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Sustainable production of drug-loaded particles by membrane emulsification

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Abstract

As the field of drug delivery is expanding into consumer products, it is essential to advance in the development of efficient synthesis technologies while preserving, at the same time, human health and the environment for future generations. Here, the sustainable development of polymeric particles for drug delivery is described. Poly(ethylene glycol) methyl ether-block-poly(lactide-co-glycolide) based particles containing dexamethasone were produced by membrane emulsification-solvent diffusion methods. The ability of the synthesis process to control particle-size distribution and morphology and its green impactful (energy consumption, simple (sEF) and complete (cEF) E factor) were evaluated.

Particles with sufficiently narrow distribution in their droplet size and mean diameter similar to the membrane pore diameter were produced by increasing the dispersed phase flux to 12.84 L $h^{-1}m^{-2}$, minimizing the maximum shear stress to 1.12 Pa and the energy consumption to 3.96 10^5 Jm^{-3}. The impact of the solvent used on size distribution, particles morphology and green performance scores was also studied. More uniform particles, with dense and slightly rough surface, high encapsulation efficiency and drug loading were obtained by replacing Dichloromethane with Ethyl acetate. The E factor was also decreased by 80%.

Results demonstrated that membrane emulsification is an environmentally improved method for the production of drug delivery systems with enormous impact in terms of formulation quality, energy consumption reduction and waste minimization.

Keywords: membrane emulsification, drug-loaded particles, energy consumption, sustainability, PLGA-PEG, Ethyl acetate, dexamethasone

Introduction

Among the new generation of pharmaceutical forms, polymeric particles have gained significant relevance due to their ability to deliver drugs at a controlled rate and toward a specific target [1] . Polymeric particles have been frequently used as drug delivery depots of drugs with low aqueous solubility. Approximately 40% of all new drug candidates in development, and about 70–80% in some therapeutic areas, are poorly absorbed orally, principally due to their low aqueous solubility. As the field of drug delivery is expanding into consumer products, it is essential to advance in the development of efficient synthesis technologies while preserving, at the same time, human health and the environment for future generations. The design of highly efficient particulate systems with high yield, minimizing solvent and energy consumption and with a reduced waste production is a significant challenge in particle engineering technologies. [2–4] Producers are making a big effort to create the basis to regulate process manufacturing procedures to reach high quality products, with high productivity and to fulfill also the requirements of the pharmacopeia [5,6].

Biodegradability or biocompatibility is an essential requirement for the polymer used for pharmaceutical applications [7]. Several drug delivery systems based on poly (D,L-lactide-co-glycolide) (PLGA) family are approved by the FDA and their ability to modulate drug release are strictly connected with the relative amount of lactic (PLA) and glycolic acids (PGA) [8,9]. The modification of PLGA with an hydrophilic and inert polymer like PEG (poly ethylene glycol) prolongs the circulation of the particles in the body and decreases the premature drug release increasing their therapeutic effect [10]. Dexamethasone (DEX) is currently used in many biomedical applications such as: cell culture, ophthalmology, proliferative vitreoretinopathy, subretinal neovascularization, arthritis and diabetic macular edema as anti-inflammatory and immunosuppressant drug [11]. The main limitations of this drug for pharmaceutical applications are its high hydrophobicity and high doses necessary to reach its therapeutic level [11,12]. Consequently,

various delivery systems have been developed and the majority of them are based on its encapsulation within both natural and synthetic polymers [11,13–15].

Microencapsulation by solvent evaporation is a widely applied technique for entrapping insoluble or poorly water-soluble drugs. Different aspects have to be taken into account to choose the most appropriate solvent for the preparation of polymeric particles by this technique: 1) the ability to dissolve the polymer 2) a reduced solubility in the continuous phase 3) high volatility 4) low toxicity [7]. Solvents used during polymer particle synthesis are often volatile organic compounds and their use is associated to some concerns about their potential environmental impact (some of them are able to form low-level ozone and smog through free radical air oxidation processes), their adverse health effects (ranging from carcinogenic properties to headaches and allergic skin reactions, eye irritations) and their hazardous properties (they are often highly flammable)[16]. Dichloromethane (DMC) is one of the most used solvents for the production of polymeric particles via emulsification and subsequent solvent-evaporation due to its high volatility, low boiling point and high immiscibility with water [7]. Ethyl acetate (EA) has been proven to be a potential substitute of DCM with less toxicity [7,17–20]. It has been classified as “recommended” considering the safety, health and environmental scores while DCM is considered “problematic” or “hazardous” [21,22].

Microengineered technologies are emerging as promising particle fabrication methods for their ability to generate droplets individually by injecting the dispersed phase in the continuous phase through a single (i.e., microfluidic device) or a multitude of channel/pores (i.e., membranes) [23,24]. These techniques allow the production of uniformly sized droplets with tuned sizes and improved encapsulation efficiency [25–28]. Polymeric particles can be obtained by combining membrane emulsification with additional physical (i.e., evaporation/solvent diffusion) or chemical (cross-linking, coacervation and interfacial polymerization) treatments. This allows controlling the

physicochemical properties, size, size distribution and drug loading in the resulting particles. Membrane systems have been indicated as new "green process engineering" able to redesign traditional operations [29] however; to the best of our knowledge, the greenness of membrane emulsification has never been measured.

