zeta Potential	Electrophoretic Mobility
1	-53.6 mV	-0.000414 cm2/Vs
2	--- mV	--- cm2/Vs
3	--- mV	--- cm2/Vs

Zeta Potential (Mean) : -53.6 mV
Electrophoretic Mobility Mean : -0.000414 cm^2/Vs

Figure 27. Data of zeta potential of optimized liquid-SMEDDS.

8.4.3 Discussion

The centrifugation results indicating no phase separation show the stability of the optimized liquid-SMEDDS. The optimized liquid-SMEDDS formed also have robustness as there was no phase separation or drug precipitation observed after 24 hours. The formulation has a very low viscosity of 5.76 cP and an acidic pH of 3.37. The formulated liquid-SMEDDS were visually clear with a slight blue tint and a percentage transmittance of 98.4%. The mean size of the liquid-SMEDDS were 125 nm, which were within the desired range of 100-200 nm. The smaller particle size of the microemulsions allow for higher surface area and better penetration. The PDI is 0.347 which indicates that the microemulsions are monodispersed with most particles being of similar size. The zeta potential of the formulation is -53.6 mV, which was tested on a 2-month-old sample. This indicates high stability of the liquid-SMEDDS even after 2 months of storage.

9 Formulation and Evaluation of Orodispersible Tablets of Budesonide

9.1 Methods

9.1.1 Preparation of Solid-SMEDDS by Adsorption onto Solid Carrier

Approach 1:

The liquid-SMEDDS that had been optimized were transformed into solid-SMEDDS by adsorbing them onto Fujicalin and Fujisil, using a ratio of 3:1. The resulting mixture was mixed thoroughly to make sure that the drug was uniformly distributed within the solid-SMEDDS. This mixture was given the name solid-SMEDDS direct compression 1 (SSDC1).

Approach 2:

The prepared liquid-SMEDDS were adsorbed onto Neusilin US2. The mixture was thoroughly mixed to ensure uniformity of the drug within the solid-SMEDDS. This mixture is denoted as solid-SMEDDS direct compression 2 (SSDC2).

9.1.2 Preparation of Solid-SMEDDS Using Wet Granulation

Approach 1:

In a 1000 mL beaker with 500 mL distilled water, 220 g of Cavasol was added and allowed to dissolve for 30 minutes under a high-speed stirrer. Next, prepared liquid-SMEDDS were added to the beaker and stirred overnight. After the mixing was complete, 880 g of cellactose was added and the mixture was thoroughly mixed. This mixture was oven dried overnight at 60°C to obtain granules. This mixture is denoted as solid-SMEDDS wet granulation 1 (SSWG1).

Approach 2:

During the preparation of liquid-SMEDDS, budesonide is dissolved in a mixture of oil and Smix, followed by the addition of 170 mL of ethanol. Prosolv and hydroxy propyl cellulose (HPC) are added to this mixture in a ratio of 25:1 and mixed thoroughly. An additional 30 mL of ethanol is added and the powder is mixed to form aggregates. This mixture is dried overnight at 60°C to evaporate the ethanol to form granules. This mixture is denoted as solid-SMEDDS wet granulation 2 (SSWG2).

Solubility Enhancement by Solid-SMEDDS:

A comparison study was done to compare the solubility of budesonide-loaded solid-SMEDDS with pure drug budesonide. Solid-SMEDDS granules containing 1 mg budesonide was accurately weighed and added to a 50-mL volumetric flask. The flask was diluted to the mark with 6.8 pH phosphate buffer and inverted 20-25 times to ensure proper mixing. Another solution with 1-mg of pure drug was prepared in a 50-mL volumetric flask diluted to the mark with 6.8 pH phosphate buffer. Both solutions was analyzed using UV-Spectrophotometer at 245 nm. The equation of the line from the 6.8 pH phosphate buffer calibration curve was used to determine the solubility of the solid-SMEDDS granules and pure drug in 6.8 pH phosphate buffer.

9.1.3 Formulation of Orodispersible Tablets of Budesonide

Various excipients were screened for the formulation of orodispersible tablets of budesonide. A 1-mg budesonide tablet was made by accurately weighing granules of budesonide that would contain 1 mg of drug in 350 mg of tablet blend. Different diluents, disintegrants, binders and flavouring agents were screened. Disintegrants were varied from 2% to 5%, lubricant was varied from 0.5% to 1.5%, sweetener from 0.85% to 4%, taste masking agent from 1% to 10%. For each composition, all excipients were accurately weighed and mixed together. The mixture was passed through a sieve of size 40 and thoroughly mixed by geometric mixing. A batch size of 500 tablets were prepared for each composition. The tablet blend was compressed using a Manesty Tablet Press.

