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Monodisperse Particles from Single Emulsions with Microfluidic Device

Edgar Barrera
Facultad de Farmacia,
Universidad Autónoma del Estado de Morelos,
Cuernavaca, Morelos, México

Carlos Martinez
School of Materials Engineering,
Purdue University, West Lafayette, Indiana, USA

Efrén Hernandez-Baltazar
Facultad de Farmacia,
Universidad Autónoma del Estado de Morelos,
Cuernavaca, Morelos, México

ABSTRACT

The goal of this study was to develop a microfluidic device, establish the optimal conditions, and adapt an antisolvent technique into microfluidic microcapillary device to produce API microparticles with uniform particle size, generated from monodisperse single emulsions, using griseofulvin as the model compound. Griseofulvin monodispersed crystals were produced using a microfluidic microcapillary device. Three different fluids mixtures were used to both create an antisolvent environment and generate monodisperse drops within the microcapillary device. Single emulsion generation was visualized using an inverted microscope equipped with a high-speed camera. Finally, the griseofulvin crystals were collected, and their particle size was measured through microscopy image analysis. An antisolvent technique was adapted into the microfluidic capillary device. The inner, middle, and outer fluids consisted of 7% griseofulvin, SDS in ultrapure water, and polysorbate 80 in ultrapure water, respectively. The optimal flow conditions were determined to generate monodisperse single emulsion drops, resulting in griseofulvin microcrystals with an average particle size of 11 µm. A novel microcapillary device process was developed, applying an antisolvent technique to generate monodisperse griseofulvin crystals starting from monodisperse single emulsions. Established the constituents and flow rates of each fluid, allowing for complete control of the system. *Single emulsions of GF in triacetin were produced with an average diameter of 75.2 ± 2.9 µm.* Finally, monodispersed griseofulvin crystals with a mean particle size of 11.60 ± 3.64 µm were obtained. Microfluidic method is excellent to obtain monodisperse particles for inhalation process and pulmonary delivery, because the span is better than the other material in the market. Microfluidic method developed is excellent to produce crystals with improved specific surface area and probably with better bioavailability.

Keywords: monodisperse crystal, microcrystal, microfluidic device.

INTRODUCTION

Griseofulvin (GF) is an antifungal, hydrophobic active pharmaceutical ingredient (API) with poor aqueous solubility, classified by the British Pharmacopeia as practically insoluble in water [1,2]. According to the Biopharmaceutical Classification System (BCS), GF belongs to Class II of drugs, which are characterized by poor solubility and high permeability [3]. Several strategies have been implemented to improve GF bioavailability by enhancing its solubility and dissolution rate. For example, the GF dissolution rate can be enhanced through micronization, complexation with cyclodextrin, preparation of griseofulvin nanoparticles from water-dilutable microemulsions, and the preparation of GF nanosuspensions from triacetin-in-water emulsions [4]. It is reported to have very low solubility (15 μg/mL at 37°C) in water. Additionally, the bioavailability of GF was reportedly improved as the specific surface area of the particles increased [5]. Drug molecules with limited aqueous solubility, like GF, pose a challenge due to their slow dissolution, which translates into inconsistent systemic exposure and consequent sub-optimal efficacy in patients [6]. Despite recent progress, a real breakthrough in increasing the solubility of sparingly soluble drugs has not yet been achieved [7].

Reducing drug particle sizes has emerged as an effective and versatile approach to improving drug solubility. Spray freezing into liquid and supercritical antisolvent precipitation have been recently developed. However, these methods require complex operating conditions and incur high production costs, including high pressure and extremely low temperatures [8]. Current approaches for nanoparticle production fall into two major categories: particle size reduction through micronization and direct particle formation.

Micronization is typically achieved through wet milling or high-pressure homogenization. However, these techniques may have several shortcomings, including difficulty in reducing the size below certain limits for some active pharmaceutical ingredients (APIs), potential contamination with grinding media, and adverse effects of high shear and temperatures on the chemical and physical stability of the materials [9]. When milling crystalline APIs, the mechanical stresses inherent in the process produce microstructural changes in the crystal. Specifically, milling induces defects in the crystal lattice of the API, which in turn alter the physical and chemical properties of crystalline pharmaceutical solids [10].