In the present work, PLGA-PEG microparticles were produced by membrane emulsification/solvent diffusion. The effect of the different solvents used for polymer dissolution (EA or DCM), fluid-dynamics and operating conditions applied during membrane emulsification and solidification steps, respectively, were investigated. In particular, the sustainability assessment of the process was evaluated by considering the properties of the polymeric particles produced (size, size uniformity, and drug encapsulation efficiency) together with the energy consumption. To determine the green impact of the particle production method proposed, the metric based on the Green Aspiration Level™ (GAL) was used [4,30] Many authors dedicated their efforts to optimize membrane emulsification processes for manufacturing structured microparticles with tailored properties [31] however; to the best of our knowledge, this work is the first one in which the greenness of the process was measured. A comparison with previous research carried out for the production of DEX-loaded PLGA particles is also reported to emphasize the advances of the present work.

Materials and Method

Materials

The polymer used in this study was Resomer RGP d 5055 (Di-block PLGA (50:50) PEG (5kDa, 5%) (PLGA-PEG), EVONIK, Germany). Dexamethasone (DEX) supplied by SIGMA–Aldrich was used as model drug. Pluronic F127 was used as stabilizer in the external phase during the

microencapsulation process and Ethyl acetate (EA) and Dichloromethane (DCM) were used as non-polar solvents. Surfactants and solvents (analytical grade) were purchased from SIGMA–Aldrich.

Dispersed Phase and continuous phase preparation

The dispersed phase used to produce the o/w emulsion was obtained by dissolving PLGA-PEG in EA at a polymer concentration of 10 mg mL^{-1}. The continuous phase was a water solution containing Pluronic F127 at 11.6 mg mL^{-1}. A continuous phase saturated in Ethyl Acetate was used during the emulsification step in order to avoid its diffusion from the formed droplets while a non-saturated continuous phase was used as dilution medium for the preparation of the particles by solvent diffusion, after emulsification.

To evaluate the dexamethasone encapsulation efficiency and drug loading, the dispersed phase was modified by including dexamethasone (1 mg mL^{-1}).

Membrane emulsification step

The o/w emulsion was prepared by using a Shirasu porous glass-based (SPG, Miyazaki, Japan), hydrophilic tubular membrane with a pore size of 1 μm having a membrane area of 31.30 cm^2. A schematic representation of the membrane and the membrane emulsification plant are reported in Figure 1. The dispersed phase was injected through the membrane under gas pressure using a transmembrane pressure (P_{TM}) between 0.18 and 0.45 Pa, corresponding to a dispersed flux (J_d) between 1.16 and 30.67 $Lh^{-1}m^{-2}$. The dispersed phase flux (J_d) was determined as follows:

Equation 1: $J_d = \frac{Q_d}{A}$

Where, Q_d is the Dispersed Phase Flow ($L{\cdot}h^{-1}$) and A is the Membrane Area (m^2). It represents a measurement of membrane emulsification throughput.

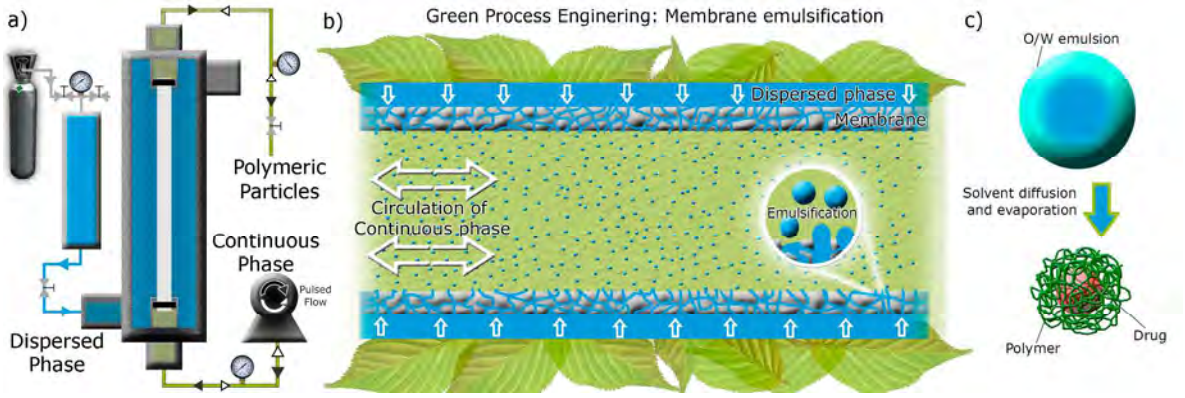

Figure 1. A) Schematic representation of the membrane emulsification set up. B) Schematic representation of membrane emulsification process. C) Schematic representation of solvent diffusion - evaporation process.