9.1.4 Evaluation of Orodispersible Tablets

Micromeritics:

Angle of Repose:

A funnel is fixed at a height of 2 cm from the bench. Tablet blend is poured on the wall of the funnel until the blend reaches the tip of the funnel. A circle is drawn around the pile of blend. The diameter and radius of 4 different spots of the circle was determined. The angle of repose was calculated using the formula:

$$\theta = \tan^{-1} h/r \qquad (1)$$

Bulk density:

Bulk density is determined by weighing 100 mL of blend in a graduated cylinder. The bulk density is calculated by the formula:

$$Density = \frac{Mass}{Volume} \qquad (2)$$

Tapped Density:

The exact volume at 100 mL of blend in a graduated cylinder is noted and the cylinder is lightly tapped 100 times. The new volume is noted. Tapped density is calculated by formula (2).

Hausner's Ratio:

$$Hausner's\ Ratio = \frac{Tapped\ Density}{Bulk\ Density} \quad (3)$$

Compressibility:

$$Compressibility: \frac{Tapped\ Density - Bulk\ Density}{Tapped\ Density} \quad (4)$$

Physical Testing:

Hardness:

The hardness of 10 tablets was tested using a ERWEKA Tablet Hardness Tester. The tablet hardness tester was calibrated prior to testing. Each tablet was placed in the middle of the slot and the start button was pressed to facilitate the crushing of the tablet. The force required to crush the tablet was noted in $kg \cdot cm^2$.

Friability:

A Vankel Friabilator was used to determine the friability of the tablets. A sample of whole tablets was accurately weighed and added into the friabilator. The RPM was set to 100 and the tester was allowed to rotate. After 100 rotations were complete, the sample of tablets were re-weighed. The percent friability of the tablets was calculated using the before and after weight.

Weight Variation:

The weight of 20 tablets was taken using a Mettler Toledo Analytical Balance.

Chemical Testing:

Drug Content:

The drug content of orodispersible tablets of budesonide was tested by crushing 20 tablets using a mortar and pestle and weighing 350 mg of the blend. The blend was added to a 25-mL volumetric flask and diluted with methanol. The volumetric flask was inverted 20-25 times and sonicated using a bath sonicator for 15 minutes. 1 ml of this solution was pipette into a 10-mL volumetric flask and diluted to the mark with methanol. The flask was inverted 20-25 times to ensure proper mixing. This solution was analyzed by UV-Spectrophotometer at 245 nm. The

equation of the line from the methanol calibration curve was used to calculate the drug content in 1 tablet.

Disintegration:

In a petri dish, a tablet was placed in 5-mL of 6.8 pH phosphate buffer. The time required for the tablet to disintegrate was noted. The wetting time of the tablet was also noted.

Dissolution:

The dissolution test of six tablets was conducted in 6.8 pH phosphate buffer utilizing the Sotax USP Type II Apparatus. The apparatus was adjusted to 37.1^{o}C and 50 RPM. Using a graduated cylinder, 200 mL of 6.8 pH phosphate buffer was added to each vessel, and the buffer was permitted to reach 37.1^{o}C in the water bath. For each vessel, 10 test tubes were labeled with time points and placed in a test tube rack. Once the dissolution medium reached the desired temperature, the paddles were lowered into the medium. A tablet was added to each of the 6 vessels and the paddles were turned on to rotate at 50 RPM. Using a pipette, 5-mL samples were removed from each vessel at 10 time points (1-10 minutes) and added into their corresponding test tubes. At each time point, 5-mL of fresh 6.8 pH phosphate buffer was replenished into each vessel. The dissolution process was terminated after 10 minutes, and the absorbance of samples taken from each vessel at different time intervals was analyzed at 245 nm using a UV-Spectrophotometer. The calibration curve of 6.8 pH phosphate buffer was used to determine the drug release at each time point in each vessel.

9.2 Results

9.2.1 Evaluation of Solid-SMEDDS

Solubility Studies of Solid-SMEDDS and Budesonide in 6.8 pH Phosphate Buffer

Table 13. Comparison of the solubility of solid-SMEDDS granules and pure budesonide in 6.8 pH phosphate buffer.

	Solubility in 6.8 pH Phosphate Buffer (mg/ml)
Budesonide	0.0412
Solid-SMEDDS	0.977

9.2.2 Formulation of Orodispersible Tablets of Budesonide

Formulations for Direct Compression:

Table 14. Composition of F1 and F2 using SSDC1 for the direct compression of budesonide orodispersible tablets.

Ingredients	F1	F2
Solid-SMEDDS (SSDC1)	96	96
Xylitol	236	238
Pharmaburst 500	20	8
Magnesium Stearate	4	2
Fujisil	4	4
Cherry Powder	20	36
Optify	4	4
Neotame	16	10

Table 15. Composition of F3 and F4 using SSDC1 for the direct compression of budesonide orodispersible tablets.

Ingredients	F3	F4
Solid-SMEDDS (SSDC1)	98	98
Ludipress	224	237
Ultraburst	20	8
Magnesium Stearate	4	2
Fujisil	4	2
Vanilla	36	36

Optify	8	10
Neotame	6	5

Table 16. Composition of F5 using SSDC1 for the direct compression of budesonide orodispersible tablets.

