

From Concept to Final Formulation: A Structured Development of Lipid-Based Nanoemulsions for Dry Powder Inhalation

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Summary

Lipid-based excipients (LBEs) provide a versatile platform for pulmonary drug delivery, especially for poorly water-soluble active pharmaceutical ingredients (APIs). Their biocompatibility, solubilizing capacity, and potential for sustained release of API make them ideal for inhalation formulations. This study aimed to develop stable, spray-dried LBE-based dry powders optimized for deep-lung delivery and improved drug loading, while expanding the portfolio of LBEs for pulmonary use. Several lipids (Miglyol® 810N, Imwitor® 742, 308, and 988) and emulsifiers (Tween® 80; HLB 15.0, Gelucire® 48/16; HLB 12) were screened with a poorly water-soluble API. To facilitate spray drying of low melting point lipids, wall materials such as L-leucine and D-mannitol were incorporated into the initial formulation. High-pressure homogenization was used to prepare the aqueous nanoemulsion feed prior to spray drying. Optimization involved screening the API solubility in lipids, nanoemulsion characterization, determining optimal feed ratios for spray drying process, and assessing regulatory compliance. The spray-dried powders were evaluated for yield, particle size, and aerodynamic performance. Results identified Imwitor® 988 as the optimal lipid due to the highest API solubilization (2.87 % w/w). Nanoemulsions of Imwitor® 988 and Tween® 80 were produced with a droplet size of ~200 nm. L-leucine served effectively as a wall material, resulting in a spray-dried powder with narrow particle size distribution, fine particle fraction above 30%, and a yield exceeding 60%. This formulation enhances drug loading and exhibits favourable characteristics for pulmonary delivery, enabling incorporation of poorly soluble drugs into lipid matrices for inhalation therapy.

Key Message

This study showcases the benefits of LBEs for the development of inhalation products. Spray-dried lipid-based powders incorporating Imwitor® 988, Tween® 80, and L-leucine were produced for efficient loading of selected API with poor water solubility. Achieved enhanced drug loading and aerosol performance can improve deep-lung targeting.

Introduction

Dry powder inhalation (DPI) formulations are increasingly recognized as one of the most efficient platforms for pulmonary drug delivery. The main benefits that make DPIs favoured over other forms are improved drug stability and minimal risk of contamination due to their powder-based formulation. As aerosolization is typically driven by the patient's inhalation, DPIs can be compact, cost-effective, and do not require an external power source. Traditional DPI formulations often use carrier particles to improve flowability and dispersion of micronized APIs, but these systems can pose challenges such as potential drug–excipient interactions and poor drug dispersion in the case of strong inter-particulate forces between API and carrier. Carrier-free DPI formulations are increasingly explored as a solution, offering advanced formulations with higher drug loading capacity, enhanced targeting of the deep lungs, and suitability for high-dose therapies like inhaled antibiotics. However, the development of carrier-free DPI formulations is limited to the application of a narrow range of approved excipients. Although phospholipids are well accepted by regulatory agencies, and used for the development of cutting-edge platform technologies such as PULMOSPHERE® [1] and ARCUS® [2], the potential of LBEs in inhalation remains largely under-investigated. LBEs offer distinct advantages, including improved solubility of poorly water-soluble drugs, targeted and controlled API release, and reduced toxicity due to their biocompatibility. They showed potential as delivery vehicles for various drugs in the form of DPI formulations, such as antibiotics [3, 4], anticancer drugs, and nucleic acids [5]. Building on our previous work with nano-lipid carriers for both nebulization and DPI applications [6, 7], we now aim to broaden the scope of applied LBEs in our nanoplatform. The aim is to enhance API solubility and loading, thus reducing the dose, and to offer targeted delivery to the deep lung. This platform is combined with spray

drying as the state-of-the-art technology [8] to engineer stable, carrier-free dry powder formulations suitable for pulmonary delivery.