The continuous phase was agitated by means of a pulsed back-and-forward mode along the lumen side of the membrane by using a programmable peristaltic pump (Digi-Staltic double-Y Masterflex® pump Micropump, model GJ-N23.JF1SAB1). [32,33] The maximum shear stress (τ_{max}) [Pa] at the membrane surface depends on the frequency (f) [Hz] and on the amplitude (α) [m] of the continuous phase flow. The amplitude and the frequency of the oscillation were calculated considering the flow rate of the pump (Qc) [$m^3 \cdot s^{-1}$] and the volume of the continuous phase that was pumped inside the membrane before the flow direction was reversed (Vc) [L]. These parameters were calculated as follows:

Equation 2: $\tau_{max} = 2\alpha(\pi f)^{1.5}(\mu_c \rho_c)^{0.5}$

Equation 3: $\alpha = \frac{4Vc}{\pi d_h^2}$

Equation 4: $f = \frac{2Qc}{Vc}$

Where μ_c is the Continuous phase viscosity [Pa·s] and ρ_c is the Continuous phase density [kg·m^{-3}]. The effect of amplitude was fixed at 4.7·10^{-2}m and frequency was modified between 1.48 and 3.57 Hz.

The volume ratio % of the dispersed phase obtained for each experiment respect to the continuous phase volume (DP/CP) was 20 %. The emulsification process was carried out at 20 ± 5°C. The membrane was pre-wetted in the continuous phase solution before each experiment. After each experiment, a membrane cleaning step was carried out by using acetone and EA [34].

The water permeability of a brand new membrane before each experiment was measured to evaluate its recovery after the cleaning procedure and it was set at 7523.00 ± 80.00 Lh^{-1}m^{-2}bar^{-1}.

Solidification Step

The liquid droplets were precipitated as solid microparticles by the addition of a certain volume of non-saturated continuous phase (diffusion volume, V_d). The diffusion volume was selected taking into account the theoretical minimum volume (V_{th}) (i.e., the minimum theoretical amount of diffusion volume necessary to ensure the complete diffusion of solvent), calculated using equation 1. The V_d/Vt_h ratio was changed from 0 to 3 in order to control the solidification rate of the droplets. V_d/V_{th} = 0 corresponded to the case in which the solidification was carried out without the addition of the non-saturated continuous phase.

Equation 5: $$V_{th} = \frac{V_{DP} + S_{solvent} * V_{CP}}{S_{solvent}}$$

Where V_{th} (mL) is the theoretical minimum volume of the organic solvent, V_{DP} (mL) is the dispersed phase volume, $S_{solvent}$ (mL solvent/mL water) is the solubility of the organic solvent in water and V_{CP} (mL) is the continuous phase volume.

The organic solvent was removed by evaporation in a fume hood under stirring for 3 hours. The resulting particles were centrifuged at 2100 g for 10 min and the supernatant was stored for further analysis while the pellet was lyophilized using a LyoAlfa 10/15 from Telstar for 24h (0.01 bar, -40^{o}C).

Particles characterization

Particle analysis

The particle size analysis of the resulting microparticles was performed by using laser diffraction in a Malvern Mastersizer 2000 (Malvern Instruments, Worcestershire, UK). The software used to collect and analyze the data was a Malvern 2000 Software 5.61 using a refractive index of 1.55 PLGA-PEG polymer.

Microparticles were also observed by Scanning Electron Microscopy (SEM) using an Inspect F50 SEM operated at 10–15 kV; FEI from Eindhoven, Netherlands at the LMA-INA-Universidad de Zaragoza facilities. To perform the measurement, the sample was stained with a phosphotungstic acid solution (75 mg mL^{-1}) and washed three times with distilled water. One drop of the particulate dispersion was placed on a glass slide, dried overnight and cover with platinum before observation.

The size distribution was expressed in terms of the surface weighed median diameter or Sauter diameter (D(3,2)) calculated according to Equation 2. Volume weighed median diameter or Brouckere diameter (D(4,3)) was calculated according Equation 3.

Equation 6: $D(3,2) = \frac{\sum D_i^3 n_i}{\sum D_i^2 n_i}$

Equation 7: $D(4,3) = \frac{\sum D_i^4 n_i}{\sum D_i^3 n_i}$

Where D_i is particle diameter of class i and ni is number of particles in class i.

The width of particle size distribution was expressed as Span number calculated by Equation 4

Equation 8: $Span = \frac{\mathrm{D(90)-D(10)}}{\mathrm{D(50)}}$

Where D(X) is the diameter corresponding to the percent of volume on a relative cumulative particle size curve.