Precipitation processes from solution are widely used in the pharmaceutical industry to manufacture particulate products in the micron and submicron size range [11]. This technique can offer significant advantages in terms of solid-state control compared to traditional milling methods. In the past decade, several methods involving antisolvent crystallization have been proposed. In all of these cases, the crystallization process requires the use of organic solvents for the crystallization of water-insoluble drugs and often involves various mixing technologies or crystal growth inhibitors. The solvent used in the crystallization process can affect both the nucleation and growth phases. Therefore, the selection of solvents in API crystallization can influence the polymorphic form and crystal habit of the final product. Solvents with different polarities strongly affect the crystalline habit, and specific interactions, such as hydrogen bonding, can also impact crystal growth [12].

Precipitation with an antisolvent is a method for precipitating and/or crystallizing solutes dissolved in liquid solvents [13]. Modification of solid-state characteristics, such as crystal habit, crystallinity, and polymorphism, has been successfully achieved through the recrystallization of drug particles using various antisolvent precipitation processes [14].

The API in organic solution may be mixed with an aqueous antisolvent solution in the presence of stabilizing surfactants to form sub-micrometer particles. The hydrophobic portion of an amphiphilic surfactant may be adsorbed onto the precipitating hydrophobic drug surface, while the hydrophilic portion provides steric and/or electrostatic stabilization in the aqueous medium. To control growth, the surfactant must diffuse to and readily adsorb onto the drug surface [15]. The surfactant monolayer formed around the droplets facilitates the emulsification process, minimizes coalescence, and often affects the overall characteristics of the emulsion. Surfactant adsorption at the interface leads to reduced surface tension, and the surfactant molecules act as a barrier, delaying droplet coalescence through electrostatic and/or steric repulsion [16]. Several surfactants have been used to solubilize insoluble substances; some are highly effective but also toxic, limiting their use. An ideal surfactant is compatible with cellular metabolism and can be easily eliminated by the organism [17].

In this research, we introduce a microfluidic microcapillary device (MMD) to obtain monodispersed microcrystals of an API, using GF as the model compound. This MMD has been used to encapsulate cells in alginate hydrogels and consists of cylindrical glass capillary tubes nested within a square glass tube [18], as shown in Fig. 1a, which illustrates the microfluidic microcapillary device, and Fig. 1b, which shows the region where the emulsion exits.

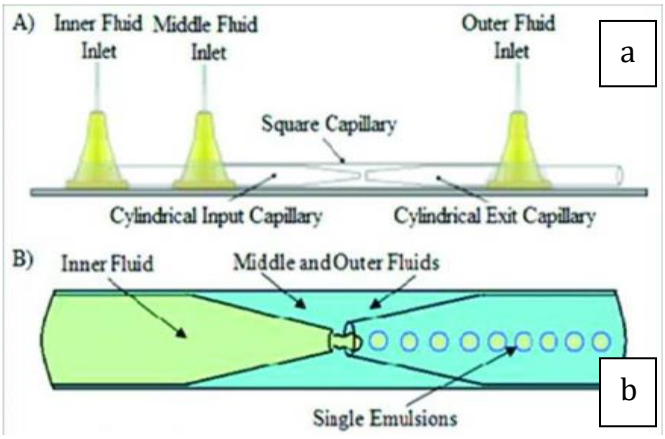

Fig 1: Schematic illustrations of the (a) microfluidic microcapillary device and (b) the region of the device where the input and exit capillaries meet.

MATERIALS AND METHODS

Chemicals and Reagents

Micronized griseofulvin, triacetin 98.5%, polysorbate 80 and sodium dodecyl sulfate were all purchased from Sigma-Aldrich. Ultra-pure water with 18-18.3 Ohms was used in throughout the study and was obtained from the department of Materials Science at Purdue University.