Ingredients	F5
Solid-SMEDDS (SSDC1)	100
Disintequik MCC	266
Magnesium Stearate	4
Cherry Powder	30

Table 17. Composition of F6 using SSDC1 for the direct compression of budesonide orodispersible tablets.

Ingredients	F6
Solid-SMEDDS (SSDC1)	45
Ludipress	224
Ultraburst	20
Magnesium Stearate	4
Fujisil	4
Vanilla	36
Optify	8
Neotame	6

Table 18. Composition of F7 using SSDC1 for the direct compression of budesonide orodispersible tablets.

Ingredients	F7
Solid-SMEDDS (SSDC1)	45
Ludipress	155.3
Cellactose	155.3

Disintequik	23
Magnesium Stearate	4
Optify	9.1
Neotame	4.3

Table 19. Composition of F8 using SSDC1 for the direct compression of budesonide orodispersible tablets.

Ingredients	F8
Solid-SMEDDS (SSDC1)	45
Galen IQ	170.5
Pharmaburst 500	170.5
Crospovidone	10
Magnesium Stearate	4
Neotame	2

Table 20. Composition of F9 using SSDC1 for the direct compression of budesonide orodispersible tablets.

Ingredients	F9
Solid-SMEDDS (SSDC1)	45
Galen IQ	170.5
Pharmaburst 500	170.5
Crospovidone	10

Table 21. Composition of F10 using SSDC2 for the direct compression of budesonide orodispersible tablets.

Ingredients	F10
Solid-SMEDDS (SSDC2)	45
Galen IQ	170.5
Pharmaburst 500	170.5

Crospovidone	10

Table 22. Composition of F11 using SSDC2 for the direct compression of budesonide orodispersible tablets.

Ingredients	F11
Solid-SMEDDS (SSDC2)	40
MCC	316
HPMC	20
Crospovidone	20
Magnesium Stearate	4

Formulations for Wet Granulation:

Table 23. Composition of F12-F16 using SSWG1 for the compression of orodispersible tablets of budesonide.

Ingredients	F12	F13	F14	F15	F16
Solid-SMEDDS (SSWG1)	132.3	132.3	132.3	132.3	132.3
Cellactose 80	244	-	122	183	61
Isomalt	-	244	122	61	183
Crospovidone	10	10	10	10	10
Peppermint flavour	10	10	10	10	10
Magnesium Stearate	4	4	4	4	4

Table 24. Composition of F17-F21 using SSWG1 for the compression of orodispersible tablets of budesonide.

Ingredients	F17	F18	F19	F20	F21

Solid-SMEDDS (SSWG1)	132.3	132.3	132.3	132.3	132.3
Cellactose 80	234	-	114.3	162.7	61
Isomalt	-	234	114.3	61	157.7
Crospovidone	10	10	10	10	10
Peppermint flavour	10	10	10	10	10
Magnesium Stearate	4	4	4	4	4
Ticalfilm	10	10	15	20	25

Table 25. Composition of F22 using SSWG1 for the compression of orodispersible tablets of budesonide.

Ingredients	F22
Solid-SMEDDS (SSDC2)	74.85
Prosolv	256.4
Crospovidone	10.5
Magnesium Stearate	5.25
Neotame	3
Vanilla Powder	10

9.2.3 Evaluation of Orodispersible Tablets

Micromeritics

Table 26. Micromeritics of budesonide tablet blend.

Angle of Repose	26.28°
Hausner's Ratio	1.162
Compressibility	13.99%

Physical Testing:

Hardness:

Table 27. Tablet hardness for 10 orodispersible tablets of budesonide reported in kg/cm^2.

Tablet	Hardness (kg/cm^2)
1	4.5
2	6.4
3	5.5
4	5.1
5	5.5
6	5.3
7	5.2
8	5.2
9	5.5
10	5.3
Average	5.35

Weight Variation:

Table 28. Weight variation of 20 orodispersble tables of budesonide.

Tablet	Weight (mg)
1	355
2	350
3	350
4	345
5	352
6	351
7	356

8	350
9	352
10	352
11	350
12	355
13	345
14	348
15	347
16	350
17	350
18	351
19	350
20	355
Average	350.7

Friability:

The friability of tablets was 0.157%.

Chemical Testing:

Drug Content:

Table 29. Drug content of 10 orodispersible tablets of budesonide in mg/ml.

