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Application of Hansen Solubility Parameters to Improve Oral Absorption of Nintedanib by a Self-Micro-Emulsifying Drug Delivery System

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for the Degree of Master of Liberal Arts in Extension Studies

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Abstract

Nintedanib is a drug used to treat Idiopathic Pulmonary Fibrosis, but it has poor solubility and low oral bioavailability. This study explored how a Self-Microemulsifying Drug Delivery System (SMEDDS) could improve these issues. By using Hansen Solubility Parameters, two solvents, Benzyl Alcohol and Eugenol, were found to dissolve Nintedanib well and used in the oil phase. HSP provides a systematic way to predict solvent compatibility, making it a valuable tool for addressing insolubility challenges in poorly soluble drugs. By ensuring compatibility between Nintedanib and the chosen excipients, HSP helped optimize drug loading within the formulation, ultimately contributing to improved bioavailability. HSP enhances bioavailability by identifying excipients that not only dissolve the drug effectively but also facilitate its incorporation into a stable microemulsion, improving its dispersion and absorption in the gastrointestinal tract. The Eugenol: Benzyl Alcohol [1:2] blend created the largest microemulsion region, showing the best self-emulsification potential. Tween 20, chosen for its good surfactant properties, was tested at higher concentrations (50%), resulting in smaller droplet sizes (5 nm) and faster emulsification.

The permeability study showed that SMEDDS significantly improved Nintedanib's ability to cross Caco-2 cell layers, with the Eugenol: Benzyl Alcohol [1:3] mix reaching a high permeability level (Papp = $1.08 \times 1\ 0^{-6}$ cm·s^{-1}). Efflux ratio tests also suggested that Nintedanib is less likely to be affected by P-glycoprotein, which is important for improving absorption. However, there were some limitations, like the lack of stability testing, the

potential for phase separation, and the need to confirm these findings in animal models. Despite these, the results show SMEDDS could be a promising strategy to boost Nintedanib's bioavailability, and further testing is needed.

Dedication

To my loving family, whose unwavering support, patience, and encouragement have guided me through this journey.

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Chapter I.

Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a serious lung disease that progressively worsens over time, impacting a significant number of individuals globally. It's caused by the gradual scarring (fibrosis) of lung tissue, which makes it harder for the lungs to function properly. As the scarring progresses, lung function declines, and eventually, it can lead to respiratory failure (Martinez, 2017). The term 'idiopathic' means that the exact cause of IPF is unknown, but factors such as genetic predisposition, environmental exposures, and abnormalities in the lung tissue repair process are believed to contribute (Raghu, 2018). IPF falls under the larger group of interstitial lung diseases (ILDs), which includes various conditions that cause inflammation and scarring of the lung's tissue. Right now, there's no cure for IPF, but there are treatments available to manage it. However, some patients choose not to take these treatments because of the side effects.

Pathophysiology of IPF

The main feature of IPF is the gradual scarring of lung tissue, which makes it harder for the lungs to exchange oxygen and causes lung function to decline (Sankari, 2025). IPF develops through a complex interplay of genetics, environmental damage, and faulty lung tissue repair mechanisms, though the exact triggers remain unclear (Sankari, 2025). Essentially, it's thought that the problem starts with an abnormal healing response to repeated damage to the cells lining the lungs (Martinez, 2017). In people with IPF, this

damage triggers a chain reaction that includes inflammation, an overgrowth of cells called fibroblasts, and an excess buildup of the substances that make up the lung's structure, eventually leading to fibrosis (Wilson, 2008).

At the beginning of the disease, lung cell damage usually happens because of things like cigarette smoke, viral infections, or exposure to harmful substances at work, such as asbestos (Selman, 2016). This damage causes the body to release signals that bring immune cells to the area to help repair the injury (Ma, 2022). But over time, the repair process starts to go wrong. The fibroblasts and other cells that help make the lung structure start overproducing collagen, forming thick scar tissue (Ma, 2022). As fibrosis gets worse, the structure of the lungs becomes seriously compromised, which affects the way oxygen is exchanged and leads to symptoms like shortness of breath, a dry cough, and fatigue (King, 2011).

One important process in IPF is called epithelial-mesenchymal transition (EMT), where the lung cells change and become more migratory and fibrous, contributing to the excessive scarring seen in the disease (Roth, 2015). New research has also pointed to certain signaling pathways, like those involving transforming growth factor-beta (TGF-β), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF), as playing a big role in encouraging the growth and survival of fibroblasts and the buildup of scar tissue (Roth, 2015). On top of that, there seems to be a genetic risk factor for IPF. Mutations in certain genes, such as those for surfactant proteins C and A2, and telomerase-related genes, are linked to a higher chance of developing the disease (Noth, 2014).

Clinical Impact and Symptoms

IPF usually starts with symptoms that come on gradually, making early detection challenging. Many patients initially experience mild shortness of breath (dyspnea) during physical activity and a dry, persistent cough. Because these symptoms are common in other respiratory conditions like chronic obstructive pulmonary disease (COPD), asthma, or even heart failure, misdiagnosis is frequent, leading to delays in appropriate management (van Manen, 2017). This delay is critical, as earlier diagnosis can provide patients access to treatments that may help slow disease progression.

The persistent cough in IPF, though non-productive, can be one of the most distressing symptoms. Its cause is not entirely understood, but researchers suggest it may be linked to airway irritation due to fibrosis, increased lung stiffness, or gastroesophageal reflux disease (GERD), which is highly prevalent in IPF patients (Raghu, 2018). Some evidence also suggests that vagus nerve dysfunction may play a role, contributing to heightened cough reflex sensitivity (van Manen, 2016). Since chronic coughing significantly affects quality of life, management strategies, including cough suppressants and GERD treatment, are often considered in patient care.

As the disease progresses, worsening dyspnea can become overwhelming, limiting physical activity and daily functioning. Pulmonary hypertension, a common complication of IPF, develops due to the remodeling of pulmonary blood vessels and increased resistance in the lung circulation. This places added strain on the right side of the heart, potentially leading to right heart failure (cor pulmonale) (Raghu, 2018). Pulmonary hypertension is associated with worse survival rates and increased symptom burden, making it an important factor in disease prognosis (Nathan, 2025).

Some patients experience acute exacerbations, sudden and severe worsening of respiratory symptoms without a clear cause. These exacerbations can be triggered by infections, aspiration events, or unknown factors and are associated with high mortality rates (King, 2011). Managing these episodes is challenging, as no widely effective treatments exist, highlighting the urgent need for therapies that can prevent or mitigate acute worsening events.

Beyond respiratory symptoms, people with IPF may experience fatigue, unexplained weight loss, and muscle wasting, which further impact daily life. Digital clubbing, a condition where fingernails become rounded and enlarged, is also seen in some cases and is often associated with chronic hypoxia (Kašiković, 2022). The psychological toll of IPF should not be overlooked, as many patients struggle with anxiety, depression, and social isolation due to the disease's relentless progression (Kašiković, 2022). Pulmonary rehabilitation and palliative care play essential roles in helping patients maintain function and improve their quality of life.

Since IPF progresses at different rates in different individuals, predicting outcomes can be challenging. However, clinical tools such as the Gender-Age-Physiology (GAP) Index help estimate disease severity and survival by incorporating pulmonary function test results along with demographic factors (Noth, 2014). Ongoing research into biomarkers and imaging advancements may further refine prognostic predictions, allowing for more personalized treatment strategies. While IPF remains a devastating disease with a median survival of 3 to 5 years after diagnosis, new treatments and a greater focus on supportive care offer hope for improving both lifespan and quality of life (Hutchinson, 2015).

Epidemiology of IPF

IPF is a lung disease that gets worse over time and affects quite a few people around the world. It's thought that between 13 and 20 out of every 100,000 people have it (Andrade, 2016). Most people who get IPF are between 50 and 70, and while it's a little more common in men, research shows that the gap is getting smaller (Castriotta, 2010). Although awareness of IPF has increased, it is still frequently misdiagnosed. This is primarily due to its gradual onset and symptoms that overlap with other lung diseases, making early detection challenging (Castriotta, 2010). While the exact causes of IPF remain unknown, factors such as smoking, occupational dust exposure, and certain viral infections are believed to contribute to its development (Nalysnyk, 2012).

IPF seems to be on the rise, which could be because we're getting better at diagnosing it or just because people are living longer (Nalsnyk, 2010). But diagnosing it is still tough. The symptoms are similar to those of other lung diseases, and not all the tests are easy to get. That's why the reported numbers can vary depending on the criteria used. In the U.S., for example, some studies show an incidence rate of 6.8 to 8.8 per 100,000 people when stricter guidelines are used, but when the criteria are broader, it jumps to 16.3 to 17.4 per 100,000 (Nalsnyk, 2010).

Current Treatment Landscape for IPF

IPF is a difficult condition to treat. The condition worsens with time and does not usually react well to standard therapies (Richeldi et al., 2017). Until about a decade ago, there were no FDA-approved medications for IPF, and doctors mainly focused on managing symptoms and improving quality of life (Raghu et al., 2015). But we're starting to see some progress with new treatments.

Pirfenidone and Nintedanib are two antifibrotic drugs that are now approved for treating IPF (Salisbury et al., 2020). They can slow down the disease, especially when measured by forced vital capacity (FVC), a key indicator of lung function (Salisbury et al., 2020). But even though these drugs help slow things down, they come with side effects, mainly stomach problems, that can make it harder for patients to stick with the treatment and reduce its effectiveness (Salisbury et al., 2020).

Pirfenidone works by blocking cytokines that promote fibrosis and lowering collagen production, which helps slow the scarring process. Nintedanib works by targeting pathways that trigger fibroblast activity and collagen buildup (Torre, 2024; Wollin et al., 2015). Both drugs have shown some benefit in trials, but they do not cure IPF, highlighting the ongoing need for further research and treatment advancements.

In more advanced cases, lung transplantation can be an option. But getting a donor lung is tough, and the surgery comes with risks, like organ rejection and complications from the medications used to prevent that (Hernandez, 2018).

IPF can really take a toll on patients' health and quality of life. The disease involves a lot of complex processes, including lung cell damage, overactive fibroblasts, and too much collagen buildup (Sankari, 2025). Even though medications like Pirfenidone and Nintedanib can help slow down the disease, they don't offer a cure, and their side effects often make it hard for patients to stick with them. There's a clear demand for better treatments. One approach that could help is using advanced drug delivery systems like SMEDDS, which might make current medications work better while cutting down on side effects (Salawi, 2022).

Nintedanib in IPF Treatment

Nintedanib is an oral medication that works by blocking several types of tyrosine kinases, and it's become one of the main treatments for IPF (Gole, 2024). It has shown great promise in slowing the progression of the disease, offering people with IPF a treatment option in a condition that's traditionally had limited choices and poor outcomes. Approved by the FDA in 2014 and the European Medicines Agency (EMA) in 2015, Nintedanib marked a shift in how we manage IPF (Crestani, 2019). Instead of just managing symptoms, it helps slow the disease's progression, which was a significant step forward in treatment.