Manufacture of Microfluidic Microcapillary Device (MMD)

The MMD device was fabricated using a pipette puller (Model P-97, Sutter Instruments, Novato, CA) to heat and pull a cylindrical glass capillary (World Precision Instruments, Sarasota, FL) with an outer diameter of 1.0 mm and an inner diameter of 0.580 mm. Heating and liquefying the glass allowed the capillary tube to be easily stretched and broken into two tapered tubes. The tip diameter of the tapered capillaries was then adjusted by breaking the glass to the desired size using a micro-forge station (Micro Forge MF830, Narishige, Japan). The round capillaries were subsequently inserted and aligned within a square capillary. Ensuring that the outer diameter of the round tubes matched the inner dimension of the square tube provided proper alignment, forming a coaxial geometry [18] (see Fig. 2).

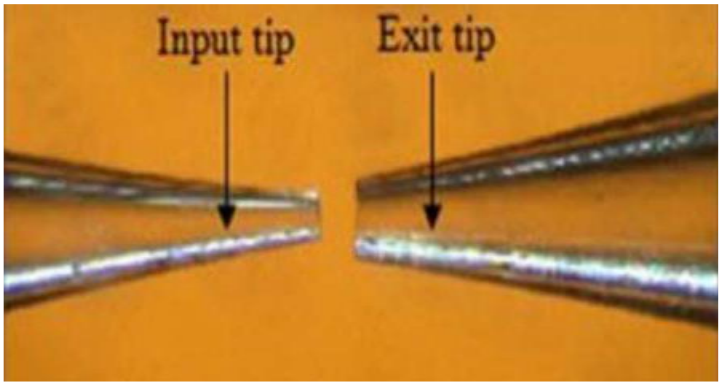

Fig 2: Round capillaries inserted and aligned within a square capillary.

Three 20-gauge Luer-stubs (Intramedic Luer Stub Adapters, Becton Dickinson, Sparks, MD) served as inlets for the fluids. To form the emulsions, the inner, middle, and outer fluids were loaded into glass syringes (Hamilton Gastight, Hamilton Co., Reno, NV) fitted with 20-gauge Luer-stubs. The inner fluid was a saturated griseofulvin solution (7 mg/mL). The middle fluid consisted of SDS surfactant (0.27 mM) in water, while the outer fluid was polysorbate 80 (0.12 mM) dissolved in ultrapure water. The syringes were connected to the Luer-stub inlets using polyethylene tubing with an outer diameter of 1.32 mm and an inner diameter of 0.86 mm. Syringe pumps (PHD2000, Harvard Apparatus, Holliston, MA) controlled the flow rates.

The innermost fluid was pumped through a tapered cylindrical capillary tube, while the middle fluid flowed through the outer coaxial region, forming a coaxial flow at the exit of the tapered tube. The outermost fluid was introduced from the opposite direction, forcing all fluids through the exit orifice formed by the remaining inner tube. This configuration resulted in the hydrodynamic focusing of the coaxial flow. As the flow passed through the exit orifice, it ruptured to form single emulsions, producing droplets of uniform and controllable size [19] (see Fig. 1b).

Flow Constituents and Flow Rate Establishment

First, a placebo was used to observe the formation of monodisperse emulsions produced by the MMD setup. The inner fluid consisted of griseofulvin (GF) dissolved in triacetin, while a mixture of polysorbate 80 and SDS surfactants in deionized water (DI-H_2O) served as the middle and outer fluids, respectively, creating an antisolvent system. The three fluid flow rates were adjusted to ensure continuous, coalescence-free generation of monodisperse single-emulsion droplets. Three MMD devices with different capillary diameters were fabricated to optimize

and visualize droplet generation, and the most effective design was selected for subsequent experiments.

Particle Size Analysis

Particle size distribution was measured using microscopy image analysis. For each production batch, sequential images of crystal formation were captured and recorded using an inverted microscope equipped with a high-speed camera (Phantom V9, Vision Research, Wayne, NJ). Image processing was then performed using ImageJ software.