Tablet	Drug Content (mg)
1	97%
2	95%
3	96%
4	96%
5	96%

6	96%
7	96%
8	95%
9	97%
10	97%
Average	96.1%

Disintegration:

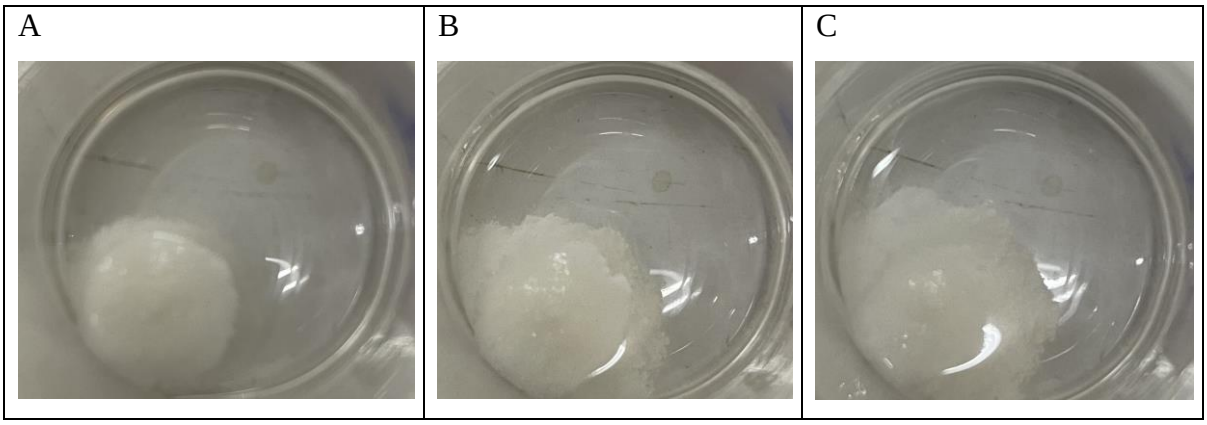


Figure 28. Disintegration of orodispersible tablets. A: Disintegration at 11 seconds. B: Disintegration at 35 seconds. C: Disintegration at 1:05 minutes.

The wetting time of the tablet was at 4 seconds and the disintegration began at 11 seconds. The tablet completely disintegrated at 1 minutes and 5 seconds.

Dissolution:

Table 30. Dissolution of 6 orodispersible tablets of budesonide.

Tablet	Drug Release
1	82.6%
2	81.5%
3	80.1%
4	82.3%
5	79.9%

6	80.0%
Average	97.40%

9.2.4 Discussion:

9.2.4.1 Preparation of Solid-SMEDDS and Compression into Tablets

Solid-SMEDDS were initially prepared by adsorbing prepared liquid-SMEDDS onto fujicalin and fujisil in a ratio of 3:1. Flavouring agents, sweetener and taste masking agents were added to the formulation to improve the bitter taste of budesonide and labrasol in the SMEDDS formulation. The potent sweetener neotame was found to be very effective in improving the taste of the blend. Neotame concentrations were varied from 0.85% to 4 % to find the optimal amount. An excess of neotame was very strong and added to the bitterness of the formulation. The ideal concentration of neotame was found to be 0.85%. Formulation F1 which contained SSDC1 did not result in sufficient hardness (0.6 $kg \cdot cm^2$) after direct compression. This may have been due to the larger crystalline particles of the diluent, xylitol, which did not compress well. Ludipress was selected as the diluent which has smaller particles with better flowability and compressibility. Formulation F2 with ludipress also resulted in poor hardness. Formulations F1-F11 all containing SSDC1 did not result in a desirable hardness. Various diluents, disintegrants, and binders were screen to improve the binding and hardness of the tablet. A blank tablet compressed without solid-SMEDDS with Galen IQ as the diluent resulted in a tablet hardness of 15 $kg \cdot cm^2$. This led to the conclusion that other solid carriers should be screened for solid-SMEDDS. Neusilin US2 was used to adsorb liquid-SMEDDS and directly compress into tablets. Desirable results were not obtained using SSDC2 for tablet formulation (table 22). HPMC was used as a binder to improve the binding of the tablets in order to increase the hardness. However, this did not improve the hardness.

Wet granulation was employed for the compression of tablets after not being able to achieve success with direct compression. In the first approach, liquid-SMEDDS were adsorbed onto Cavasol and Cellactose to give granules (SSWG1). It was proposed that making granules would improve the flow properties and binding of the tablet. However, this approach did not improve the table hardness (table 23 and table 24). Another approach was used for wet granulation in which liquid-SMEDDS were adsorbed onto Prosolv and HPC in a ratio of 25:1

(SSWG2). The composition using SSWG2 had successful results, having an average hardness of 5.35 kg·cm^2.

9.2.4.2 Evaluation of Orodispersible Tablets of Budesonide

The micromeritics testing of the F21 (table 25) indicated that the blend had good flow properties with an angle of repose of 26.28°. The Hausner's ratio and compressibility index value was 1.162 and 13.99%, respectively. Both indicate that the blend had good compressibility. The compressed tablets of F21 had an average hardness of 5.35 kg·cm^2, an average weight of 350.7 mg, and a friability of 0.157%. The tablets showed an average drug content of 0.965 mg, indicating that most of the 1 mg budesonide in the tablet has been released from the granules and tablet. The disintegration of orodispersible tablets should occur within 30 seconds to 1 minute. The wetting time of orodispersible tablets of budesonide was observed at 4 seconds, the disintegration of the tablet began at 11 seconds and the tablet completely disintegrated within 57 seconds. The dissolution of 6 tablets of budesonide indicated a drug release of 96.40% with a standard deviation of 0.00556. The hardness of the tablet showed to be adequate enough to have low friability, fast disintegration as well as high dissolution rate. The high drug release indicates that the incorporation of budesonide-loaded SMEDDS into a solid oral dosage form increased the solubility of budesonide and allowed for a higher dissolution rate.