Materials and Methods

Medium-chain triglycerides (Miglyol® 810N) and mono-/diglycerides of caprylic (C8) and capric acid (C10) (Imwitor® 742, 308 and 988) (IOI OLEO GmbH, Germany) were investigated as LBEs, in combination with emulsifiers such as Tween® 80 (HLB 15.0) (Sigma-Aldrich, Austria) and Gelucire® 48/16 (HLB 12) (Gattefosse, France). The selected API was a BCS Class II glucocorticoid with a logP of 3. All other excipients were of analytical grade and purchased from Sigma-Aldrich (Austria). Solubility of API in LBEs and emulsifiers was screened by adding excessive amounts of API to each system, followed by incubation for 48 or 72 hours. Two incubation times were selected to ensure that the equilibrium solubility was reached across the systems with different HLB and polarity. After centrifugation, the concentration of API in the supernatant was quantified using High-Performance Liquid Chromatography (HPLC). The procedure is depicted in Figure 1. HPLC analysis was performed using a mobile phase consisting of 10mM ammonium formate, pH = 3 / Acetonitrile (35:65 v/v) with water/ethanol (35:65 v/v) as diluent. Separation was achieved on a YMC-Triart C18 (2,1x50mm; 1.9 µm) at 30°C, using a flow rate of 0.2 mL/min and detection at 254 nm.

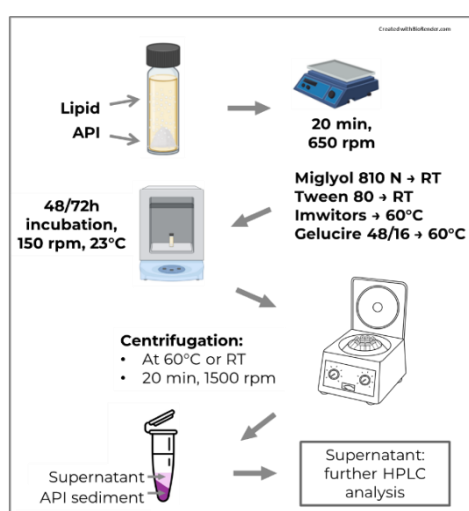


Figure 1 - Method for solubility assessment of API in lipid and emulsifier

Nanoemulsions were prepared through a two-step process involving pre-emulsification with an Ultra-Turrax device (operated at 12,400 rpm or 8,400 rpm for 5 minutes), followed by high-pressure homogenization at 700 ± 50 bar for 5, 10, or 15 cycles. The resulting nanoemulsions were subsequently spray-dried using L-leucine or D-mannitol as wall materials. Wall materials were incorporated at concentrations of 2% or 4% (w/w), while lipids were used at 0.5% or 1% (w/w). Emulsifier concentrations were adjusted to 5% (w/w) relative to the lipid phase. The API was incorporated at 80% of its determined solubility within the lipid matrix. The droplet size and polydispersity index (PDI) of the nanoemulsions were determined using dynamic light scattering. A systematic screening of LBE–emulsifier–wall ratio, and critical processing parameters for nanoemulsion preparation and spray drying was performed. The procedure and parameter-settings for the preparation of nanoemulsions and spray drying are depicted in Figure 2. The particle size distribution of the spray-