RESULTS AND DISCUSION

Manufacture of Microfluidic Microcapillary Device

In this microfluidic device, the input and exit capillaries have diameters of 40 μm and 80 μm, respectively. The capillary sizes are among the most critical parameters in the microfluidic device setup. The input tubes were connected to the pipette pullers, and a collection tube was added. Previous studies on microfluidic geometries have shown that the input and exit capillary tip sizes significantly affect the size of the emulsions produced. Larger capillary diameters result in larger droplet diameters [20].

Flow Constituents and Flow Rate Results.

Extensive research on microfluidic techniques for producing highly uniform droplets in two-step processes has been published [20]. In this study, droplet production was achieved in a single step by combining three fluids, offering the advantage of producing highly uniform droplets through tighter process control.

To achieve stable emulsion production, flow rates of 8000, 1000, and 300 μL/hr were used for the three fluid streams, respectively, resulting in monodisperse emulsions with controlled formation rates under placebo conditions. However, droplet coalescence was observed, as illustrated in Fig. 3, due to significant size differences between the droplets. To prevent coalescence, SDS and polysorbate surfactants were used [21].

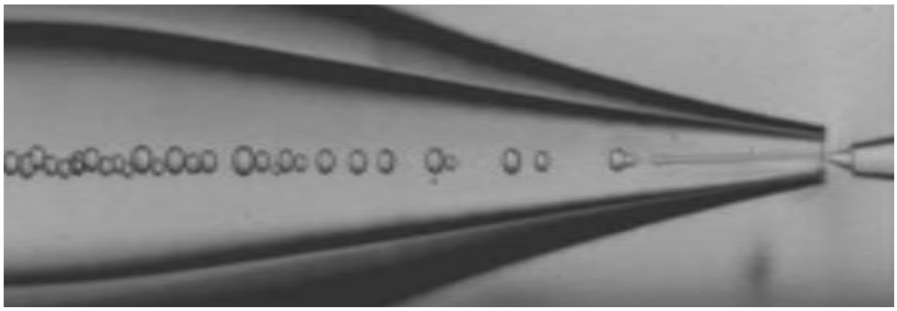

Fig 3: Emulsions coalescence observed in the MMD production.

The necessary amount of surfactant was calculated based on the reported SDS molecular interfacial area of 50 $Å^2$/molecule [16, 22]. For a triacetin spherical droplet with a diameter of 70 μm, a surface area of 15,393.8 μm^2, and a volume of 179,594.4 μm^3 (equivalent to 1.9×10^{-7} mL), approximately 3.1×10^{10} SDS molecules are required to cover a single droplet. Using Avogadro's number, the optimal SDS concentration was determined to be 1.4×10^{-4} M. Since the preferential partitioning of SDS to the interface increases linearly with the total surfactant

concentration [23], this process minimizes the concentration of free SDS in the bulk aqueous phase. Two alternative pathways have been reported for oil solubilization into droplets: molecular and drop-mediated. In the molecular pathway, oil molecules must individually diffuse away from the oil/water interface before being taken up by surfactant molecules. In the drop-mediated pathway, oil molecules are directly detached from the interface by surfactant molecules [24]. Production of uniform droplet emulsions: In this study, surfactant was included in all three fluid phases. However, for the inner fluid, neither of the proposed pathways for oil solubilization into droplets could occur. This was due to the presence of surfactant in the inner fluid, which prevented oil diffusion through the triacetin/water interface.

The second pathway could not be developed either, as surfactant molecules were unable to detach directly from the oil/water interface. This was due to the lack of an established interface when the surfactant was dissolved in the inner fluid. As a result, droplet coalescence occurred, leading to polydisperse emulsions, as seen in Fig. 3.

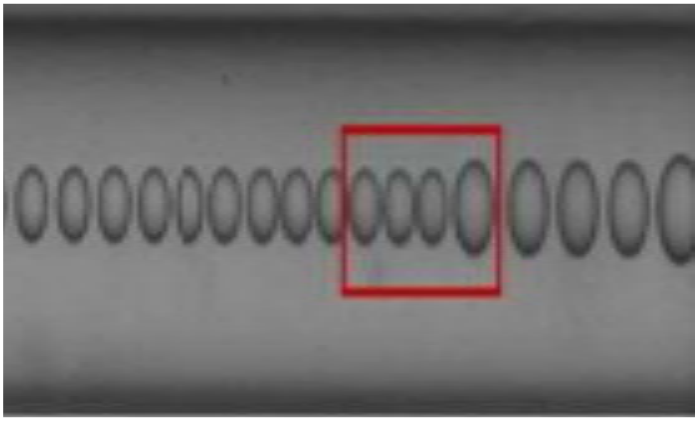

Fig 4: Production of uniform drop emulsions when a surfactant it is added in inner fluid.