10 Conclusion

The development of a safe and effective therapy for the treatment of eosinophilic esophagitis is required due to the drawbacks of current therapies in which patients often have to prepare their suspensions of fluticasone or budesonide or take drugs through inhalation which leads to systemic side effects. The aim of this project was to develop, characterize and evaluate orodispersible tablets of budesonide using solid-SMEDDS technology. Budesonide-loaded liquid-SMEDDS were prepared and optimized using design of experiment. The optimized formulation of liquid-SMEDDS formed monodispersed, highly stable and small particle size microemulsions. The formulated orodispersible tablets disintegrated within 1 minute, with a high dissolution rate and drug content. The use of Solid-SMEDDS technology increased the solubility of budesonide and the incorporation into solid oral dosage forms can be used to increase patient compliance.

The liquid-SMEDDS were adsorbed onto a carrier to form solid-SMEDDS that can be compressed into orodispersible tablets to increase patience compliance. The solubility of the solid-SMEDDS was compared to the solubility of pure budesonide in 6.8 pH phosphate buffer. The results indicated that incorporating budesonide into liquid-SMEDDS significantly improved its solubility in 6.8 pH buffer. The formulated orodispersible tablets of budesonide had an average drug release of 81.1% and an average drug content of 96.1%.

References

Abdalla, M. I., & Herfarth, H. (2016). Budesonide for the treatment of ulcerative colitis. *Expert Opinion on Pharmacotherapy*, *17*(11), 1549–1559. https://doi.org/10.1080/14656566.2016.1183648

Antonino, R. S. C. M. Q., Nascimento, T. L., de Oliveira Junior, E. R., Souza, L. G., Batista, A. C., & Lima, E. M. (2019). Thermoreversible mucoadhesive polymer-drug dispersion for sustained local delivery of Budesonide to treat inflammatory disorders of the GI tract. *Journal of Controlled Release*, *303*, 12–23. https://doi.org/10.1016/j.jconrel.2019.04.011

Arif, M., Chi, Z., Liu, Y.-J., & Liu, C.-G. (2020). Preparation, characterization, and *in vitro* drug release behavior of thiolated alginate nanoparticles loaded Budesonide as a potential drug delivery system toward inflammatory bowel diseases. *Journal of Biomaterials Science, Polymer Edition*, *31*(18), 2299–2317. https://doi.org/10.1080/09205063.2020.1803034

Bakry, A. M., Abbas, S., Ali, B., Majeed, H., Abouelwafa, M. Y., Mousa, A., & Liang, L. (2015). Microencapsulation of oils: A comprehensive review of benefits, techniques, and applications. *Comprehensive Reviews in Food Science and Food Safety*, *15*(1), 143–182. https://doi.org/10.1111/1541-4337.12179

Barnes, P. J. (2006). Corticosteroid effects on cell signalling. *European Respiratory Journal*, *27*(2), 413–426. https://doi.org/10.1183/09031936.06.00125404

Bodas, D. S., & Ige, P. P. (2019). Central composite rotatable design for optimization of Budesonide-loaded cross-linked chitosan–dextran sulfate nanodispersion: Characterization, *in vitro* diffusion and aerodynamic study. *Drug Development and Industrial Pharmacy*, *45*(7), 1193–1204. https://doi.org/10.1080/03639045.2019.1606823

Cao, M., Wang, Y., Jing, H., Wang, Z., Meng, Y., Geng, Y., Miao, M., & Li, X.-M. (2022). Development of an oral isoliquiritigenin self-nano-emulsifying drug delivery system (ILQ-SNEDDS) for effective treatment of eosinophilic esophagitis induced by food allergy. *Pharmaceuticals*, *15*(12), 1587. https://doi.org/10.3390/ph15121587

Casiraghi, A., Gennari, C. G., Musazzi, U. M., Ortenzi, M. A., Bordignon, S., & Minghetti, P. (2020). Mucoadhesive Budesonide formulation for the treatment of eosinophilic

esophagitis. *Pharmaceutics*, *12*(3), 211. https://doi.org/10.3390/pharmaceutics12030211

Chen, X., & Li, X. (2022). Budesonide oral suspension improves outcomes in patients with eosinophilic esophagitis. *Clinical Gastroenterology and Hepatology*, *20*(5), 1188–1189. https://doi.org/10.1016/j.cgh.2021.05.028