Encapsulation Efficiency and Drug Loading

The encapsulation efficiency (EE) and drug loading (DL) were evaluated according to the following equations (Equation 5 and Equation 6):

Equation 9: $\mathrm{EE} = \frac{\mathrm{DEX\ encap}}{\mathrm{DEX\ total}} * 100$

Equation 10: $\mathrm{DL} = \frac{\mathrm{DEX\ encap}}{\mathrm{PLGA\ total}} * 100$

Where EE is the encapsulation efficiency (%), DEX_{encap} stands for Dexamethasone mass encapsulated (mg) measured by mass balance, DEX_{total} stands for the initial Dexamethasone mass in the dispersed phase (mg), DL represents the drug loading efficiency (%) and $PLGA_{total}$ stands for the initial PLGA mass in the dispersed phase (mg). The particles were separated from the liquid by centrifugation at 2100 g. DEX content in the supernatant was determined by HPLC. A reversed-phase C18 column (2.6 μm, 50x4.6mm Phenomenex kinetex) was used. The mobile phase was acetonitrile/water at a pH 3 (50/50 v/v). The flow rate was 0.4 mL min^{-1} and the detection was obtained at 260 nm with a UV detector. The linear regression coefficient (R2) was determined in the range 0.01–30 μg/mL as 0.9993 (n=10).

Green analysis and energy consumption

Energy consumption calculation

The energy consumption was evaluated considering the production with a DP/CP of 20%. The energy required was calculated in terms of energy density (Ev, J m^{-3}), according to the following equation [35]:

Equation 11: $\mathrm{Ev} = \frac{P}{Q_E}$

where P stands for the effective power input (J s-1) and QE stands for the volume flow rate of the emulsion ($m^3 s^{-1}$). Power input was calculated as follows:

Equation 12: $P = \left(\frac{\Delta P_{CP} * Q_{CP}}{\eta_{CP}}\right)$

Where ΔP_{CP} is the pressure drop along the membrane module, Q_{CP} is the flow rate of the pump used to generate the pulsed flow and η_{CP} is the pump efficiency.

Green factor calculation

E factor is a simple analysis used to calculate the greenness of a process. Process waste was determined via complete E factor calculation based on a simple mass-balance [4]. Two factors were determined: simple E factor (sEF) and complete E factor (cEF) (in which solvent and water consumed during the process are also included) using equation 13 and equation 14, respectively, adapted to the specific case of particle production:

Equation

13: $\mathrm{sEF} = \frac{\sum \mathrm{m(Raw\ Materials)} + \sum \mathrm{m(Reagents)} - \mathrm{m(Product)}}{\mathrm{m(Product)}} =$

$$\frac{\mathrm{m(Polymer)} + \mathrm{m(Drug)} + \mathrm{m(surfactant)} - \mathrm{m(particles)}}{\mathrm{m(particles)}}$$

Equation 14:

$$\frac{\sum \mathrm{m(Raw\ Materials)}+\sum \mathrm{m(Reagents)}+\sum \mathrm{m(Solvents)}+\sum \mathrm{(Water)}-\mathrm{m(Product)}}{\mathrm{m(Product)}} =$$

$$\frac{\mathrm{m(Polymer)}+\mathrm{m(Drug)}+\mathrm{m(surfactant)}+\mathrm{m(solvent)}+\mathrm{m(water)}-\mathrm{m(particles)}}{\mathrm{m(particles)}}$$

Where Σm(Raw Materials) represents the total mass of polymer and drug used for producing a batch of product. Σm(Reagent) represents the total mass of the reagents used in the process, principally the surfactant. m(Product), Σm(solvent) and Σm(water) represent the masses of particles produced, mass of solvent and mass of water, respectively. cEF is used in GAL-based analysis enabling organizations to calculate their green performance scores.

The process mass intensity (PMI), calculated as the ratio of the total mass of materials to the mass of the product, has been selected from ACS Green Chemistry Institute Pharmaceutical Roundtable as indicator of sustainability for the pharmaceutical sector:

Equation 15: $\mathrm{PMI} = \frac{\sum \mathrm{m(\ Materials\ input)}}{\mathrm{m(Product)}} = \mathrm{cEF} + 1$

Where the Σm(Materials input) includes the total mass of polymer, drug, reagents used in the process (i.e., surfactant), mass of solvent and mass of water. The cEF and PMI can be used interchangeably in the GAL methodology[36] and in this article, we will refer to it as cEF.

Percent's relation (%cEF and % solvent+water) was calculated using equation 16 and 17:

Equation 16: $\%cEF = \frac{sEF}{cEF} * 100\%$

Equation 17: $\%solvent + water = \frac{m(solvent)+m(water)}{m(total)}$

Results and Discussion

Effect of fluid-dynamic conditions during membrane emulsification process

The fluid-dynamic conditions play an important role during particle manufacturing by membrane emulsification, determining the droplet size and droplet size distribution of the emulsion before the solidification step. The influence of the dispersed phase flux and shear stress on PLGA-PEG particle sizes and size distributions have been studied in order to identify the operation conditions that provide the smaller droplets with the highest uniformity and productivity. On the other hand, the dispersed phase flux and shear stress are strictly correlated with the throughput and energy consumption, respectively. These two parameters have also been evaluated in order to demonstrate the sustainability of the productive process.