Conversely, when a surfactant was used in the middle and outer fluids, a stable droplet production was achieved, as shown in Fig. 4. Depending on the dimensions of the microfluidic capillary device, the applied flow rate, and the flow composition, it is possible to produce single-file monodisperse emulsions of a specific and controllable size. This is demonstrated in Fig. 5, where three different sizes of single emulsions are shown. To achieve this, three different devices were designed, utilizing the new surfactant system and a saturated griseofulvin (GF) solution in triacetin (Table I).

Table I: Assays using surfactant in middle and outer fluid and GF in inner fluid.

Flow rate (ml/hr) and Device Dimensions (mm)	**Assay 1**	**Assay 2**	**Assay 3**
Input Capillary Tip *	40	60	80
Exit Capillary Tip *	100	120	140
Outer Fluid	80	150	200
Middle Fluid	9000	13000	15000
Inner Fluid	7000	12000	14000
Diameter of Droplet Produced (mm)	50	70	80

* See the figure 5 to view the combination of capillaries radios.

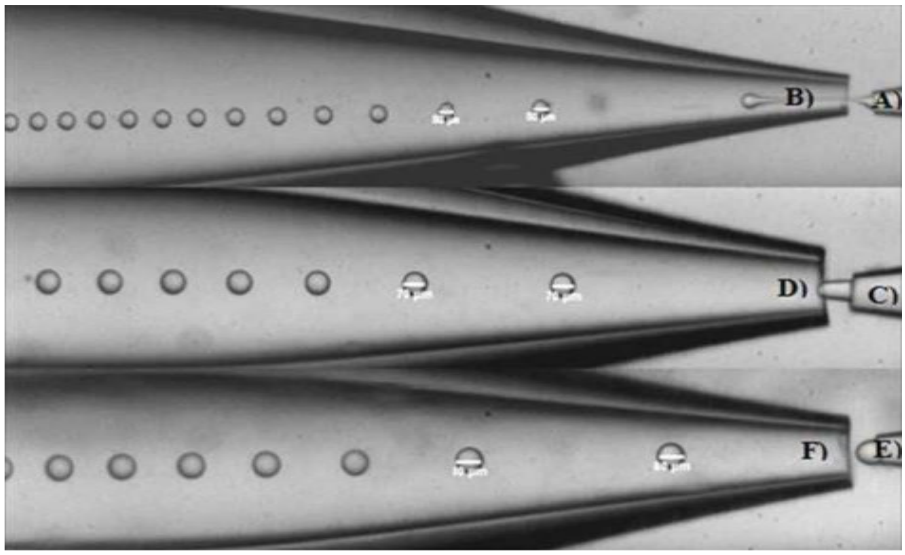

Fig 5: Production in the MMD using SDS surfactant and GF in inner flow, showing different sizes of single emulsions. Diameter of the capillaries in mm A) 40 B) 100, C) 60, D) 120, E) 80 and F) 140.

The **Assay 2** configuration was selected as the optimal MMD setup for microcrystal production. The chosen flow rates were **150, 12,000, and 13,000 µL/hr** for the inner, middle, and outer fluids, respectively, resulting in single emulsions with a **diameter of 70 µm**. Under these conditions, the system produced GF microcrystals with an average particle size of approximately **10 µm**, as shown in Fig. 6a.