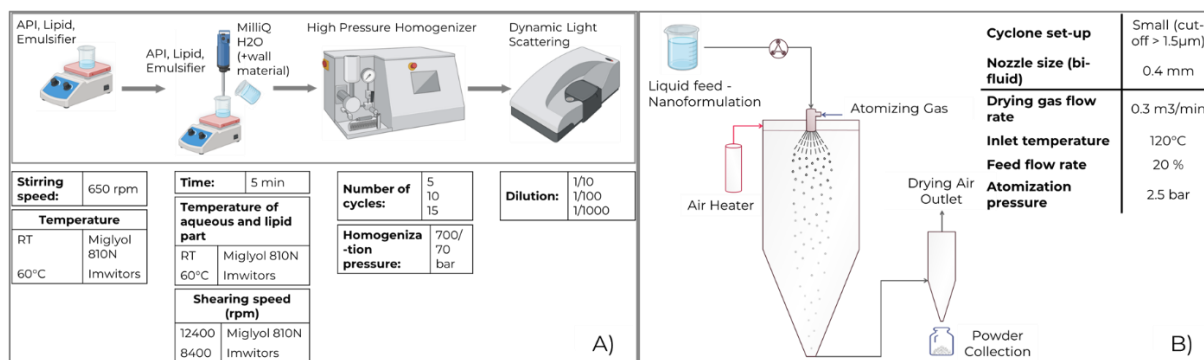


Figure 2 - Screening of process parameters: A) Preparation of nanoemulsions, B) Spray drying process

dried powders was analyzed via laser diffraction under dry dispersion conditions. The mass median aerodynamic diameter (MMAD) of the best spray-dried formulations was investigated using a fast-screening impactor (FSI) and evaluation of drug content per stage with HPLC. The HPLC method was the same described above for the determination of API solubility investigation. XSelect C18 (4.6x250 mm; 2.5 µm) column was used at 35°C, with flow rate of 1.5 mL/min and detection at 254 nm.

Results and Discussion

The primary criterion for lipid selection was its capacity to solubilize the selected API. As shown in Table 1, the initial screening revealed that the API possesses the highest solubility in Imwitor® 988 and the lowest in Miglyol® 810 N. High solubility of API in Imwitor® 988 can be explained due to the composition of this lipid, containing more than 90% of mono- and diacylglycerides, thus providing available hydrogen bonding sites, and its logP of 3.8, being the closest value to the logP of API. Given the substantial solubility of the API in the emulsifiers used, the further processing strategy involved the pre-dissolving of API in the lipid-emulsifier mixture.

Lipid/Emulsifier	API solubility [w/w %]
Miglyol 810 N	0.33
Imwitor 308	2.01
Imwitor 742	2.14
Imwitor 988	2.87
Tween 80	1.48
Gelucire 48	2.39

Table 1 - API solubility in different lipids and emulsifiers

An additional key parameter was the ability of the formulation to form a monodisperse nanoemulsion within the target droplet size range of 100 to 500 nm, which balances physical stability, efficient drying, and preservation of nano-properties in the final powder. Both emulsifiers, when combined with lipids in various ratios, enabled the formation of nanoemulsions within this range. In contrast, emulsions prepared without emulsifier exhibited hydrodynamic diameters exceeding 1000 nm, showing significantly high standard deviations, system heterogeneity, and a highly polydisperse profile, with a PDI greater than 0.30, potentially, due to the unstable system and droplet aggregation (Figure 3**Error! Reference source not found.**).