Mechanism of Action

Nintedanib is generally prescribed more frequently than Pirfenidone for the treatment of idiopathic pulmonary fibrosis (IPF) due to several factors that make it a more commonly preferred option in clinical practice (Salibury, 2020). One of the primary reasons for this preference is Nintedanib's comprehensive mechanism of action. Nintedanib is a tyrosine kinase inhibitor that helps slow down the progression of IPF by targeting a few key processes involved in the disease (Richeldi, 2015). It works by blocking certain enzymes, known as tyrosine kinases, which play a major role in fibroblast activity (Wollin, 2014). Fibroblasts are the cells responsible for the scarring in the lungs, producing too much collagen and extracellular matrix (ECM).

Nintedanib blocks the Platelet-Derived Growth Factor (PDGF) Receptor, which is essential for fibroblasts to grow and begin producing collagen. By inhibiting this receptor, Nintedanib helps reduce fibroblast growth and ECM buildup (Wollin, 2014). Additionally, it targets the Fibroblast Growth Factor Receptor (FGFR), which encourages fibroblast

growth and promotes fibrosis. By blocking this pathway, Nintedanib further reduces the fibrotic activity in the lungs (Wollin, 2014). Nintedanib also blocks the Vascular Endothelial Growth Factor Receptor (VEGFR), which is involved in the formation of new blood vessels. In fibrotic diseases, this process is often overly active, contributing to disease progression. By inhibiting VEGFR, Nintedanib limits abnormal blood vessel formation, helping to reduce fibrosis.

Finally, Nintedanib targets Sarcoma Family Kinases, which are involved in cell movement and ECM remodeling, further reducing fibroblast activity and slowing the progression of fibrosis (Wollin, 2014). By targeting all these pathways, Nintedanib provides a more extensive approach to managing IPF, though it does not cure the disease (Wollin, 2014). Despite this, Nintedanib remains a solid treatment option, and its broad targeting of fibrotic pathways contributes to its higher prescription rate compared to Pirfenidone.

In addition to its comprehensive mechanism, Nintedanib tends to have a more favorable side effect profile than Pirfenidone, making it the more commonly prescribed drug in clinical settings. Both drugs are associated with gastrointestinal side effects like nausea and diarrhea, but Pirfenidone also has a higher risk of liver toxicity, requiring regular monitoring of liver enzymes (Salisbury, 2020). This added burden of liver function tests and potential hepatotoxicity can make Pirfenidone less appealing for some patients (Salisbury, 2020). Nintedanib, while still causing gastrointestinal issues, is often perceived as more tolerable over time, and its side effects are generally easier to manage (Crestani, 2019). This makes Nintedanib a more attractive option for patients, as it can lead to better adherence and fewer interruptions in treatment.

Moreover, Nintedanib has demonstrated stronger efficacy in slowing disease progression, especially in patients with more advanced stages of IPF (Crestani, 2019). Clinical trials have shown that Nintedanib significantly reduces the rate of decline in forced vital capacity (FVC), a key marker of lung function (Richeldi, 2015). While Pirfenidone also slows the disease, Nintedanib has been shown to have a slightly more pronounced effect in halting the progression of IPF, particularly in those at higher risk for rapid disease deterioration (Torre, 2024). This efficacy, combined with its broader mechanism of action, makes Nintedanib a preferred option for physicians managing moderate to severe IPF.

The convenience of Nintedanib's dosing regimen also contributes to its popularity. Nintedanib is typically taken in two daily doses, which is easier for patients to manage compared to Pirfenidone, which requires a more complex dosing schedule with gradual titration to minimize side effects (Sankari, 2025). This simpler regimen makes it easier for patients to adhere to the treatment plan, reducing the risk of missed doses and improving overall patient satisfaction. While both drugs are effective, Nintedanib's broader efficacy, more manageable side effect profile, and convenient dosing have made it the preferred choice for many healthcare providers in treating IPF.

Clinical Efficacy

Nintedanib has shown real promise in clinical trials looking at its impact on IPF progression. The INPULSIS-2 trial, in particular, showed that Nintedanib can significantly slow the decline in Forced Vital Capacity (FVC), which is a key test used to measure lung function in IPF patients. In fact, Nintedanib reduced the rate of FVC decline by about 50% within 52 weeks for people with various types of pulmonary fibrosis (Richeldi et al., 2015).

The INPULSIS-2 trial was a phase III, randomized, double-blind, placebo-controlled study that really helped prove how effective Nintedanib can be in treating IPF. The trial found that patients on Nintedanib had a much slower decline in FVC compared to those on placebo. Plus, the treatment helped lower the risk of acute exacerbations and slowed disease progression, with similar results across different patient groups, no matter their baseline FVC levels or disease severity (Richeldi et al., 2015).

Nintedanib has also worked well in a variety of patient populations. It's been helpful for both people who are just starting treatment and those with more advanced disease. It's also shown good results in people with a history of smoking or exposure to environmental factors that increase the risk of IPF. This shows that Nintedanib could be a helpful option for a wide range of patients, no matter their background (Richeldi et al., 2015).

Of course, there are some side effects to consider. About 21% of patients needed to reduce their dose, and 26.3% had to stop treatment altogether. But even with those dose reductions and treatment interruptions, which were recommended to manage side effects in the INPULSIS-ON extension trial, there was no impact on the rate of FVC decline. This suggests that Nintedanib's long-term ability to slow disease progression holds up, even if patients need dose adjustments (Crestani, 2019). On the other hand, those who stopped taking Nintedanib showed a significant drop in FVC at 12 months compared to where they started (55.0 ± 13.5 vs. 70.0 ± 23.0; $p = 0.035$) (Richeldi et al., 2015).

Side Effects and Safety Profile

Nintedanib has been demonstrated to be effective in managing IPF, but it does come with side effects, particularly those related to the gastrointestinal system. While these side effects can impact adherence to treatment and quality of life, they are generally manageable through dose adjustments or other supportive measures. Diarrhea is the most common gastrointestinal issue, affecting 60-70% of patients. However, in most cases, it is mild to moderate and can be controlled through dose reductions or anti-diarrheal medications (Richeldi et al., 2015).

Another consideration is the potential for liver enzyme elevations, which have been observed in some patients. These increases are typically not concerning and resolve with either a dose adjustment or discontinuation of the medication. Despite the occasional occurrence of more serious side effects, such as bleeding or blood clots, these are rare, and close monitoring during treatment is crucial to catch any potential issues early (Richeldi et al., 2015).

Overall, Nintedanib has shown promise in slowing the progression of IPF, improving lung function, and enhancing the quality of life for patients. The INPULSIS trials revealed that patients treated with Nintedanib had better preservation of lung function and fewer respiratory-related hospitalizations compared to those receiving a placebo (Richeldi et al., 2015).

However, the treatment does come with challenges in terms of discontinuation and dose reduction. While Nintedanib helped slow the decline in lung function, a notable proportion of patients had to reduce their dose or discontinue treatment due to side effects, especially gastrointestinal problems like diarrhea. In the INPULSIS-1 trial, 25.2%

of patients in the Nintedanib group discontinued treatment, compared to 17.6% in the placebo group. Similarly, in INPULSIS-2, 23.7% of the Nintedanib group discontinued treatment, compared to 20.1% in the placebo group. While dose reductions were more common in the Nintedanib group, the majority of patients still maintained high dose intensity throughout the trial, helping to minimize the impact of discontinuations (Richeldi et al., 2015).

Treatment Considerations and Discontinuation

The decision to start Nintedanib treatment should be tailored to each person, considering things like how severe the disease is, how well they tolerate the medication, and the risk of side effects. Nintedanib is generally well tolerated, but some patients may need dose adjustments, especially if gastrointestinal side effects are an issue (Richeldi et al., 2015). The usual starting dose for Nintedanib in IPF is 150 mg twice a day with food. If gastrointestinal side effects become a problem, it can be lowered to 100 mg twice a day. That's often enough to keep the treatment effective while minimizing side effects (Richeldi et al., 2015).

In some cases, patients might have to stop Nintedanib because of intolerable side effects or because the disease is still progressing despite treatment. Studies show that stopping Nintedanib can lead to a sharp decline in lung function, especially when looking at forced vital capacity (FVC) (Richeldi et al., 2015). This highlights how important it is to monitor closely and intervene early when side effects pop up. A lot of times, reducing the dose lets patients keep going with treatment while avoiding some of those tough side effects (Ogura, 2023).

Real-world data shows a broad range of discontinuation rates. In the US and Europe, it's between 11% and 26%, but in Asia, it's a bit higher, ranging from 47% to 53% (Ogura, 2023). Most of these discontinuations are because of side effects like diarrhea, liver issues, nausea, vomiting, and stomach pain. Despite that, some researchers are suggesting lowering the dose or adjusting the frequency to help reduce side effects and make it easier for patients to stay on track with their treatment (Ogura, 2023).

Adherence to Nintedanib can be tough, mainly because of those gastrointestinal side effects. But, the fact that it can slow disease progression, especially when started early, makes sticking to the treatment plan important for patients. Educating them about how sticking with treatment can really help might be key in improving adherence (Richeldi et al., 2015).

Nintedanib has made a big impact in treating IPF, giving patients a way to slow disease progression and improve their outcomes. By targeting several tyrosine kinases involved in the disease process, it provides a comprehensive approach to managing IPF (Richeldi et al., 2015). Even though gastrointestinal side effects are common, they can usually be managed with dose adjustments and other supportive care. With its proven effectiveness in clinical trials, Nintedanib has become a go-to treatment for IPF, offering hope for those dealing with the disease. That said, ongoing research to optimize its use and explore other treatments is still crucial for improving IPF patient outcomes.

That said, balancing effectiveness with tolerability is still a big challenge. The fact that so many patients stop taking Nintedanib because of side effects shows that better formulation strategies are needed. Finding ways to improve drug absorption while reducing side effects could help more patients stick with treatment. New approaches, like

SMEDDs, could make a big difference by making the medication easier to tolerate without sacrificing its benefits.

The Need for Improved Formulation Strategies

To overcome these limitations, the development of advanced formulation strategies is crucial. Several approaches have been proposed to enhance the solubility and bioavailability of poorly soluble drugs like Nintedanib. These include:

SMEDDS: SMEDDS are lipid-based formulations that consist of oils, surfactants, and co-surfactants, which spontaneously form fine micro-emulsions when introduced to aqueous environments, such as the gastrointestinal tract. The oil phase in SMEDDS can dissolve hydrophobic drugs, thus improving their solubility and absorption. SMEDDS also offer protection to sensitive APIs, reducing their degradation in the gastrointestinal tract and enhancing the stability of the formulation. This approach is particularly effective for drugs like Nintedanib, which have poor solubility in water but can dissolve in lipids. By utilizing this technology, it is possible to improve the bioavailability of Nintedanib, potentially lowering the required dose and minimizing side effects (Liu H, 2024).