Effect of dispersed phase flux

The effect of dispersed phase flux on PLGA-PEG particle size and particle size distribution has also been investigated. Figure 2A describes the resulting particle sizes for D[4,3], D[3,2] and span of PLGA-PEG microparticles produced by pulsed back-and-forward ME as a function of the dispersed phase flux in the range from 1.15 to 30.67 $Lh^{-1}m^{-2}$, keeping constant the maximum shear stress (2.48 Pa).

Results demonstrated that the dispersed phase flux does not have a significant influence on particle size and span in the range from 1.15 to 12.84 $Lh^{-1}m^{-2}$. An average diameter (D[3,2]) and a span of distribution equal to 1.10 µm and 0.50 were obtained, respectively. This flux range is identified as “dripping” regime [31,34]. The droplets are rapidly detached from the membrane surface and the contribution of the inertial force from the dispersed phase to the droplet sizes was negligible respect to the viscous drag and capillary forces. SEM images of the particles produced in this range are reported in Figure 2 (C1). The images reveal the homogenous size distributions and

spherical shapes. An approximately linear increase in the particle size and span was observed when the dispersed phase flux was further increased in the range from 12.84 to 30.67 $Lh^{-1}m^{-2}$. A similar trend was previously reported in the literature for the production of other polymeric particles and emulsions.[33,34,36] The formation of larger droplets was the result of the faster increase in the droplet growth as the dispersed phase flux was increased. At 18.02 L $h^{-1}m^{-2}$ droplets were sheared off from the membrane surface before coalescence at the pore level. Uniform droplets (span = 0.8) were then produced although a slight increase in the droplet sizes was obtained (D[3,2]= 1.65 μm) (Figure 2, C2). The further increase of the dispersed phase flux generated less uniform (span = 1.6) and larger particles (D[3,2]= 3.6 μm) (Figure 2, C3).

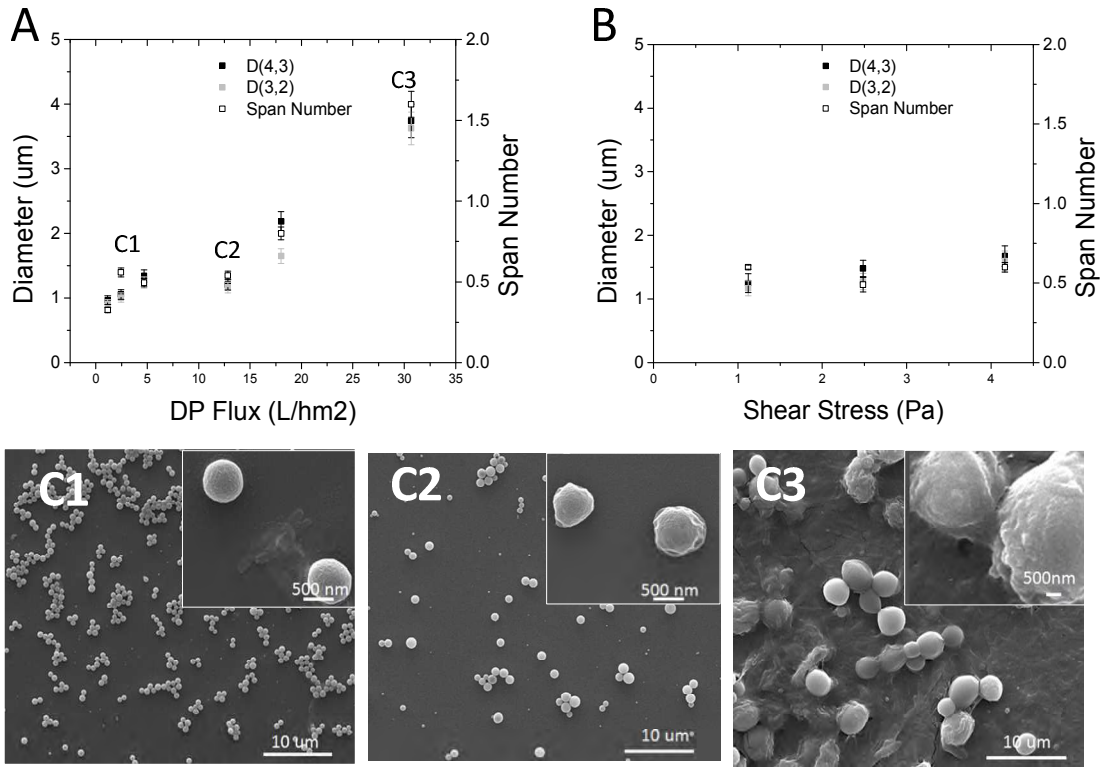

Figure 2. Effect of maximum shear stress and dispersed phase flux on particle size and particle size distribution at lower. A) Modification of dispersed phase flux at maximum shear stress of 2.48 Pa.