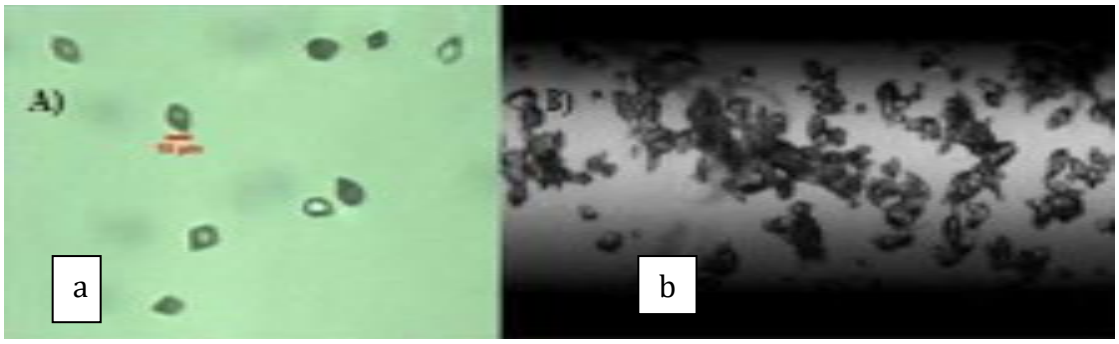

Fig 6: Optical microscopy images of monodispersed GF crystals. A) 20X, B) crystals of drug precipitates in the collection vial.

During droplet generation, a solid deposit was observed adhering to the internal wall of the device (Fig. 6b). This deposit interfered with the free flow of emulsion droplets and, consequently, the production of individual microcrystals. To address this issue, Polysorbate 80 was introduced. It has been reported that combinations of surfactants, particularly ionic and non-ionic, can effectively increase the stability of the emulsion region [25]. Therefore, a combination of SDS and Polysorbate 80 was used, resulting in a system with monodisperse and well-controlled droplet production. The adjusted flow rate conditions were **12,000, 13,000, and 150 µL/hr** for the three fluid phases.

Controlling Satellite Droplet Formation

Under certain conditions, **satellite droplets** (secondary droplets forming around the main droplets) were observed, as shown in Fig. 7a. This issue was mitigated by adjusting the flow rate. Emulsion formation occurs via two mechanisms: **dripping** and **jetting**.

- **Dripping** occurs when droplets are generated near the entrance of the collection tube, within a single orifice diameter, similar to a dripping faucet. This method typically produces highly monodisperse droplets.
- **Jetting** occurs when a long liquid jet extends three or more orifice diameters downstream into the collection tube before breaking into droplets. The jetting regime is generally irregular, leading to polydisperse droplets with radii significantly larger than the jet diameter [19].

By fine-tuning the flow rate, the **jet length was reduced**, promoting droplet formation via **dripping** rather than jetting, as illustrated in Fig. 7b. Working under these optimized conditions, we successfully obtained monodisperse griseofulvin crystals.