Nanotechnology-Based Formulations: Nanotechnology offers a novel approach for overcoming the limitations of traditional formulations. Nanoparticle-based drug delivery systems can improve the solubility, stability, and bioavailability of hydrophobic drugs by reducing particle size and enhancing the surface area available for absorption (Liu Y, 2024). These systems can also be engineered to release drugs in a controlled manner, improving therapeutic efficacy and reducing the frequency of dosing.

Nanoparticles may also reduce gastrointestinal irritation by enabling better distribution of the drug within the digestive tract (Kim, 2023).

Solid Lipid Nanoparticles (SLNs) and Liposomes: SLNs and liposomes are lipid-based carriers that can encapsulate hydrophobic drugs, improving their solubility in aqueous environments. These systems protect drugs from enzymatic degradation and can provide sustained release of the drug, thereby enhancing its efficacy. SLNs and liposomes have been shown to reduce the gastrointestinal side effects associated with oral administration of poorly soluble drugs, making them a promising strategy for improving patient compliance (Salah, 2020).

Cyclodextrin Complexes: Cyclodextrins are cyclic oligosaccharides that can form inclusion complexes with hydrophobic drugs. This complexation can enhance the solubility and stability of poorly water-soluble drugs, improving their dissolution rate and bioavailability (Bhalani, 2022). For drugs like Nintedanib, cyclodextrins could offer a cost-effective and efficient means to enhance drug delivery and reduce gastrointestinal irritation.

Targeted Delivery Systems: Another strategy is the development of targeted drug delivery systems that direct the therapeutic agent specifically to the site of action, such as the lungs (Khan, 2012). Pulmonary drug delivery systems, including inhalers or nebulizers, could bypass the gastrointestinal system entirely, reducing the occurrence of side effects like diarrhea and nausea (Vaidya, 2019). Targeted delivery not only improves the drug's therapeutic index but also minimizes systemic exposure, thereby reducing adverse effects (Vaidya, 2019).

Improved formulations can also have a significant impact on patient adherence to treatment. For IPF patients, who often require long-term treatment with drugs like Nintedanib, adherence to prescribed therapies is crucial for maintaining stable lung function and preventing disease progression (Vaidya, 2019). However, gastrointestinal side effects and the complexity of managing multiple medications may lead to treatment discontinuation or dose reductions, negatively impacting patient outcomes (Salah, 2020). Formulation strategies that minimize side effects, improve drug absorption, and reduce the need for frequent dosing can significantly enhance patient compliance, leading to better long-term outcomes.

Additionally, reduced side effects improve the patient's overall quality of life, making it easier for them to adhere to the prescribed regimen. In the case of Nintedanib, the development of a more tolerable formulation could help prevent the dose adjustments or discontinuation often required due to gastrointestinal intolerance, ensuring that patients receive the full benefit of the treatment (Vaidya, 2019).

In conclusion, better formulation strategies are needed to improve IPF treatments, especially for drugs like Nintedanib. Finding ways to enhance solubility, bioavailability, and tolerability could make a big difference in treatment effectiveness and patient adherence. Advances in drug delivery, including SMEDDS, nanotechnology, and targeted systems, offer promising ways to tackle these challenges. Among these, SMEDDS is particularly useful for improving the solubility and absorption of poorly water-soluble drugs like Nintedanib. By forming fine emulsions in the gastrointestinal tract, SMEDDS can help overcome some of the biggest formulation challenges, making it a strong candidate for optimizing IPF treatment.

Introduction to SMEDDS

SMEDDS offer a promising approach to enhancing the solubility, bioavailability, and stability of poorly water-soluble drugs like Nintedanib. Essentially, SMEDDS are a mix of oils, surfactants, and co-surfactants that, when they hit an aqueous environment, automatically form fine emulsions or microemulsions. These emulsions create tiny droplets that help the drug dissolve and get absorbed in the gastrointestinal tract much better. This self-emulsifying feature is what makes SMEDDS stand out, especially for drugs that struggle with bioavailability (Liu H, 2024).

SMEDDS enhance a drug's bioavailability in a sophisticated manner. By forming fine emulsions when in contact with the gastrointestinal fluids, they improve the solubility of poorly water-soluble drugs. This allows for better absorption, ensuring that more of the active ingredient reaches the bloodstream, ultimately improving the drug’s therapeutic effect. The oil phase in SMEDDS helps dissolve poorly soluble drugs, which then allows them to absorb more easily in the gastrointestinal tract. When this formulation meets an aqueous environment, it spontaneously breaks down into tiny droplets, which increases the surface area and helps the drug absorb faster through the intestines. This means the drug has a much better chance of getting into the bloodstream and doing its job. Plus, the oil phase helps protect the drug from being broken down by enzymes in the stomach (Liu H, 2024).

One big advantage here is that SMEDDS can actually reduce the dose needed for the drug to work. Because SMEDDS improve the drug's solubility and bioavailability, you often don’t need as much of it to get the same results. This can lower the risk of side effects, especially the stomach issues you might see with drugs like Nintedanib (Liu H,

2024). And with the way SMEDDS release the drug gradually, it can improve therapeutic outcomes and cut down on how often a patient needs to take their medicine (Liu H, 2024).

Another bonus is that SMEDDS tend to be well-tolerated by patients, which helps with sticking to the treatment plan. Fewer side effects and a steady release over time make the whole experience smoother, especially for people on long-term treatments like for IPF (Liu H, 2024). In other words, SMEDDS could make the medicine easier to take and help patients stay on track with their therapy.

That said, there are a few challenges with SMEDDS. Choosing the right oils, surfactants, and co-surfactants is essential to making sure the formulation works well, is stable, and doesn't cause issues like stomach irritation. It's also important to think about how to scale these formulations for mass production (Liu H, 2024).

For Nintedanib, SMEDDS could really help with its solubility problems and reduce the stomach-related side effects that often cause doctors to cut doses or stop treatment altogether. By improving the drug's solubility and bioavailability, SMEDDS could make Nintedanib more effective and easier on the stomach. The controlled release aspect of SMEDDS could also help keep Nintedanib at steady levels in the bloodstream, which would make it more effective over time in treating IPF (Liu H, 2024).

In conclusion, SMEDDS present a significant approach to enhance the effectiveness of poorly soluble drugs like Nintedanib, improving their potential for treating conditions such as IPF. They could reduce side effects, improve patient compliance, and ultimately lead to better outcomes. Naturally, there are challenges to

overcome, but with continued research, SMEDDS could play a key role in the future of chronic disease treatments (Liu H, 2024).

FDA Approved SMEDDS Literature Review

SMEDDS have become an important tool for improving the solubility and bioavailability of drugs that don't dissolve well in water. These systems work by forming fine oil-in-water emulsions when they come into contact with fluids in the gastrointestinal tract, allowing drugs to dissolve more efficiently and be absorbed more consistently. Because of this, SMEDDS have played a key role in overcoming the challenges of poorly soluble drugs, and several FDA-approved formulations already rely on this technology to enhance drug delivery, reduce variability between patients, and improve treatment outcomes.

One of the most well-known examples is Sandimmune® (cyclosporine A), an immunosuppressant used to prevent organ rejection in transplant patients (Lodge, 1994). Cyclosporine A is highly lipophilic, meaning it doesn't dissolve easily in water, leading to poor and inconsistent absorption when taken orally. The SMEDDS formulation of Sandimmune includes surfactants like Cremophor EL, along with ethanol and medium-chain triglycerides, which help form a microemulsion in the gut (Lodge, 1994). This process significantly boosts absorption by enhancing lymphatic transport and reducing metabolism in the liver. However, Sandimmune's absorption still varied between patients, which led to the development of Neoral® (cyclosporine A, modified)—a more optimized SMEDDS formulation that offers better bioavailability and more predictable drug levels (Wang, 2014).

Another example of an FDA-approved SMEDDS formulation is Kaletra® (lopinavir/ritonavir), a combination drug used in HIV treatment. Lopinavir, one of its active ingredients, is poorly soluble in water, which limits its absorption (Kalepu, 2013). Kaletra's SMEDDS formulation contains lipid-based excipients like oleic acid, ethanol, and tocopherol, which promote self-microemulsification in the gut, allowing the drug to dissolve and be absorbed more efficiently (Kalepu, 2013). A similar approach was taken with Norvir® (ritonavir soft gel capsules), another SMEDDS-based antiretroviral medication (Lei, 2010). In both cases, the technology helped improve solubility and bioavailability, making lower doses possible while maintaining effectiveness, ultimately leading to better patient adherence.

Another SMEDDS-based FDA-approved drug is Lipofen® (fenofibrate), which treats high cholesterol and triglyceride levels. Like many other BCS Class II drugs, fenofibrate has low solubility but high permeability, meaning it can be absorbed well once it dissolves (Huang, 2021). The SMEDDS formulation of Lipofen ensures that, upon ingestion, the drug rapidly forms a fine emulsion, improving solubility and absorption. This not only enhances its cholesterol-lowering effects but also reduces gastrointestinal discomfort compared to traditional formulations, making it easier for patients to tolerate (Huang, 2021).

To gain FDA approval, SMEDDS formulations must meet strict regulatory requirements. One of the biggest factors is proving that the formulation significantly improves bioavailability compared to conventional versions. Stability is another major consideration these formulations must maintain their physical and chemical properties over time, ensuring they still form microemulsions as intended even after long storage

periods. Safety is also critical; excipients like surfactants and co-surfactants must be either Generally Recognized as Safe (GRAS) or have a well-documented safety profile. Finally, large-scale manufacturing must maintain batch-to-batch consistency so that every dose delivers the same therapeutic effect.

Given how well SMEDDS have worked for other drugs, this technology has huge potential for improving treatments for idiopathic pulmonary fibrosis (IPF), particularly with Nintedanib. Like many of the drugs mentioned earlier, Nintedanib is a BCS Class II drug, meaning it has low solubility but high permeability. A SMEDDS formulation could help dissolve the drug more efficiently, leading to more consistent absorption and better therapeutic outcomes. This is especially important in IPF treatment, where maintaining steady drug levels is key to slowing disease progression.

One of the biggest challenges with Nintedanib is its dose-limiting side effects, particularly gastrointestinal issues like diarrhea and nausea. A well-designed SMEDDS formulation could potentially reduce these side effects by providing more controlled drug release and absorption. Instead of large amounts of the drug suddenly reaching the gut and causing irritation, the SMEDDS approach could allow for a gradual and sustained release, leading to better tolerability. Additionally, because SMEDDS improve bioavailability, lower doses could still achieve the same therapeutic effect, further reducing side effects and making long-term treatment more manageable for patients.

Looking at the success of FDA-approved SMEDDS formulations, there is a clear regulatory pathway for future SMEDDS-based therapies. If a Nintedanib SMEDDS formulation can demonstrate bioequivalence to the currently approved version while improving tolerability, the approval process could be more straightforward. Advances in

excipient selection, stability, and formulation optimization continue to push SMEDDS technology forward, making it a promising strategy for the next generation of IPF treatments. By improving solubility, absorption, and patient adherence, SMEDDS could play a key role in creating more effective therapies with fewer side effects, ultimately leading to better patient outcomes.