Dellon, E. S., Lucendo, A. J., Schlag, C., Schoepfer, A. M., Falk, G. W., Eagle, G., Nezamis, J., Comer, G. M., Knoop, K., & Hirano, I. (2022). Fluticasone propionate orally disintegrating tablet (APT-1011) for EOSINOPHILIC ESOPHAGITIS: Randomized controlled trial. *Clinical Gastroenterology and Hepatology*, *20*(11). https://doi.org/10.1016/j.cgh.2022.02.013

Dey, P., & Maiti, S. (2010). Orodispersible tablets: A new trend in drug delivery. *Journal of Natural Science, Biology and Medicine*, *1*(1), 2. https://doi.org/10.4103/0976-9668.71663

Dokania, S., & Joshi, A. K. (2014). Self-microemulsifying drug delivery system (SMEDDS) – challenges and Road ahead. *Drug Delivery*, *22*(6), 675–690. https://doi.org/10.3109/10717544.2014.896058

Eluri, S., & Dellon, E. S. (2015a). Proton pump inhibitor-responsive oesophageal eosinophilia and eosinophilic oesophagitis. *Current Opinion in Gastroenterology*, *31*(4), 309–315. doi:10.1097/mog.0000000000000185

Gonsalves, N. P., & Aceves, S. S. (2020). Diagnosis and treatment of eosinophilic esophagitis. *Journal of Allergy and Clinical Immunology*, *145*(1), 1–7. doi:10.1016/j.jaci.2019.11.011

Hirano, I., & Dellon, E. S. (2021). Eosinophilic esophagitis. *The Esophagus*, 679–712. doi:10.1002/9781119599692.ch40

Home - Clinicaltrials.gov. (n.d.-a). https://clinicaltrials.gov/ProvidedDocs/58/NCT02019758/Prot_SAP_000.pdf

Ketchem, C. J., Reed, C. C., Stefanadis, Z., & Dellon, E. S. (2020). Treatment with compounded fluticasone suspension improves the clinical, endoscopic, and histologic features of eosinophilic esophagitis. *Diseases of the Esophagus*, *34*(7). https://doi.org/10.1093/dote/doaa120

Khoshyari, S., & Mahjub, R. (2020). Preparation, box-behnken statistical optimization, and *in vitro* characterization of a self-nanoemulsifying drug delivery system for the oral delivery of Budesonide as a poorly soluble drug. *Avicenna Journal of Pharmaceutical Research*, *1*(1), 24–32. https://doi.org/10.34172/ajpr.2020.05

Kia, L., Nelson, M., Zalewski, A., Gregory, D., Gonsalves, N., Straumann, A., & Hirano, I. (2018). Oral delivery of fluticasone powder improves esophageal eosinophilic inflammation and symptoms in adults with eosinophilic esophagitis. *Diseases of the Esophagus*, *31*(12). https://doi.org/10.1093/dote/doy098

Kim, D. S., Cho, J. H., Park, J. H., Kim, J. S., Song, E. S., Kwon, J., Giri, B. R., Jin, S. G., Kim, K. S., Choi, H.-G., & Kim, D. W. (2019). self-microemulsifying drug delivery system (SMEDDS) for improved oral delivery and photostability of methotrexate. *International Journal of Nanomedicine*, *Volume 14*, 4949–4960. https://doi.org/10.2147/ijn.s211014

Kovačević, M., German Ilić, I., Bolko Seljak, K., & Zvonar Pobirk, A. (2022). High-shear wet granulation of SMEDDS based on mesoporous carriers for improved carvedilol solubility. *Pharmaceutics*, *14*(10), 2077. https://doi.org/10.3390/pharmaceutics14102077

Krause, J., Rosenbaum, C., Grimm, M., Rump, A., Keßler, R., Hosten, N., & Weitschies, W. (2020). The ESOCAP-system – an innovative platform to drug targeting in the esophagus. *Journal of Controlled Release*, *327*, 1–7. https://doi.org/10.1016/j.jconrel.2020.08.011

Laquintana, V., Asim, M. H., Lopedota, A., Cutrignelli, A., Lopalco, A., Franco, M., Bernkop-Schnürch, A., & Denora, N. (2019). Thiolated hydroxypropyl-β-cyclodextrin as mucoadhesive excipient for oral delivery of Budesonide in liquid paediatric formulation. *International Journal of Pharmaceutics*, *572*, 118820. https://doi.org/10.1016/j.ijpharm.2019.118820

Lee, J.-H., & Lee, G.-W. (2022). Formulation approaches for improving the dissolution behavior and bioavailability of tolvaptan using SMEDDS. *Pharmaceutics*, *14*(2), 415. https://doi.org/10.3390/pharmaceutics14020415

Liu, Y., Bos, I. S., Oenema, T. A., Meurs, H., Maarsingh, H., & Hirsch, A. K. H. (2018). Delivery system for Budesonide based on lipid-DNA. *European Journal of Pharmaceutics and Biopharmaceutics*, *130*, 123–127. https://doi.org/10.1016/j.ejpb.2018.06.012