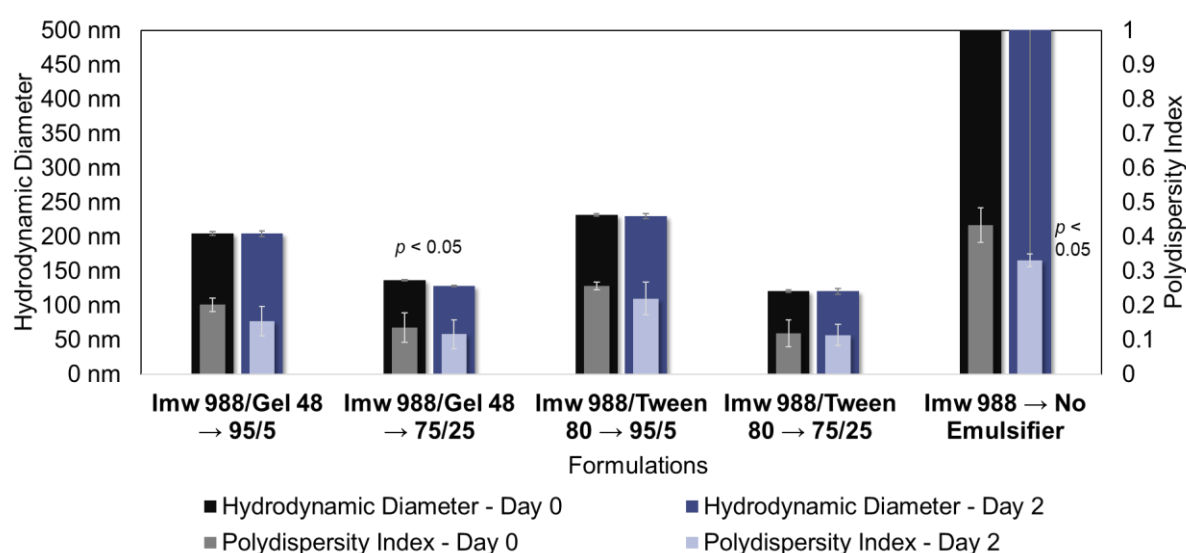


Figure 3 – Hydrodynamic diameter and PDI of nanoemulsions of sole Imwitor® 988 (Imw 988) and in combination with emulsifiers Tween® 80 and Gelucire® 48 (Gel 48). Measurements conducted in triplicates, sample size 1 ml, dilution 1/10

Although Miglyol® 810 N, a medium-chain triglyceride, was capable of forming nanoemulsions with droplet sizes between 150 to 200 nm and PDI values ranging from 0.10 to 0.20 with fewer homogenization cycles at room temperature compared to Imwitors, it was excluded due to its insufficient API solubilization capacity. As Imwitor® 988 showed the most API solubilization capacity (Table 1) as

well as the ability to produce stable nanoemulsions, it was chosen for the formulation development. Tween® 80 was selected as an emulsifier due to its FDA approval for pulmonary formulations in maximum exposure of 1 mg per day [9]. **Error! Reference source not found.** Formulations of Imwitor® 988, Tween® 80 and wall materials were spray dried. Formulations A and B listed in Table 2 with the lipid/emulsifier ratios of 95/5 and 75/25, and L-leucine as wall material achieved yield exceeding 60%, with corresponding $D_{90.3}$ values of 11.71 μm and 5.12 μm , respectively. The aerodynamic performance of both formulations A and B were tested with FSI by examination of 3 capsules per actuation. Each capsule was filled with 30 mg of dry powder formulations. The exhibited emitted fractions were above 90%. Fine particle fractions were calculated based on the emitted dose and presented in Table 2. These results indicate the efficient aerosolization and suitable particle size distribution of both formulations for inhalation delivery.

Spray-dried powder composition	Imwitor 988 (%w/w)	Tween 80 (%w/w)	API (%w/w)	L-leucine (%w/w)	Emitted fraction %	Fine particle fraction %
A	19.0	1.0	0.46	79.54	94.79 $\pm$ 0.49	34.70 $\pm$ 1.48
B	15.0	5.0	0.46	79.54	92.19 $\pm$ 0.28	46.58 $\pm$ 4.36

Table 2 - Composition and FSI performance of spray-dried powder with the best performance. Lipid/Emulsifier ratios in formulations A and B are 95/5 and 75/25.

Conclusion and Next Steps

Nanoemulsions were successfully spray-dried through careful optimization of formulation and process parameters, resulting in particle size distributions suitable for pulmonary drug delivery. A systematic evaluation of API solubility in various lipid matrices enabled enhanced drug loading capacity. Future work will focus on a comprehensive evaluation of further improvement of API solubility, solid-state of API in spray-dried powder, encapsulation efficiency, and API release from spray-dried matrix, as well as DPI performance, including screening the MMAD via the next generation impactor (NGI) and flowability. *In vitro* permeability and toxicity studies will be conducted to evaluate the safety of both excipients and the final product. While this study does not provide any direct pharmacokinetic data, current results on the improved solubility and planned *in vitro* studies provide a foundation for future direct evaluation. This work paves the way for the expansion of the LBE portfolio for pulmonary applications.

Acknowledgement

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