Formulation Development of Nintedanib-SMEDDs

Nintedanib is an oral drug used to treat IPF, and it works by blocking certain kinases involved in the fibrosis process. However, it has a significant drawback—it's not very soluble in water. This poor solubility makes it harder for the body to absorb, which in turn limits how effective the drug is. Because of this, patients often need higher doses to reach effective plasma concentrations, which can increase the risk of side effects, especially stomach-related issues. To address these challenges, researchers have turned to SMEDDS, which could significantly improve how well Nintedanib works.

SMEDDS have shown a lot of promise when it comes to improving the solubility, dissolution rate, and overall bioavailability of drugs like Nintedanib, which don’t dissolve easily in water. To make an effective Nintedanib-SMEDDS formulation, the right ingredients have to be chosen. These include oils, surfactants, and co-surfactants, and each one has a specific role in making the formulation stable and effective.

The oil phase, which includes ingredients like medium-chain triglycerides (MCT) or long-chain triglycerides (LCT), is especially important because it helps dissolve Nintedanib. These oils are chosen for their ability to solvate the drug, allowing more of it to be absorbed by the body. Surfactants are needed to form stable microemulsions, and non-ionic surfactants like Tween 80 or Cremophor EL are often used because they’re

great at solubilizing lipophilic drugs while being safe for the body. Co-surfactants, such as ethanol or propylene glycol, help mix the oil and surfactant and ensure the formulation works when exposed to water. Some stabilizers might also be added to keep the formulation from separating over time and to protect the drug from breaking down.

Once the ingredients are chosen, the next step is to optimize the formulation to ensure it works as effectively as possible. This involves testing different combinations and ratios of oils, surfactants, and co-surfactants to achieve the right balance. The goal is to find the ideal mixture that forms a stable microemulsion, improves drug solubility, and enhances absorption while maintaining the formulation's overall stability. A stable microemulsion is crucial because it ensures that the drug remains uniformly dispersed and doesn't separate over time. This stability prevents the formulation from losing its effectiveness, ensuring consistent dosing and reliable bioavailability. A stable microemulsion also improves the solubility and absorption of poorly soluble drugs by maintaining small droplet sizes, which increases surface area for faster absorption in the body. Without stability, the formulation could degrade, leading to inconsistent therapeutic effects and potentially lower efficacy. Optimization ensures the best possible performance of the final product. This is where pseudo-ternary phase diagrams come into play. These diagrams help map out different combinations of oil, surfactant, and co-surfactant, showing which ones form stable microemulsions when water is added. This makes it easier to find the right balance of ingredients to get the droplet size and overall stability just right. The ratio of oil to surfactant is crucial because more surfactant usually means smaller droplets, which is better for absorption, but too much surfactant can irritate the gut. Getting this ratio right is key to creating an effective and stable

formulation. Co-surfactant screening is another important step to make sure everything works well together. The right co-surfactant helps achieve the best droplet size, clarity, and solubility. Finally, checking how well the oil phase can solvate Nintedanib is important, as it ensures that the formulation can carry enough of the drug without losing stability.

Once the formulation is optimized, it's time to characterize it to make sure it meets the right standards. One of the first things to check is droplet size. Smaller droplets create more surface area, which improves how quickly and effectively the drug can be absorbed in the body. Techniques like Dynamic Light Scattering (DLS) are used to measure droplet size and confirm the formulation is on track. Zeta potential measurements are also important because they help determine the stability of the formulation. A high zeta potential means the droplets will repel each other, reducing the risk of aggregation and ensuring long-term stability. In vitro release studies simulate how the drug will dissolve in the body and compare how fast Nintedanib dissolves in the SMEDDS formulation versus a regular tablet. Faster dissolution is usually a good indicator of improved bioavailability. Stability testing is also crucial to make sure the formulation stays effective over time. This includes checking both physical and chemical stability to ensure the drug won't break down when stored. Accelerated stability studies can help predict the shelf life of the formulation. Finally, in vivo studies are necessary to assess the formulation's effectiveness in real-world conditions, either in animal models or human trials. These studies will show if the SMEDDS formulation actually improves Nintedanib's bioavailability and therapeutic effects compared to the standard formulation.

Developing Nintedanib-SMEDDS could be a big step forward in improving the drug's effectiveness for IPF treatment. By carefully selecting the right ingredients, optimizing the formulation, and rigorously testing it, researchers can create a stable and effective formulation that increases Nintedanib's solubility and absorption. This could not only boost the drug's bioavailability but also reduce side effects, leading to better outcomes for patients. As research in lipid-based drug delivery systems continues to grow, SMEDDS could provide a promising solution for delivering challenging drugs like Nintedanib, ultimately improving the quality of care for patients with chronic conditions like IPF.

Potential Impact on IPF Treatment

Nintedanib is a key treatment for IPF, but it faces a significant hurdle: its poor water solubility, which limits its ability to be absorbed effectively into the bloodstream. This can lead to issues with achieving the desired therapeutic effect, requiring higher doses and possibly causing side effects. To address this problem, SMEDDs have been developed for Nintedanib, offering a solution that enhances its solubility and absorption. When taken, SMEDDs form tiny oil droplets in the digestive system, increasing the surface area available for absorption and allowing Nintedanib to dissolve more efficiently. This process improves its absorption into the bloodstream, helping the body get the most out of the medication.

The enhanced bioavailability that SMEDDs provide also means that lower doses of Nintedanib can be used to achieve the same therapeutic effect. This can help reduce the side effects that often come with higher doses, such as gastrointestinal discomfort,

making the treatment easier for patients to tolerate. For people with IPF, who may need to take the medication over a long period, minimizing side effects is a critical benefit.

Another common issue with Nintedanib is inconsistent absorption, which can lead to fluctuating drug levels in the bloodstream. This inconsistency can diminish the medication's effectiveness, especially when taken with food or by individuals with certain digestive conditions. However, SMEDDs offer a more predictable and consistent release of Nintedanib. By stabilizing the dissolution process, SMEDDs help maintain steady levels of the drug in the blood, which is key for controlling IPF symptoms and improving overall patient outcomes.

In addition to improving absorption, SMEDDs help reduce side effects. Conventional formulations of Nintedanib can cause discomfort in the gastrointestinal tract, particularly at higher doses. By improving the solubility and dissolution of the drug, SMEDDs enable Nintedanib to be absorbed in a way that minimizes local irritation in the gut. This leads to fewer side effects like nausea and diarrhea, which are often seen with standard formulations. Furthermore, because SMEDDs can achieve the desired therapeutic effect with a lower dose, systemic side effects are also less likely to occur, making the drug more tolerable for patients.

One of the major challenges in treating IPF is ensuring that patients stick with their medication regimen. Chronic conditions like IPF require ongoing treatment, and if a medication causes too many side effects, patients may be less likely to continue taking it. The improved tolerability of Nintedanib with SMEDDs could increase patient compliance, helping individuals stay on track with their treatment. In some cases,

SMEDDs might even reduce the frequency of dosing, which would further improve patient adherence by simplifying the treatment regimen.

Personalized treatment is another area where SMEDDs could play a crucial role (Algahtani, 2023). Not all IPF patients respond to Nintedanib in the same way, and some may have gastrointestinal conditions that make drug absorption more difficult. Because SMEDDs can be tailored to optimize the release and absorption of the drug, they can be adjusted to suit individual patient needs. This adaptability could lead to more effective treatment and better outcomes for patients with varying health profiles.

Beyond IPF, Nintedanib has potential applications for other fibrotic diseases like systemic sclerosis, chronic kidney disease, and non-alcoholic steatohepatitis (Wollin, 2015). By improving Nintedanib's bioavailability with SMEDDs, it could become a viable treatment option for these conditions as well. SMEDDs could help maintain stable drug levels, reduce side effects, and improve patient adherence, making Nintedanib a valuable treatment for a broader range of fibrotic diseases.

In conclusion, the development of Nintedanib-SMEDDs represents an exciting advancement in the treatment of IPF and other fibrotic diseases. SMEDDs not only enhance the drug’s solubility and bioavailability but also improve its overall effectiveness by offering a more controlled and consistent release. The benefits of SMEDDs extend to reducing side effects, improving patient compliance, and even personalizing treatment. This approach has the potential to transform how Nintedanib is used, improving patient care and offering a more effective long-term treatment for chronic diseases like IPF.

Chapter II.

Materials and Methods

The process of developing Nintedanib-SMEDDs started with testing how well Nintedanib dissolves in different solvents. Since Nintedanib doesn't mix well with water, an oil-in-water emulsion system was the best option. In this setup, the drug dissolves in the oil, surfactant, and co-solvent phase—but not in the water phase. After selecting the appropriate agents, pseudo-ternary diagrams were used to determine the optimal ratios for forming a self-micro-emulsion. After that, they were analyzed for particle size, and finally, an in vitro permeation study was done to see if the formulation could improve drug delivery. The goal of this investigation is to propose a feasible Nintedanib-SMEDD formulation that can be encapsulated, allowing self-emulsification to occur within the gastrointestinal tract.

Hansen Solubility

To determine the best excipients for Nintedanib-SMEDDs, Hansen Solubility studies were conducted using a mix of solvents. A total of 32 solvents from the Hansen library were selected based on their polarity, dispersion forces, and hydrogen bonding abilities. Each one was tested by adding 15 mg of Nintedanib into individual HPLC vials, followed by 150 µL of the assigned solvent. The vials were vortexed and left rocking overnight at room temperature to ensure thorough mixing.

After 24 hours, the samples were checked to see if the drug had dissolved. A simple scoring system was used—soluble samples were given a "1," and insoluble ones received a "0" (Hansen, 2000). These results were entered into the Hansen Solubility Parameters Software, which helped determine how well different excipients would work. If a solvent failed to fully dissolve the drug, another 300 µL was added, and the process was repeated for another 24 hours. To refine the selection, the Hansen Software was also used with the Simplified Molecular-Input Line-Entry System (SMILES) for Nintedanib to predict other solvents that could be compatible. Using these values, the Hansen Software identified compatible solvents, oils, and surfactants from its library based on the calculated relative energy distance (RED) values (Equation 1).

Equation 1. Calculation for Relative Energy Distance

$$Ra^2 = 4(\delta D1-\delta D2)^2 + (\delta P1-\delta P2)^2 + (\delta H1-\delta H2)^2$$

$$RED = Ra/Ro$$

Ro = Radius of Hansen Solubility Parameter Sphere

Ra, or Hansen distance, represents how different two substances are based on their HSP values, while Ro, the interaction radius, indicates how much variation a material can tolerate in these values. RED helps assess compatibility: when RED < 1, the substances are highly compatible and likely to mix well; when RED ≈ 1, they may be somewhat compatible; and when RED > 1, they are less compatible, meaning solubility or miscibility is poor.

Since the end application was pharmaceutical, the focus remained on chemicals listed as Generally Recognized as Safe (GRAS) by the FDA. Given the preference for

GRAS excipients in pharmaceutical formulations, solubility testing was repeated with these candidates and analyzed via HPLC method.