Lu, Y., Sun, Z., Zhang, Y., Chen, X., & Zhong, D. (2013). Simultaneous quantification of 22R and 22s epimers of Budesonide in human plasma by ultra-high-performance liquid chromatography–tandem mass spectrometry: Application in a stereoselective pharmacokinetic study. *Journal of Chromatography B*, *921–922*, 27–34. https://doi.org/10.1016/j.jchromb.2013.01.015

Laserna-Mendieta, E. J., Casabona, S., Savarino, E., Perelló, A., Pérez-Martínez, I., Guagnozzi, D., … Lucendo, A. J. (2020a). Efficacy of therapy for eosinophilic

esophagitis in real-world practice. *Clinical Gastroenterology and Hepatology*, *18*(13). doi:10.1016/j.cgh.2020.01.024

Molina-Infante, J., & Lucendo, A. J. (2018a). Dietary therapy for eosinophilic esophagitis. *Journal of Allergy and Clinical Immunology*, *142*(1), 41–47. doi:10.1016/j.jaci.2018.02.028

Meloche, C. A., Sharma, V., Swedmark, S., Andersson, P., & Falany, C. N. (2002). Sulfation of Budesonide by human cytosolic sulfotransferase, dehydroepiandrosterone-sulfotransferase (DHEA-ST). *Drug Metabolism and Disposition*, *30*(5), 582–585. https://doi.org/10.1124/dmd.30.5.582

National Center for Biotechnology Information. (n.d.-b). https://www.ncbi.nlm.nih.gov/books/NBK563201/

Oh, D. H., Kang, J. H., Kim, D. W., Lee, B.-J., Kim, J. O., Yong, C. S., & Choi, H.-G. (2011). Comparison of solid self-microemulsifying drug delivery system (SOLID SMEDDS) prepared with hydrophilic and hydrophobic solid carrier. *International Journal of Pharmaceutics*, *420*(2), 412–418. https://doi.org/10.1016/j.ijpharm.2011.09.007

Pattanaik, S., Nandi, S., Sahoo, R. N., Nanda, A., Swain, R., Das, S., & Mallick, S. (2020). Budesonide-Cyclodextrin in hydrogel system: Impact of quaternary surfactant on in vitro-in vivo assessment of Mucosal Drug Delivery. *Revista de Chimie*, *71*(6), 332–345. https://doi.org/10.37358/rc.20.6.8200

Pawar, H., Varkhade, C., Jadhav, P., & Mehra, K. (2014). Development and evaluation of Orodispersible tablets using a natural polysaccharide isolated from Cassia Tora seeds. *Integrative Medicine Research*, *3*(2), 91–98. https://doi.org/10.1016/j.imr.2014.03.002

Prasad, K. L., & Hari, K. (2021). Formulation and evaluation of solid self-nanoemulsifying drug delivery system for enhancing the solubility and dissolution rate of Budesonide. *Research Journal of Pharmacy and Technology*, 5755–5763. https://doi.org/10.52711/0974-360x.2021.01001

Prasher, A., Shrivastava, R., Dahl, D., Sharma-Huynh, P., Maturavongsadit, P., Pridgen, T., Schorzman, A., Zamboni, W., Ban, J., Blikslager, A., Dellon, E. S., & Benhabbour, S. R. (2021). Steroid eluting esophageal-targeted drug delivery devices for treatment of eosinophilic esophagitis. *Polymers*, *13*(4), 557. https://doi.org/10.3390/polym13040557

Rao, Y., Bandari, S., Mittapalli, R., & Gannu, R. (2008). Orodispersible tablets: An overview. *Asian Journal of Pharmaceutics*, *2*(1), 2. https://doi.org/10.4103/0973-8398.41557

Reed, C. C., Fan, C., Koutlas, N. T., Stefanidis, Z. S., Eluri, S., Shaheen, N. J., & Dellon, E. S. (2017). Treatment with compounded oral viscous Budesonide is effective and provides a durable response in patients with eosinophilic esophagitis. *Gastroenterology*, *152*(5). https://doi.org/10.1016/s0016-5085(17)32970-0

Rothenberg, M. E. (2009). Biology and treatment of eosinophilic esophagitis. *Gastroenterology*, *137*(4), 1238–1249. doi:10.1053/j.gastro.2009.07.007

Ryrfeldt A, Andersson P, Edsbäcker S, Tönnesson M, Davies D, Pauwels R. Pharmacokinetics and metabolism of budesonide, a selective glucocorticoid. Eur J Respir Dis Suppl. 1982;122:86-95. PMID: 6958498.