B) Modification maximum shear stress at dispersed phase flux of 2.5 $Lh^{-1}m^{-2}$. C1, C2, C3 SEM images of the particles represented in the graph

Results demonstrate that PLGA-PEG particles with sufficiently narrow distribution in the droplet size (span lower than 0.55) and mean diameter tending to the membrane pore diameter can be produced for dispersed phase fluxes in the range of 1.15 to 12.84 $Lh^{-1}m^{-2}$. The increase in the dispersed phase flow determines an increase in the throughput from 36.18 mg h^{-1} to 402 mg h^{-1} reducing the operation time from 1.38 to 0.12 h. Data indicate that membrane emulsification can satisfy the demand of advanced manufacturing processes for industrial scale production by connecting efficiency and productivity. With their easy scale-up and large operational flexibility, membrane operations have been developed to the stage of large scale manufacture [29] and membrane emulsification has also demonstrated its capability for large scale industrial operations [37].

Effect of maximum shear stress

In pulsed back-and-forward ME, the shear stress is a function of the frequency and the amplitude of the pulsation along the lumen side of the membrane. The amplitude of the pulsation was kept constant (47.1 mm) while the increase of the continuous phase flow rate in the range from 500 to 1200 mL min^{-1} determined an increase in the frequency from 1.49 to 3.57 Hz. Figure 2B shows the effect of the maximum wall shear stress on PLGA-PEG particle size and particle-size distribution. Particle size (mean droplet diameter = 1.25 ± 0.13 μm) was not significantly influenced as the shear stress was increased in the range of values investigated (from 1.12 to 4.16 Pa). Typically, the mean particle decreases sharply as the wall shear stress increases and reaches a size where it

becomes more or less independent of the shear. This effect is decreased in case of the production of submicron droplets and relatively small droplets are produced at lower shear stress.

The development of environmentally benign methods for manufacturing processes has become increasingly relevant in the last years determining a significant expansion in the development of more energy-efficient methodologies. Unutilized energy may be considered as a waste and the design of manufacturing processes that do not require intensive energy use is highly desirable. Membrane emulsification is a valuable technology to asses this goal. In the present work, the energy consumption used during the membrane emulsification process was reduced in the range from 9.50 10^5 to 3.90 10^5 Jm^{-3} as the maximum shear stress was decreased from 4.16 and 1.12 Pa. Considering that a shear stress of 1.12 Pa was enough to produce uniform particles (span = 0.6) with D[3,2] of 1.17 μm (tending to the membrane pore size), the further increase of the shear stress was not needed minimizing also energy consumption. Furthermore, traditional emulsification techniques are known to be rather energy consuming[38,39]. The energy consumption associated with the use of an homogenizer, a sonicator and a magnetic stirrer is 10^6-10^8 Jm^{-3} [40] that is 1-3 orders of magnitude higher that the value measured in the present work.

Results clearly indicate that membrane emulsification allows operating under mild conditions to generate uniform droplets with mean diameters tending to the pore diameter reducing, at the same time, energy consumption.

Effect of process conditions used in the solidification step

In the production of PLGA-PEG microparticles by membrane emulsification- solvent diffusion method, both the organic solvent phase, in which the polymer is dissolved, and the aqueous continuous phase saturated with the organic solvent, are in the state of thermodynamic equilibrium. The addition of a certain volume of continuous phase to the system destabilizes the

equilibrium. It causes the organic solvent to diffuse to the external phase and precipitates the polymer to form the solidified particles. Solvent removal determines droplet volume reduction by a shrinkage factor given by the chemical composition of the organic phase and defined as the ratio between the liquid droplet diameter and the solidified particle diameter [41] .

The effect of the type of organic phase solvents (EA or DCM) and solidification diffusion velocity on PLGA-PEG mean particle size, size distribution and particle morphology were investigated. On the other hand, for drug encapsulation, it is required that all the chemicals are used (such as solvents, polymer, and reagents) reducing or eliminating the generation of undesirable products that could be harmful both for human health and the environment. For that reason, sEF and cEF were evaluated for each chemical used in the production of PLGA-PEG microparticles.

Effect of organic solvent phase

Variations in particle size and particle morphology were observed when different organic solvents were used in the preparation of PLGA-PEG microparticles by the membrane emulsification/solvent diffusion method. Figure 3A reports the average diameter and span of PLGA-PEG particles produced by using EA or DCM as polymer solvent while SEM images of PLGA-PEG particles are reported in Figure 3C. More heterogeneous particles (span = 0.95) with an average diameter of three times the pore size of the membrane (D[3,2] =3.15 μm) were obtained when DCM was used. SEM images confirmed the heterogeneous distribution of the particles and revealed the presence of large holes and protuberances on the particles (Figure 3C1). On the contrary, uniform particles (span = 0.62) with an average diameter close to the pore size of the membrane (D[3,2] =1.25 μm) were produced by using EA. SEM images show a dense and slightly rough surface without pores (Figure 3 C2). The differences observed in terms of particle-size distribution and morphology are strictly correlated with the solvent solubility in the water phase. The miscibility of the solvent in