HPLC Method

The separation was carried out using a Shimadzu C18 column (250 × 4.6 mm, 5 µm) as the stationary phase. An isocratic elution was performed with a mobile phase made up of 0.1% triethylamine (TEA) in HPLC-grade water and acetonitrile (ACN) in a 35:65% ratio (Singh, 2023). The mobile phase flowed at 1.0 mL/min, with a total run time of 15 minutes. Detection was conducted at a wavelength of 390 nm (Singh, 2023).

Hydrophilic-Lipophilic Balance (HLB)

The Hydrophilic-Lipophilic Balance (HLB) was calculated using the values provided by the manufacturer, which made it possible to rank pure substances based on their relative hydrophobicity. This method is similar to the partition coefficient logP, which measures how a molecule partitions between two immiscible solvents, though it doesn't necessarily explain how oils and surfactants interact (Smejkal, 2024). To optimize the formulation, the required HLB of the oil phase was determined using the manufacturer's data. When preparing oil-in-water (o/w) emulsions, emulsifiers were chosen based on their HLB values, typically ranging from 0 to 20. For oils that were easier to emulsify or formulations with less water, emulsifiers with HLB between 8 and 20 were selected (Smejkal, 2024). Emulsifiers, either alone or in combination, were then chosen to match the required HLB and achieve the desired emulsion properties (Equation 2).

Equation 2. Calculation to determine HLB

$$HLB_{\text{blend}} = \frac{(HLB_A \times \%_A) + (HLB_B \times \%_B)}{100}$$

When blending two or more surfactants to create an emulsion, the HLB of the mixture can be calculated as the weighted average of the HLB values of the individual surfactants, based on their proportion in the blend. This calculation ensures that the desired hydrophilic-lipophilic balance is achieved for a stable emulsion.

The surfactant-to-oil ratio (SOR) was also calculated to examine its effect on droplet size and stability, with higher SORs linked to smaller oil droplets. It was noted that nanoemulsions required higher surfactant concentrations than macroemulsions, as the increased surface area of the smaller droplets needed greater stabilization (Smejkal, 2024).

Pseudoternary Phase Diagram

To map out the ternary phase diagram and understand the system's phase behavior, mixtures with varying ratios of oil, surfactant, and water were prepared to observe the general phase transitions as the composition changed. The oil phase was prepared by mixing selected oil components in specific ratios, carefully measured using an analytical balance. These components were combined and mixed thoroughly to ensure uniformity, with the total volume adjusted based on the required composition for each trial. A measured amount of surfactant was then added to the oil phase, as its role in stabilizing the oil-water interface was a key factor in determining phase formation (Berkman, 2021). The concentration of the surfactant was varied across trials to assess its effect on phase behavior.

Water was then introduced gradually, drop by drop, using a burette or pipette while continuously stirring (Berkman, 2021). This controlled addition was necessary to prevent sudden phase separation and allow for careful observation of any phase transitions. Initially, with small amounts of water, the system remained as a single phase, but as more water was added, distinct phase separations or turbidity was observed (Berkman, 2021). These changes were documented to track the impact of different compositions. Throughout the process, the mixtures were closely monitored for visual changes. Some exhibited clear phase separation, forming distinct oil-rich and water-rich layers, while others developed stable emulsions that appeared milky or gel-like. Water was continuously added until a noticeable shift in phase behavior occurred, and these transitions were carefully recorded.

To fully construct the phase diagram, multiple mixtures with varying ratios of oil, surfactant, and water were prepared and classified based on their observed behavior. Systems were categorized as single-phase when no separation occurred, two-phase when distinct layers formed, or micellar/emulsion phases when stable dispersions were achieved. Once the phase behavior was mapped, adjustments were made as necessary, and samples were collected for further characterization (Berkman, 2021). The dropwise addition of water played a critical role in identifying phase boundaries, allowing for a more precise understanding of how different components interacted. These findings provided valuable insights that would inform the selection of the most suitable oil and surfactant for further formulation development.

Particle Size Analysis

The Nintedanib-SMEDDs (0.5 g) was quickly added to 50 mL of distilled water while stirring gently at room temperature. The time it took for the emulsion to form was recorded, from the moment it was injected to when the self-microemulsion became clear with a slight bluish tint (Liu H, 2019). After that, the droplet size of the Nintedanib-SMEDDs was measured using the Litesizer 500, following a 50-fold dilution with distilled water at room temperature (Liu H, 2019).

In-vitro Permeability Assay

The bi-directional permeability of the test compound was assessed using the EpiIntestinal™ model (SMI-100 MatTek), a 3D human small intestinal epithelium model that mimics the human intestinal transport system, per supplier's protocol. Upon receiving the tissues, they were removed from their shipping conditions and placed in culture plates with the appropriate assay medium. The tissues were then equilibrated at 37°C with 5% CO_2 overnight, with media supplied, to ensure proper conditions before starting the experiment.

After the overnight incubation, the media was aspirated from both sides, and 75 µL of A-side transport buffer (1.98 g/L glucose in 10 mM HEPES, HBSS pH 6.5) was added to the top (apical) chamber, while 200 µL of B-side transport buffer (1.98 g/L HEPES, HBSS pH 7.4) was placed in the bottom (basal) chamber (Vaidya, 2019). For the bi-directional permeability assay, two transport directions were tested: apical-to-basolateral (A→B) and basolateral-to-apical (B→A). For the A→B transport, the test compound was added to the apical compartment (upper side of the insert), and the basolateral compartment (lower well) was filled with fresh assay medium. In the B→A

transport direction, the test compound was applied to the basolateral compartment, and the apical compartment was filled with assay medium.

The system was incubated at 37°C for predetermined time points (30, 60, 90, and 120 minutes). At each time point, 200 µL or 75 µL samples were collected from the receiver compartment (either basolateral or apical, depending on the transport direction) to measure the concentration of the test compound that had permeated through the tissue. The concentration of the test compound in the samples was determined using the HPLC method.

The apparent permeability coefficient (Papp) was then calculated using the Equation 3:

Equation 3. Apparent Permeability Coefficient (Papp)

$$P_{\text{app}} = \frac{dQ/dt}{A \times C_0}$$

Where dQ/dt is the rate of drug transport (µmol/s), A is the surface area of the tissue insert (cm^2), and $C0$ is the initial drug concentration (µM).

The data from both transport directions were also used to calculate the efflux ratio (ER), using Equation 4:

Equation 4. Efflux Ratio

$$ER = \frac{P_{\text{app (B}\rightarrow\text{A)}}}{P_{\text{app (A}\rightarrow\text{B)}}}$$

An ER value greater than 2 suggests that the compound may be a substrate for active efflux transporters, while an ER value close to 1 indicates passive diffusion as the primary transport mechanism.

This method provides a comprehensive evaluation of the compound's permeability and its potential interaction with efflux transporters.

Chapter III.

Results

This study focused on creating a SMEDD formulation for Nintedanib, which is used in treating conditions like IPF. The objective was to boost the oral bioavailability of Nintedanib by developing a stable and efficient SMEDD formulation.

Screening Using Hansen Solubility Parameters

The study began with screening the API using Hansen Solubility Parameters (HSP) to pinpoint potential solvents, co-solvents, and oils for the SMEDD formulation. HSP provides a methodical approach to predict the solubility of compounds based on molecular interactions such as dispersion, polar, and hydrogen bonding forces. For the predictions to be valid, the API must show at least three “hits” where it’s miscible in the solvent. Nintedanib, however, showed little to no solubility in all 32 solvents (Table 7). The SMILES for Nintedanib was entered into the HSP software to estimate theoretical values for its dispersion, polar, and hydrogen bonding forces (Table 1).

Table 1. SMILES in Hansen

	D	P	H
Nintedanib Free Base	22.1	8.1	9.4
SMILES input	COC1=CC=C(C=C1OC2=CC=C(C=C2)-C3=CC=C(C=C3CN(C)C)C(=O)N4CCN(CC4)C5=NC6=C(C=C5F)C=CC=C6)O		

The software calculated the polarity, dispersion forces, and hydrogen bonding values based on the SMILES input for Nintedanib.

Since the end application was pharmaceutical, the focus remained on chemicals listed as Generally Recognized as Safe (GRAS) by the FDA (**Error! Reference source not found.**). Given the preference for GRAS excipients in pharmaceutical formulations, solubility testing was repeated with these candidates and analyzed via HPLC method (**Error! Reference source not found.**).

Based on the inclusion of these new hits, the Hansen values were adjusted and the libraries were screened again for possible solvents and oils that could be incorporated into a SMEDD formulation (Table 2).

Table 2. Revised HSP Values for Nintedanib

	D	P	H
Nintedanib Free Base	18.8	6.7	13.2

However, these values didn't show other possible components that could be formulated into SMEDDs.

For solvents miscible with Nintedanib, oversaturated solutions were prepared with 2 ml of respective solvents. Nintedanib was weighed into the solvent and vortexed until

Nintedanib was no longer soluble. Then the oversaturated solutions were centrifuged at 10,000 RPMs for 30 minutes. With the Nintedanib precipitate settled at the bottom, while the clear supernatant will be on top 0.5 ml of supernatant was transferred to an HPLC vial to determine solubility of Nintedanib.

Eugenol and benzyl alcohol both solubilize Nintedanib and seemed to be compatible when mixed together. Consequently, based on these observations, eugenol and benzyl alcohol were selected as the oil phase for the formulation containing Nintedanib.

Hydrophilic-Lipophilic Balance Calculations

The next step was to determine a suitable surfactant that can help stabilize the emulsion and prevent coalescence. Typically for an oil-in-water system the ideal HLB of the surfactant is around 8-20. This range indicates that the surfactant has a balance of hydrophilic and lipophilic components, allowing it to effectively stabilize the oil droplets in the aqueous phase. Since the HLB values for Benzyl Alcohol and Eugenol are similar (5 and 6 respectively) it was essential to find a surfactant with a higher HLB value. Tween 20, Span 20 and Potassium Oleate were selected because of their HLB values 16.7, 8.6 and 20, respectively. Although Tween 20 and Span 20 are non-ionic surfactants, Potassium Oleate is an anionic surfactant and is not considered an ideal agent for SMEDDs due to toxicity concerns even when formulations achieve HLB values in the 8–16 range (Table 5).

Table 3. HLB Calculations with Tween 20 as the Surfactant

%Tween 20 (HLB 16.7)	%Benzyl Alcohol (HLB 5)	%Eugenol (HLB 6)	HLB of Solution
0	50	50	5.5
10	45	45	6.62
20	40	40	7.74
30	35	35	8.86
40	30	30	9.98
50	25	25	11.1
60	20	20	12.22
70	15	15	13.34
80	10	10	14.46
90	5	5	15.58
100	0	0	16.7

Table 4. HLB Calculations with Span 20 as the Surfactant

%Span 20 (HLB 8.6)	%Benzyl Alcohol (HLB 5)	%Eugenol (HLB 6)	HLB of Solution
0	50	50	5.5
10	45	45	5.81
20	40	40	6.12
30	35	35	6.43
40	30	30	6.74
50	25	25	7.05
60	20	20	7.36
70	15	15	7.67
80	10	10	7.98
90	5	5	8.29
100	0	0	8.6

Table 5. HLB Calculations with Potassium Oleate as the Surfactant

%Potassium Oleate (HLB 20)	%Benzyl Alcohol (HLB 5)	%Eugenol (HLB 6)	HLB of Solution
0	50	50	5.5
10	45	45	6.95
20	40	40	8.4
30	35	35	9.85
40	30	30	11.3
50	25	25	12.75
60	20	20	14.2
70	15	15	15.65
80	10	10	17.1
90	5	5	18.55
100	0	0	20

Note Tables 6-8 assume equal parts Benzyl Alcohol and Eugenol. Since their HLB values are similar, changes in their composition are not expected to make a significant difference.