Sahib, M., Darwis, Peh, Abdulameer, S. A., & Tan. (2011). Rehydrated sterically stabilized phospholipid nanomicelles of Budesonide for nebulization: Physicochemical characterization and in vitro, in vivo evaluations. *International Journal of Nanomedicine*, 2351. https://doi.org/10.2147/ijn.s25363

Suram, D., & Veerabrahma, K. (2022). Design and development of solid SMEDDS and Liquisolid formulations of lovastatin, for improved drug dissolution and in vivo effects—a pharmacokinetic and pharmacodynamic assessment. *AAPS PharmSciTech*, *23*(5). https://doi.org/10.1208/s12249-022-02272-2

Spergel, J. M. (2007). Eosinophilic esophagitis in adults and children: Evidence for a food allergy component in many patients. *Current Opinion in Allergy & Clinical Immunology*, *7*(3), 274–278. doi:10.1097/aci.0b013e32813aee4a

Turanlı, Y., & Acartürk, F. (2021). Fabrication and characterization of Budesonide loaded colon-specific nanofiber drug delivery systems using anionic and cationic polymethacrylate polymers. *Journal of Drug Delivery Science and Technology*, *63*, 102511. https://doi.org/10.1016/j.jddst.2021.102511

Warzecha, J., Dziekiewicz, M., Bieńkowska-Tokarczyk, A., Małecki, M., & Banaszkiewicz, A. (2022). A new viscous Budesonide formulation for the treatment of eosinophilic esophagitis in children: A preliminary experience and review of the literature. *Journal of Clinical Medicine*, *11*(22), 6730. https://doi.org/10.3390/jcm11226730

Zhang, L., Yang, L., Zhang, X., Jiaqi, L., Fan, L., Beck-Broichsitter, M., Zhang, X., Muenster, U., Wang, X., Zhao, J., Zhang, Y., & Mao, S. (2018). Sustained therapeutic efficacy of Budesonide-loaded chitosan swellable microparticles after lung delivery: Influence of in vitro release, treatment interval and dose. *Journal of Controlled Release*, *283*, 163–174. https://doi.org/10.1016/j.jconrel.2018.05.031

Zhu, Z., Liu, J., Yang, Y., Adu-Frimpong, M., Ji, H., Toreniyazov, E., Wang, Q., Yu, J., & Xu, X. (2021). SMEDDS for improved oral bioavailability and anti-hyperuricemic activity

of licochalcone a. *Journal of Microencapsulation*, *38*(7–8), 459–471. https://doi.org/10.1080/02652048.2021.1963341

Eluri, S., & Dellon, E. S. (2015a). Proton pump inhibitor-responsive oesophageal eosinophilia and eosinophilic oesophagitis. *Current Opinion in Gastroenterology*, *31*(4), 309–315. doi:10.1097/mog.0000000000000185

Gonsalves, N. P., & Aceves, S. S. (2020). Diagnosis and treatment of eosinophilic esophagitis. *Journal of Allergy and Clinical Immunology*, *145*(1), 1–7. doi:10.1016/j.jaci.2019.11.011

Hirano, I., & Dellon, E. S. (2021). Eosinophilic esophagitis. *The Esophagus*, 679–712. doi:10.1002/9781119599692.ch40

Laserna-Mendieta, E. J., Casabona, S., Savarino, E., Perelló, A., Pérez-Martínez, I., Guagnozzi, D., … Lucendo, A. J. (2020a). Efficacy of therapy for eosinophilic esophagitis in real-world practice. *Clinical Gastroenterology and Hepatology*, *18*(13). doi:10.1016/j.cgh.2020.01.024

Molina-Infante, J., & Lucendo, A. J. (2018a). Dietary therapy for eosinophilic esophagitis. *Journal of Allergy and Clinical Immunology*, *142*(1), 41–47. doi:10.1016/j.jaci.2018.02.028

Rothenberg, M. E. (2009). Biology and treatment of eosinophilic esophagitis. *Gastroenterology*, *137*(4), 1238–1249. doi:10.1053/j.gastro.2009.07.007

Spergel, J. M. (2007). Eosinophilic esophagitis in adults and children: Evidence for a food allergy component in many patients. *Current Opinion in Allergy & Clinical Immunology*, *7*(3), 274–278. doi:10.1097/aci.0b013e32813aee4a

Ryrfeldt A, Andersson P, Edsbäcker S, Tönnesson M, Davies D, Pauwels R. Pharmacokinetics and metabolism of budesonide, a selective glucocorticoid. Eur J Respir Dis Suppl. 1982;122:86-95. PMID: 6958498.

Muskan_final MPharm file

ORIGINALITY REPORT

2%	1%	2%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Dokania, Shambhu, and Amita K. Joshi. "Self-microemulsifying drug delivery system (SMEDDS) – challenges and road ahead", Drug Delivery, 2015. Publication	1%
2	www.science.gov Internet Source	1%
3	Shravan Kumar Y, Shireesha G, Harika S. "Formulation and Evaluation of Metoprolol Tartrate Sustained Release Matrix Tablets", International Journal of Pharmaceutical Sciences and Nanotechnology, 2019 Publication	1%

Exclude quotes	Off	Exclude matches	< 1%
Exclude bibliography	On		