water influences the diffusion velocity and has a direct impact on the final size of the particles [20]. EA has a water miscibility (S_{EA}=9.7 wt%) 4.5 times higher than DCM and, as a result, EA-Water interfacial tension (6.8 ±0.6mN m^{-1}) is significant lower than DCM-Water interfacial tension (28.28 ± 0.40 m Nm^{-1}) [42,43]. In addition, since PLGA-PEG microparticles are formed from the emulsion droplets after organic solvent diffusion, emulsion droplets stability plays an important role to tune the properties of the structured particles. Uniform and smaller particles produced by using EA resulted from both the ability of the emulsifier (Pluronic P127) to prevent droplet coalescence, and the low interfacial tension between the aqueous and the organic phases, due to the partially water-soluble nature of EA. On the contrary, the boiling point of DCM is lower than the one of EA, allowing a flash solvent evaporation. Its miscibility with water is also lower, delaying solvent diffusion and increasing the solidification time. This determines the formation of pores and holes (Figure 3C1) as well as droplet aggregation probably responsible for the production of larger mean particle sizes. Similar results were found by Song et al. using PLGA as polymer, EA and DCM as solvents and Dimethylamine borane (DMAB) as surfactant [20].

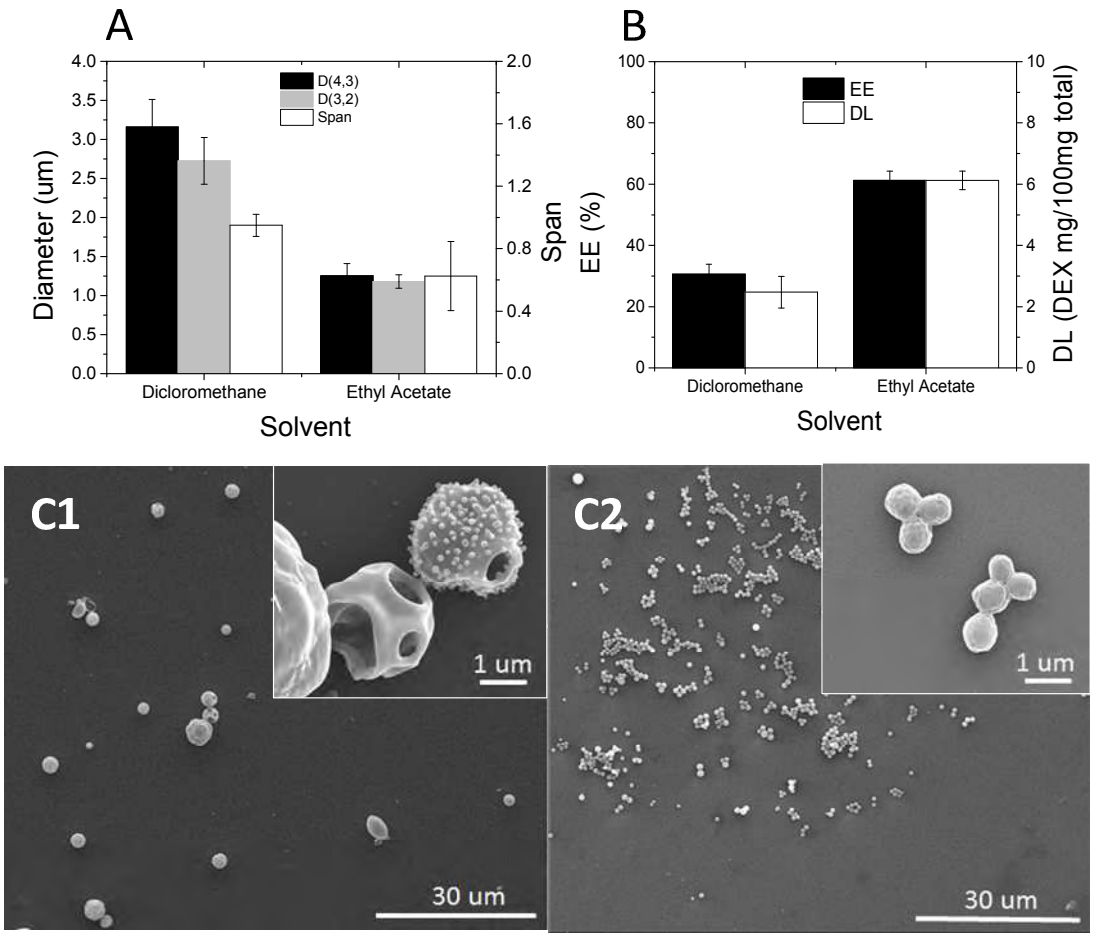

Figure 3. The effect of organic solvent type on A) particle size, particle-size distribution of particles. B) EE and DL (membrane emulsification/ solvent diffusion) and on particles morphology. C) (Polymer: PLGA-PEG, Surfactant: Pluronic, Vd/Vth= 3, PTM/Pc= 1.20, Shear stress: 2.48Pa). C1) SEM image of the particles PLGA-PEG particles produced with DCM. C2) SEM image of the particles PLGA-PEG particles produced with EA.