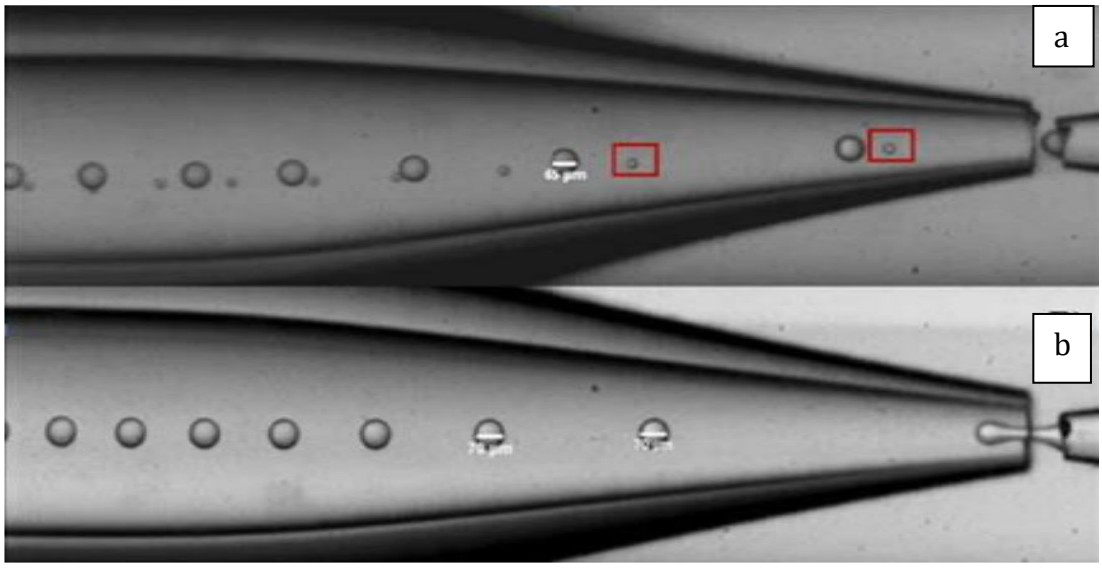

Fig 7: System using a surfactant combination. A) Small satellites remaining of emulsion production. B) Short jet produced allowing monodisperse emulsion production.

Particle Size Results

The particle size distribution of the produced emulsions was initially analyzed using ImageJ software. The average emulsion diameter was determined by analyzing recorded video frames of production batches. Five different videos were analyzed, and from each video, 10 droplets were selected for measurement. Table II summarizes the diameter size analysis performed on 50 emulsions. Following the emulsion diameter analysis, the particle size distribution of griseofulvin (GF) microcrystals was evaluated. Images of GF crystals were analyzed for each batch over a five-day period to conduct a statistical assessment. A total of 291 particles, distributed across five images, were scanned and measured. The results, shown in Table III, indicate a mean particle size of 11.66 µm.

These findings suggest that producing single emulsions of GF in triacetin within the MMD, with an emulsion diameter of approximately 70 µm, results in highly monodisperse GF crystals with an average final particle size of around 12 µm. Since triacetin is a solvent that is partially soluble in water, only water was used in the MMD to create an antisolvent system. The resulting supersaturation and molecular aggregation of GF led to the formation of a crystalline phase [26].

Table II: Emulsions Size Results (mm).

Droplets	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Average	76.08	74.10	71.28	75.11	79.17
Total Emulsions = 50		Mean = 75.15		SD= 2.87	

Table III: Griseofulvin Crystals Size Results (mm).

Samples	Day 1	Day 2	Day 3	Day 4	Day 5
Average	**11.23**	**10.94**	**11.87**	**12.83**	**11.10**
Total Crystals = 291		Mean = 11.67		SD = 3.64	

The complete analysis of GF monodisperse crystals obtained state a narrow distribution of particle size, as shown in Fig. 8.

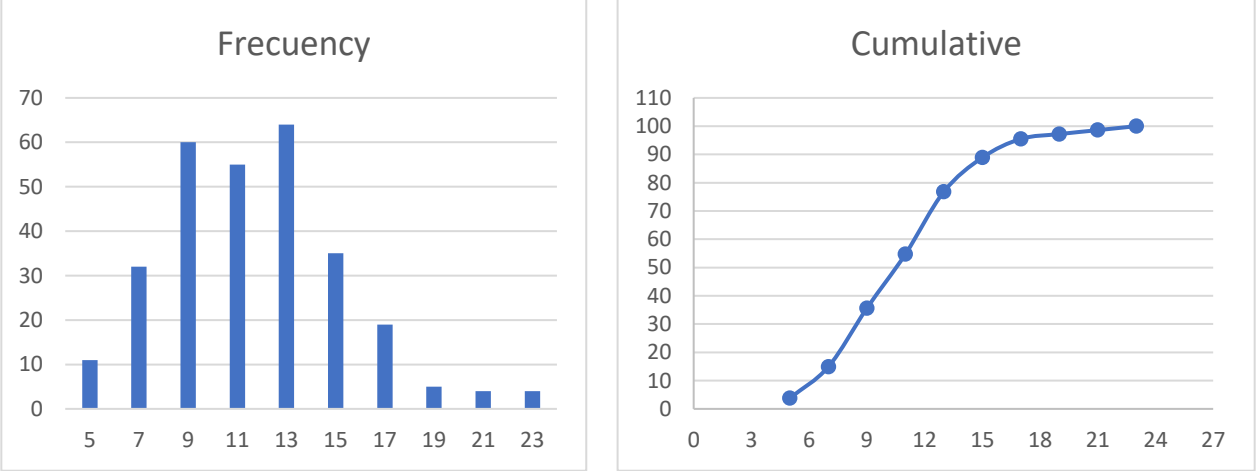

Fig 8: GF crystals obtained showing a narrow distribution. 8a Histogram and 8b Cumulative distribution

Comparison with excipients for inhalation an pulmonary delivery. In table IV show the particle size and densities of some inhalation excipients with their Carr Index, process and Span.