Tween 20 (HLB 16.7) is a non-ionic, biocompatible surfactant approved for oral administration, offering a broader range for the final composition to achieve an HLB within the desired 8-16 range (Table 3). Only formulations with a substantially high concentration of Span 20 (HLB 8.6) narrowly fall within the desired range (Table 4). Therefore, in the purposed SMEDD, Benzyl Alcohol dissolves the lipophilic drug, reduces interfacial tension along side Tween 20 and helps to stabilize the emulsion due to compatibility with Eugenol. Eugenol makes up the oil phase ensuring good

emulsification. Tween 20 promotes spontaneous emulsification, forms hydrophilic shell around oil droplets solubilizing poorly water-soluble drugs by incorporating them into micelles.

Constructing Pseudoternary Phase Diagram

In this study Eugenol and Benzyl Alcohol were assessed at various ratios. The pseudoternary phase diagram is well documented in the literature and has extensively been reported for the selection of components and ratios for microemulsions. The grayed areas of the phase diagrams indicate microemulsion area, whereas the white area represents the turbid region (Figure 2). The microemulsion area of diagram C (Eugenol/ Benzyl Alcohol [1:2]) was larger compared to the other ratios. Based on this finding, the formulation containing Eugenol/ Benzyl Alcohol [1:2] was selected for further investigation.

Particle Size Data

As previously discussed, the concentration of surfactant significantly influences droplet size. In this analysis, the ratio of Eugenol and Benzyl Alcohol [1:2] and the amount of Nintedanib were held constant, while the concentration of Tween 20 was varied between 20% and 50%. The SMEDDs formulation with 20% Tween 20 exhibited a larger average particle size of 215 nm and an emulsion time of 80 ± 5 seconds (Figure 1). In contrast, the formulation with 50% Tween 20 resulted in a smaller average particle size of 5 nm and a reduced emulsion time of 45 ± 5 seconds (Figure 1).

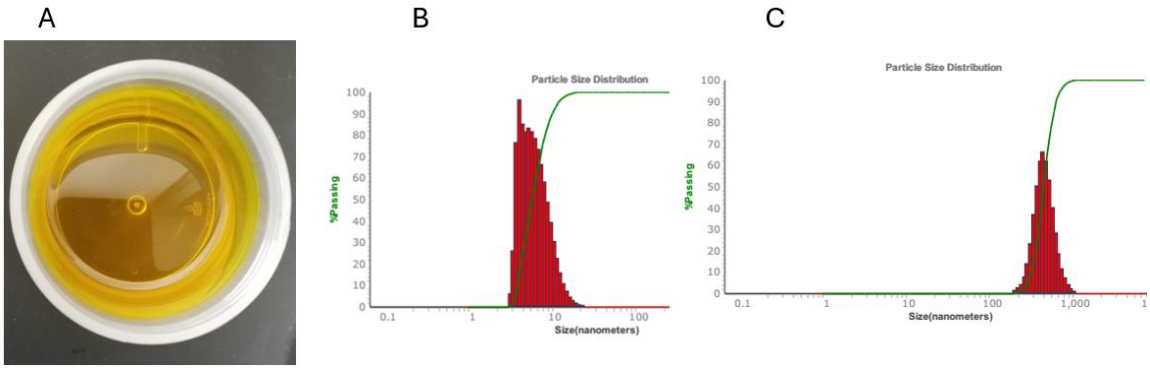


Figure 1. Sample and Size Distribution

Figure 2A is a picture of the Nintedanib-SMEDD system before it is added to water. Figure 2B contains 50% Tween 20 and Figure 2C contains 20% Tween 20.

In-vitro Permeability Assay

The Caco-2 cell permeability assay was conducted to evaluate the transport efficiency of Nintedanib in solution and in SMEDDs formulations. The apparent permeability coefficients (Papp) for both apical-to-basolateral (A → B) and basolateral-to-apical (B → A) transport are summarized in Table 6.

Permeability is typically categorized based on Papp values, where high permeability is defined as Papp > 1×10^{-5} cm·s^{-1}, medium permeability falls between 1×10^{-5} and 1×10^{-6} cm·s^{-1}, and low permeability is assigned to Papp < 1×10^{-6} cm·s^{-1}. According to this classification, the Nintedanib control exhibited low permeability (Papp A → B: 1.58×10^{-7} cm·s^{-1}), confirming its poor absorption potential.

In comparison, the Nintedanib-SMEDDs formulations (Eugenol: Benzyl Alcohol at [1:2], [1:3], and [2:1] ratios) demonstrated modest improvements in permeability. The [1:3] formulation (Papp A → B: 1.08×10^{-6} cm·s^{-1}) reached the threshold for high

permeability, while the [1:2] formulation (9.13×10^{-7} cm·s^{-1}) was near the upper limit of the medium permeability range. The [2:1] formulation (7.37×10^{-7} cm·s^{-1}) also fell within the medium category but showed lower permeability than the other SMEDDs formulations.

Additionally, all tested systems had efflux ratios below 1, suggesting that Nintedanib permeability was not significantly influenced by active efflux transporters. The Papp values in the A → B direction were slightly higher than in the B → A direction across all formulations, further indicating that Nintedanib is unlikely to be a P-gp substrate.

Overall, these findings suggest that while SMEDDs formulations improved the permeability of Nintedanib compared to the control, the extent of enhancement was modest. The Eugenol: Benzyl Alcohol [1:3] formulation exhibited the highest permeability, reaching the lower boundary of the high-permeability category, making it a promising candidate for further development.

Table 6. Permeability Coefficient Papp

Systems	A to B	B to A	Efflux Ratio	Permeability
Eugenol: Benzyl Alcohol [1:2]	9.13E-07	7.35E-07	7.50E-07	High
Eugenol: Benzyl Alcohol [1:3]	1.08E-06	7.05E-07	7.23E-07	High
Benzyl Alcohol	8.45E-07	6.61E-07	5.24E-07	Medium
Eugenol: Benzyl Alcohol [2:1]	7.37E-07	5.34E-07	9.79E-07	Medium
Eugenol	2.28E-07	3.69E-07	8.21E-07	Low
Nintedanib Control	1.58E-07	3.79E-07	4.18E-01	Low

This table presents the permeability coefficients (Papp) for various chemical systems, measured in both A to B and B to A directions, along with their efflux ratios and overall permeability classifications (High, Medium, Low). The data includes combinations of Eugenol and Benzyl Alcohol in different ratios, pure components, and a control substance (Nintedanib Control).

Chapter VI.

Discussion

The findings from this study demonstrate that formulating Nintedanib into a SMEDDs significantly enhances its solubility and permeability, addressing the drug's inherent challenges regarding poor oral bioavailability. To identify suitable excipients, the HSP were applied, providing a systematic method for selecting solvents and oils based on their compatibility with Nintedanib. This approach ensured that only excipients with a high likelihood of dissolving the drug were considered, reducing trial-and-error in formulation development. Although initial screening of solvents suggested that Nintedanib had poor solubility in most of the tested options, further solubility assessments revealed that Benzyl Alcohol and Eugenol were capable of dissolving the drug. These two solvents were therefore chosen to serve as the oil phase in SMEDDs development, as their ability to solubilize Nintedanib directly impacts its dissolution and absorption in the gastrointestinal tract.

Pseudoternary phase diagram analysis allowed for the identification of the best oil-to-surfactant ratio, a critical factor in achieving optimal emulsification and stability. It was found that the Eugenol: Benzyl Alcohol [1:2] system exhibited the largest microemulsion region, suggesting superior self-emulsification properties. This composition was then further optimized by varying the surfactant concentration to determine its influence on droplet size, emulsification time, and overall stability. Tween 20, known for its high hydrophilic-lipophilic balance (HLB) and established biocompatibility, was selected as the surfactant. Its amphiphilic nature facilitated the formation of a stable emulsion, ensuring that the formulation remained homogenous upon

dilution. Formulations with higher concentrations of Tween 20 (50%) demonstrated significantly smaller droplet sizes (5 nm) and faster emulsification times compared to those with lower surfactant concentrations, suggesting that these formulations could provide improved dispersion, enhanced stability, and better absorption of Nintedanib in the gastrointestinal tract.

In addition to evaluating the formulation's physical properties, the impact of SMEDDs on Nintedanib's permeability was assessed using a permeability assay across Caco-2 monolayers, a widely used in vitro model for predicting intestinal absorption. The control formulation exhibited low permeability, with a Papp value of 1.58×10^{-7} cm·s^{-1}, which aligns with the drug's poor absorption profile. However, SMEDDs formulations demonstrated marked improvements in permeability. Specifically, the Eugenol: Benzyl Alcohol [1:3] formulation achieved a Papp value of 1.08×10^{-6} cm·s^{-1}, indicating it was approaching the threshold of high permeability. Meanwhile, the [1:2] and [2:1] formulations also exhibited enhanced permeability, though they remained within the medium permeability range. These findings highlight the potential of SMEDDs formulations to improve the oral bioavailability of Nintedanib by facilitating its transport across the intestinal epithelium, a key step in improving drug absorption and ensuring its therapeutic efficacy.

Further supporting the permeability results, efflux ratio calculations were also performed to determine whether Nintedanib was a substrate for active efflux transporters such as P-glycoprotein (P-gp), which can significantly reduce the bioavailability of poorly permeable drugs. All SMEDDs formulations demonstrated efflux ratios below 1, suggesting that Nintedanib is unlikely to undergo active efflux. This finding is crucial

because efflux transporters are known to limit drug absorption by actively removing compounds from enterocytes before they reach systemic circulation. The inhibition or avoidance of efflux mechanisms by SMEDDs further underscores their potential in enhancing Nintedanib's oral bioavailability and ensuring a more consistent drug plasma concentration over time.

The results of this study provide compelling evidence that SMEDDs has the potential to significantly improve the solubility and permeability of Nintedanib. The Eugenol: Benzyl Alcohol [1:3] formulation, in particular, shows great promise, warranting further investigation. Future studies should focus on evaluating the dissolution profiles of this formulation to confirm that the solubility enhancement translates into improved drug release. Additionally, in vivo pharmacokinetic assessments are necessary to validate its effectiveness in enhancing the bioavailability of Nintedanib. Beyond pharmacokinetics, long-term stability studies under physiological and storage conditions should be conducted to assess the formulation's viability for future clinical applications. Stability assessments, including stress testing and degradation analysis, will provide insights into potential formulation modifications necessary for ensuring commercial feasibility. Exploring the formulation's stability over time and under different storage conditions will be important for understanding its practical application in drug delivery.

The enhanced permeability observed with the SMEDDs formulations is likely attributed to multiple mechanisms beyond simple solubility improvement. One key factor is the ability of the self-emulsifying system to generate nano-sized droplets, which increase the drug's surface area and facilitate more efficient diffusion across the intestinal epithelium. This phenomenon is well-documented in lipid-based drug delivery systems,

where nanoemulsions enhance the rate and extent of drug absorption by reducing particle aggregation and providing a more uniform drug distribution. The reduction in droplet size observed with the optimized formulations, particularly those containing 50% Tween 20, likely contributed to the observed increase in permeability by promoting better interaction between Nintedanib and the epithelial surface.

In addition to nano-size effects, the choice of excipients plays a critical role in improving permeability. Eugenol and Benzyl Alcohol, which were selected as the oil phase, may act as permeation enhancers by disrupting the lipid bilayer of intestinal cells, thereby increasing passive diffusion of Nintedanib. Eugenol, in particular, has been reported to enhance drug transport by modulating membrane fluidity and opening tight junctions, which may facilitate paracellular transport. These excipients may also inhibit efflux transporters such as P-glycoprotein (P-gp), which could otherwise reduce drug absorption by actively pumping Nintedanib out of enterocytes. The efflux ratio calculations, which showed values below 1 for all SMEDDs formulations, suggest that efflux inhibition may be a contributing factor to improved permeability.

Another potential mechanism involves the role of surfactants in altering membrane permeability. Tween 20, known for its high HLB, can act as a solubilizing agent while also interacting with the lipid bilayer of intestinal cells. Surfactants can disrupt the integrity of the phospholipid membrane, facilitating transcellular diffusion of the drug. Moreover, they may also impact mucosal adhesion, increasing the residence time of the formulation at the absorption site and improving drug uptake. Future studies should investigate the extent to which these mechanisms contribute to permeability

enhancement, potentially using fluorescence-based membrane integrity assays or transporter inhibition studies.

The potential clinical impact of the SMEDDs formulation of Nintedanib extends beyond improved bioavailability. Enhancing solubility and permeability could lead to more consistent plasma drug levels, reducing variability in patient responses and potentially lowering the required dosage to achieve therapeutic efficacy. This could, in turn, minimize adverse effects associated with high doses, such as gastrointestinal discomfort, which is a known side effect of Nintedanib. Additionally, by overcoming the limitations of conventional formulations, SMEDDs may facilitate the development of alternative dosage forms, such as capsules or liquid suspensions, that could improve patient compliance, particularly in populations who struggle with swallowing tablets. Future clinical research should explore these possibilities, assessing not only pharmacokinetic improvements but also patient-centered outcomes, including tolerability and ease of administration.

This study explored a practical approach to formulating Nintedanib into a SMEDDs, with the goal of improving its solubility and permeability while making it suitable for encapsulation and self-emulsification in the gastrointestinal tract. By systematically selecting excipients using HSP analysis and optimizing the oil-to-surfactant ratio through pseudoternary phase diagrams, the formulation demonstrated significant improvements in emulsification properties and drug permeability. The Eugenol: Benzyl Alcohol [1:3] system stood out, showing promising permeability enhancements while avoiding the impact of efflux transporters. While these findings are encouraging, additional studies are needed to assess long-term stability, in vivo

pharmacokinetics, and alternative delivery formats like solid SMEDDs. Overall, this study highlights SMEDDs as a promising strategy for enhancing the oral bioavailability of Nintedanib and lays the groundwork for future research aimed at refining the formulation for clinical use.

Appendix 1.

Supplemental Tables

Table 7. Hansen Solubility for Nintedanib Free Base

Solvents	D	P	H	Score w/150 µL	Score w/300 µL (450 µL Total)
Methanol	14.7	12.3	22.3	0	0
Phosphoric Acid	14.7	18.6	28.4	0	0
Hexane	14.9	0	0	0	0
Water	15.1	20.4	16.5	0	0
Acetonitrile	15.3	18	6.1	0	0
Methyl Isobutyl Ketone	15.3	6.1	4.1	0	0
Acetone	15.5	10.4	7.0	0	0
n-Butyl Acetate	15.8	3.7	6.3	0	0
Diacetone Alcohol	15.8	8.2	10.8	0	0
Ethanol	15.8	8.8	19.4	0	0
Ethyl Acetate	15.8	5.3	7.2	0	0
2-Propanol	15.8	6.1	16.4	0	0
Methyl Ethyl Ketone	16.0	9.0	5.1	0	0
Hexadecane	16.3	0	0	0	0
1,3-Propanediol	16.8	13.5	23.2	0	0
Tetrahydrofuran	16.8	5.7	8.0	0	0
Ethanolamine	17.0	15.5	21.0	0	0

Solvents	D	P	H	Score w/150 µL	Score w/300 µL (450 µL Total)
Formamide	17.2	26.2	19.0	0	0
Triethanolamine	17.3	7.6	21.0	0	0
Glycerol	17.4	11.3	27.2	0	0
Dimethyl Formamide	17.4	13.7	11.3	0	0
1,4-Dioxane	17.5	13.7	11.3	0	0
2-Phenoxy Ethanol	17.8	5.7	14.3	0	0
Caprolactone	18.0	15.0	7.4	0	0
Toluene	18.0	1.4	2.0	0	0
Trichloroethylene	18.0	3.1	5.3	0	0
Dimethyl Sulfoxide	18.4	16.4	10.2	0	0
Propylene Carbonate	20.0	18.0	4.1	0	0
Ethylene Glycol Sulfite	20.0	15.9	5.1	0	0
Aniline	20.1	5.8	11.2	0	0
1-Chloronaphthalene	20.5	4.9	2.5	0	0
1-Bromonaphthalene	20.6	3.1	4.1	0	0

A score of 0 indicated that the API was insoluble in the solvent, while a score of 1 meant the API was soluble. For the software to calculate the polarity, dispersion forces, and hydrogen bonding values, the API needed at least 3 "hits," meaning the solvent had to be miscible with the API.

Table 8. Hansen GRAS Library Screening for Nintedanib

Solvents	D	P	H	RED
Benzoic Acid	20	6.9	10.8	0.57
Caffeine	19.5	10.1	13	0.83
Vitamin D3 (Cholecalciferol)	20	3	9	0.83
Nutmeg And Mace	19.4	10	5.4	0.87
Niacinamide (Nicotinamide)	18.9	11.3	10	0.9
Clove Oil (As Eugenol)	19	7.5	13	0.9
Vitamin D2 (Ergocalciferol)	20	3	5	0.99
Niacin (Nicotinic Acid)	18.9	11.5	12.5	0.99
Glycocholic Acid	18.2	6.2	11.8	1.05
Taurocholic Acid	18.3	4.6	10.8	1.06
Cholic Acid	18.3	4.6	10.8	1.06
Benzyl Alcohol	18.4	6.3	13.7	1.09
Desoxycholic Acid	18.4	3.6	10	1.09
Glycyrrhiza	18	12	12	1.18
Propyl Paraben	17.7	7	12.8	1.19
Vitamin A Acetate	18.1	3.3	7.6	1.19
Methyl Paraben	18.4	9.2	15.4	1.2

Solvents	D	P	H	RED
Butylated Hydroxyanisole (Bha)	17.6	4.8	7.9	1.21
Thiodipropionic Acid	17.4	7.4	11.9	1.22
Vitamin A	17.5	4	9.1	1.26
Vitamin A Palmitate	17.8	4.5	5.6	1.26
Stearyl Citrate	17.3	5	11.4	1.29
Ascorbyl Palmitate (Palmitoyl L-Ascorbic)	17	9.1	11.1	1.3
Vitamin B12	17	9.3	11.5	1.31
α-Tocopherols	17.8	1.9	8.3	1.33

Sampling of a few GRAS excipients and corresponding RED scores for Nintedanib.

Table 9. Selected Solvents and Solubility Screening

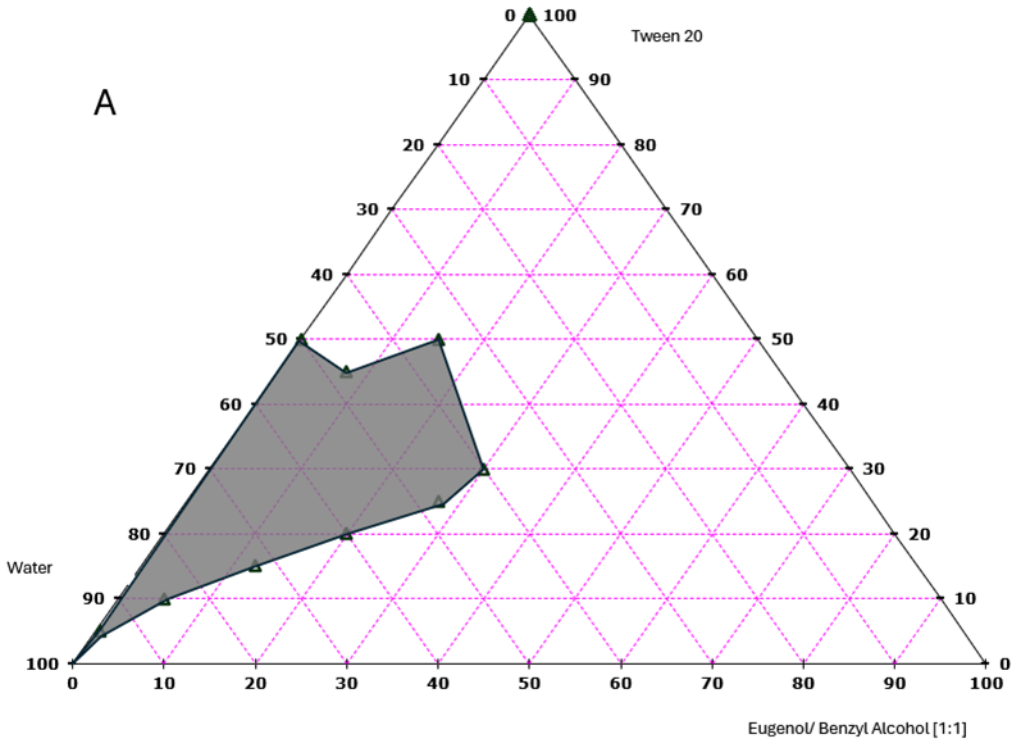
Solvents	D	P	H	RED	Score w/150 µL	Score w/450 µL
Vanillin Acetate	19.2	9.1	10.8	0.76	0	0
Benzyl Alcohol	18.4	6.3	13.7	1.09	1	1
Benzyl Salicylate	19.1	7.3	10.4	0.77	0	0