Table IV: Comparison of particle properties [27, 28].

Name	D10	D50	D90	Bulk density mg/ml	Tapped density mg/ml	Carr Index	Span	Process
Meggle Pharma								
InhaLac 300	2	14	40	430	720	40	2.71	Milled
InhaLac 400	1	8	28	330	530	38	3.38	Milled
InhaLac 500	0	3	8	240	370	35	2.67	Milled
InhaLac 251	11	49	91	640	880	27	1.63	Sieved

InhaLac 240	31	65	101	700	880	20	1.08	Sieved
InhaLac 230	45	97	144	700	850	18	1.02	Sieved
FlowLac 100	48	126	220	590	710	16.9	1.37	Spray-dried
FlowLac 90	63	133	211	560	670	16.42	1.11	Spray-dried
Tablettose 100	35	125	297	580	720	19.44	2.10	Granulated
Tablettose 80	35	145	377	620	770	19.48	2.36	Granulated
Tablettose 70	86	191	331	530	640	17.19	1.28	Granulated
DFE Pharma								
Pharmatose 350M	4	30	80	364	542	32.8	2.53	Milled
Respitose ML001	4.7	48	147	570	880	-25	2.96	Milled
Respitose ML003	27	38	112	560	850	-25	2.24	Milled
Respitose SV003	31	61	95	630	780	19	1.05	Sieved
Respitose SV010	51	109	178	690	830	17	1.17	Sieved
LactoHale 100	58	132	214	840	960	12	1.18	Sieved
Griseofulvine MF	**6.2**	**10.5**	**15.2**	**ND**	**ND**	**ND**	**0.86**	**Microfluidics**

ND No data (because the GF obtained was a little amount)

The microfluidics process obtained a very good particle size distribution with a lower Span even better than the specialty excipients for inhalation process and pulmonary delivery. Only the excipients obtained by sieving are near in the span value, both the process of sieving is time consuming and need more equipment. Narrower particle size distribution for samples prepared by Microfluidics with respect to particles prepared by conventional methods, this result was the same like a PLGA particles [29]. Actually, the tendency to use Microfluidics device is to use in obtain polymer and co-polymer particles [29, 30], hollow spheres [31].

CONCLUSIONS

A novel technique for producing **monodisperse** griseofulvin (GF) microcrystals was developed by incorporating an **antisolvent method**—using water as the antisolvent—into a **microfluidic microcapillary device (MMD)**. The composition and flow rates of the three inflows were optimized, allowing for complete control over the system to produce highly uniform GF microcrystals.

Starting from a **single-stream emulsion**, the MMD—configured with **40 µm and 80 µm** input and exit capillary tip sizes, respectively—operated at flow rates of **150, 13,000, and 12,000 µL/hr** for the inner, middle, and outer flows, respectively. Under these conditions, single emulsions of GF in triacetin were produced with an average diameter of **75.2 ± 2.9 µm**. Crystallization of GF then proceeded from the resulting emulsion.

To stabilize single emulsion production and prevent coalescence, **two surfactants, SDS and polysorbate 80,** were required. Ultimately, monodisperse GF crystals were successfully obtained using the MMD, with a **mean particle size of 11.7** ± 3.64 **µm**. Microfluidic method is excellent to obtain monodisperse particles for inhalation process and pulmonary delivery, because the span is better than the other material in the market. Microfluidic method developed

is excellent to produce crystals with improved specific surface area and probably with better bioavailability.

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Rodolfo Pinal Department of Industrial and Molecular Pharmaceutics. Purdue University

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