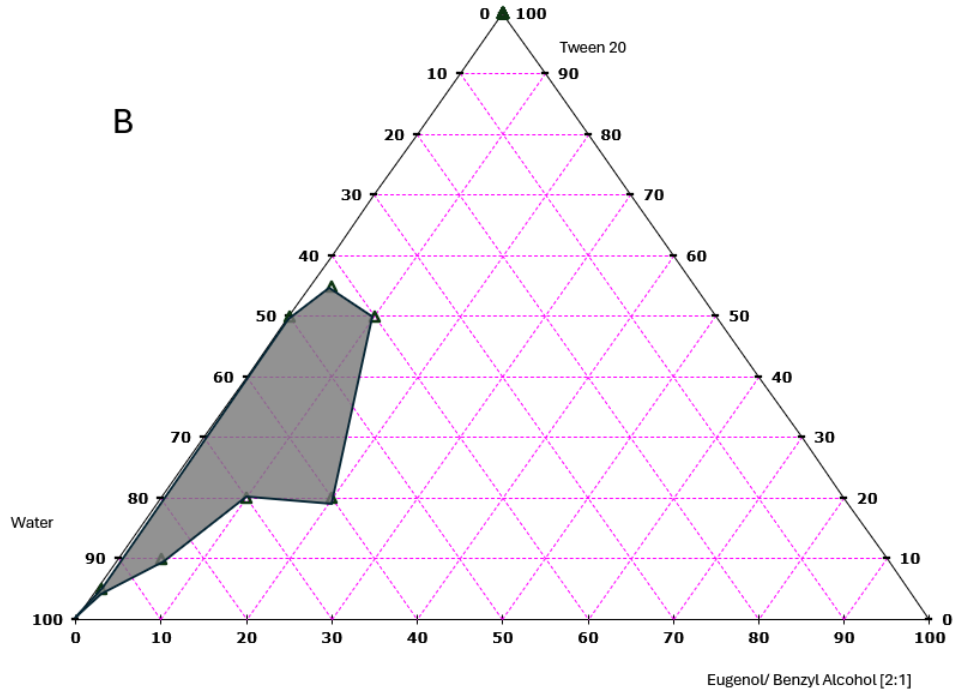
Solvents	D	P	H	RED	Score w/150 µL	Score w/450 µL
Benzoyl Peroxide	20	8.6	4.6	0.8	0	0
Ethyl Vanillin	19.1	10.5	10.9	0.83	0	0
Eugenol	19	7.5	13	0.9	0	1
Cinnamyl Alcohol	19.1	6	13	0.91	1	1

Although some RED values were below 1, suggesting that Nintedanib would be soluble in those agents, experimental results did not always confirm this. Conversely, Benzyl Alcohol had a RED of 1.09, indicating poor solubility, yet Nintedanib was found to be soluble in it.

Appendix 2.

Supplemental Figures

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Tween 20
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Eugenol/ Benzyl Alcohol [2:1]
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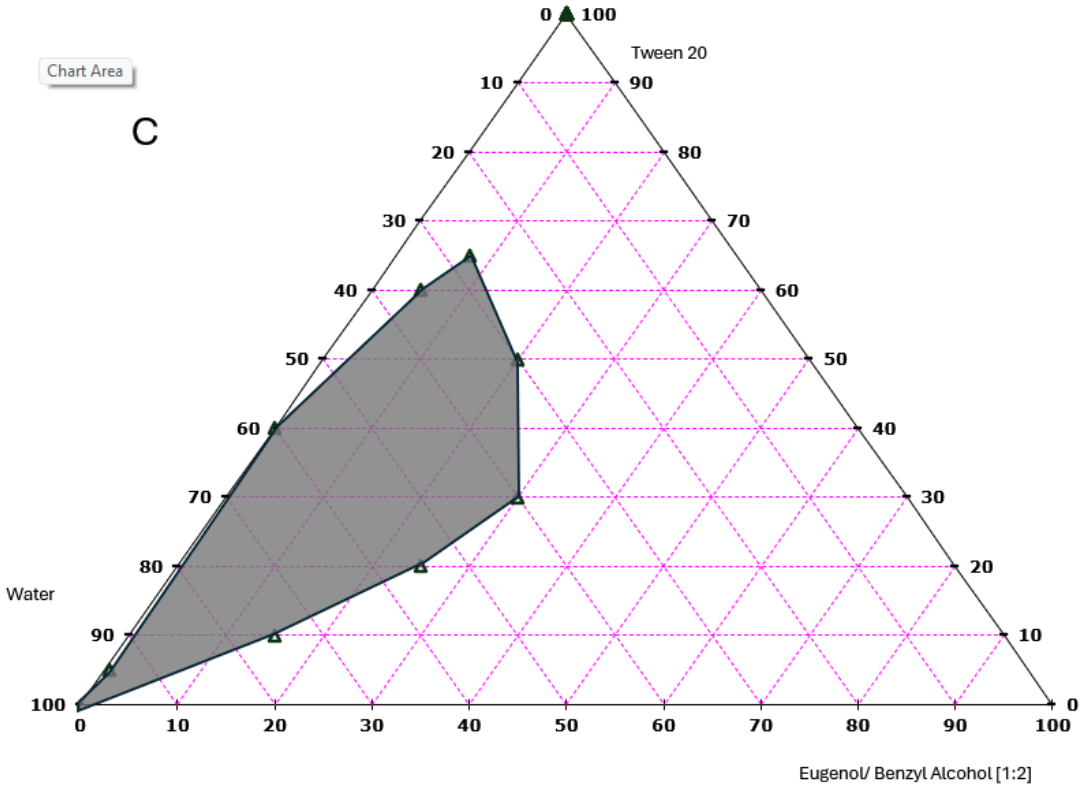
Chart Area
C
Tween 20
Water
Eugenol/ Benzyl Alcohol [1:2]
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20 80
30 70
40 60
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70 30
80 20
90 10
100 0
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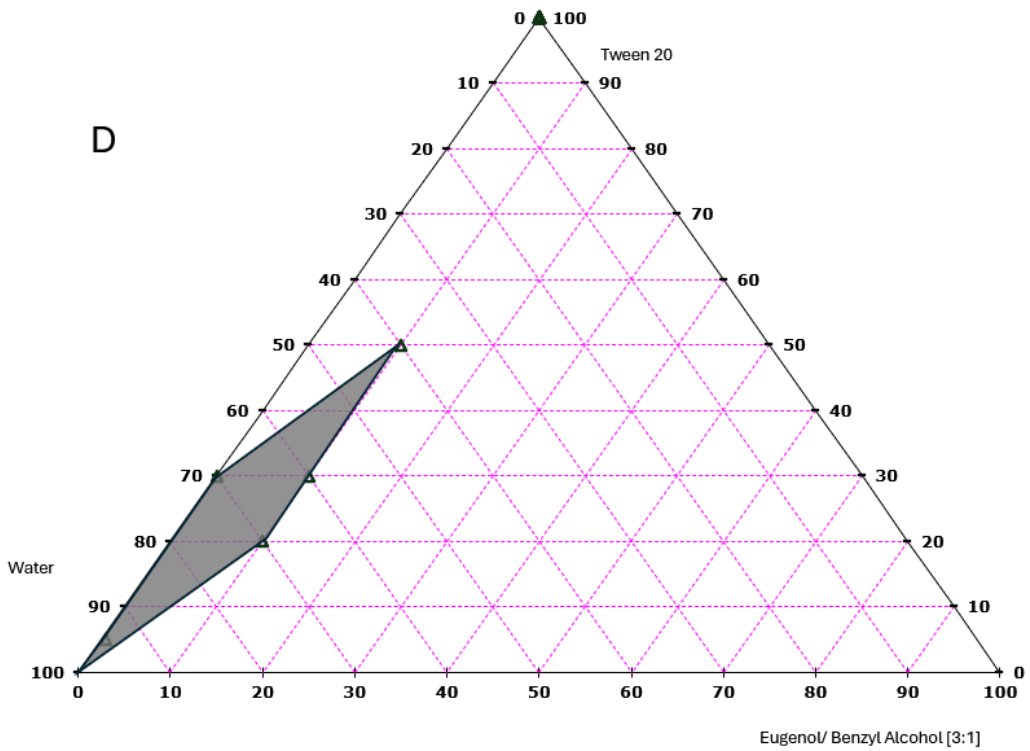
D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Eugenol/ Benzyl Alcohol [3:1]
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100

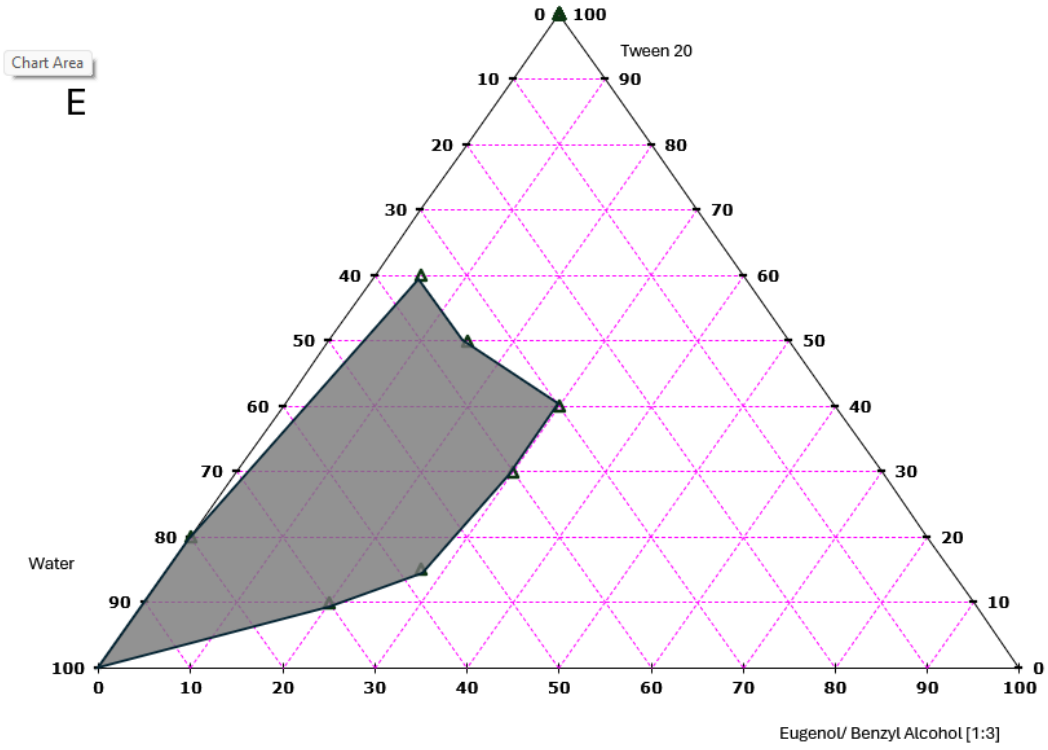

Figure 2. (A-E) Pseudoternary Diagrams

The shaded regions for Figures 1C and 1E visually seem similar. These shaded regions were carefully cut and weighed to determine which oil phase ratio to proceed with.

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