EE and DL were also evaluated (Figure 3B). The use of EA improves the encapsulation efficiency up to 50% respect to the use of DCM. The analysis of the particle morphology previously discussed can suggest that the porous surface of PLGA-PEG particles produced with DCM determined the enhanced leakage of the dexamethasone into the continuous phase. Similar results were

previously reported by Imbrogno et al. for porous particles produced by using Polycaprolactone as polymer and DCM as solvent [44]. The use of EA also improved DL up to 50% reducing the content of the carrier material [45] minimizing waste generation and improving production profitability. For that reason, sEF and cEF values and particle costs were evaluated in this section (Table 1).

The generation of any material that does not have realizable value, such as the non-encapsulated drug, can be considered as a waste. The non-encapsulated drug may affect the environment differently depending on its nature, toxicity or dose. On the other hand, maximizing the use of raw materials (such as drugs and carrier materials) so that the final formulation contains the maximum number of atoms coming from the reactants is the key point to design an efficient and sustainable manufacturing process.

sEF and cEF values were calculated when EA or DCM were used as organic solvents (Table 1). The evaluation of sEF and cEF plays a major role when focusing the attention on the problem of waste generation in pharmaceutical particle manufacturing and provides the impetus for developing cleaner and more sustainable processes. sEF and cEF values were reduced by 80%, when EA was used compared to DCM.

Table 1. The effect of organic solvent type and solidification velocity on green metric factors in memrane emulsification/solvent diffusion

	Solvent	**DCM**	**EA**	**EA**	**EA**	**EA**
	Vd/Vth	**3**	**3**	**1**	**0.5**	**0**
Green Analysis	sEF (mg/mg)	290.99	59.18	23.66	14.78	5.90
	cEF	25503.38	5237.41	2140.03	1365.69	591.35
	% cEF litd	1.14%	1.13%	1.11%	1.08%	1.00%
	% solvent + water	98.86%	98.85%	98.85%	98.85%	98.84%

Economic Analysis	Polymer Price (Euros/g product)	50.00				
	Drug Price(Euros/g product)	34.50				
	Surfactant Price (Euros/g product)	581.78	118.15	47.12	29.36	11.60
	Solvent Price (Euros/g product)	0.57	0.54			
	Water Price (Euros/g product)	25.07	5.04	1.98	1.22	0.45
	Total (Euros/g product)	691.92	208.23	134.14	115.61	97.09

Table 1 summarizes the economic analysis and the breakdown of the chemical reagents involved in the production of Dexamethasone loaded PLGA-PEG particles. Particle cost was reduced by 70%, when EA was used compared to DCM using V_d/V_{th} =3 (Table 1) as a result of the low amount of water and emulsifier required to obtain particle solidification when using EA. When particle solidification occurs by solvent diffusion, solvent solubility strictly influences the amount of non-solvent (i.e., water) and surfactant required for solvent-non-solvent exchange [7]. EA is more soluble in water than DCM and the amount of water and surfactant required for droplet solidification is lower (Table I). This difference is the main reason to explain why costs were reduced for PLGA-PEG particles produced at the same Vd/Vth ratio with EA (208.23 Euros/g product) and DCM (691.92 Euros/g product). In addition, EA results to be a greener solvent for the production of drug delivery systems based on PLGA-PEG considering both its E factor and its low toxicity. Several researchers have analyzed the toxicity on human cell lines of PLGA-PEG particles produced using EA as a solvent, observing that particles do not alter cell proliferation. This indicates that the PLGA delivery systems prepared by using EA are nontoxic at the doses used [46–48].

Solidification diffusion velocity

The influence of V_d/V_{th} ratio on PLGA-PEG particle size and span is presented in Figure 4. The solidification rate of the emulsion droplets is directly related to the solvent diffusion volume. Results indicate that particle sizes were almost independent on V_d/V_{th} ratio. Uniform particles (span <0.60) with an average diameter of 1.25 μm were produced (Figure 4A, 4C). EA has a low vapour pressure that makes its evaporation very fast (EA Vapor Pressure: 0.13 bar at 25°C). This promotes the solidification process because the emulsification-diffusion method guarantees the free solvent diffusion as long as the organic solvent solubility condition is satisfied [49]. Considering the partially water-soluble nature of EA, its fast diffusion from the droplets was expected.

DEX EE was decreased from 61.22 (±3.00)% to 57.12(±3.56)% when the V_{th}/V_o was increased from 0 to 3 (Figure 4B) as a result of the increase in the concentration gradient of the encapsulated DEX toward the external aqueous phase during the solidification process [25].

Green metric factors were calculated and are presented in Table 1. sEF and cEF values were reduced by 90.03%, when V_d/Vt_h =0 (no diffusion solution added) was used compared to V_d/Vt_h =3. Data indicate that the use of EA allowed reducing the water consumption and the surfactant amount used in the solidification step. This determines also a cost reduction of 53.38% as a function of V_d/Vt_h (from 3 to 0). (Table 1).

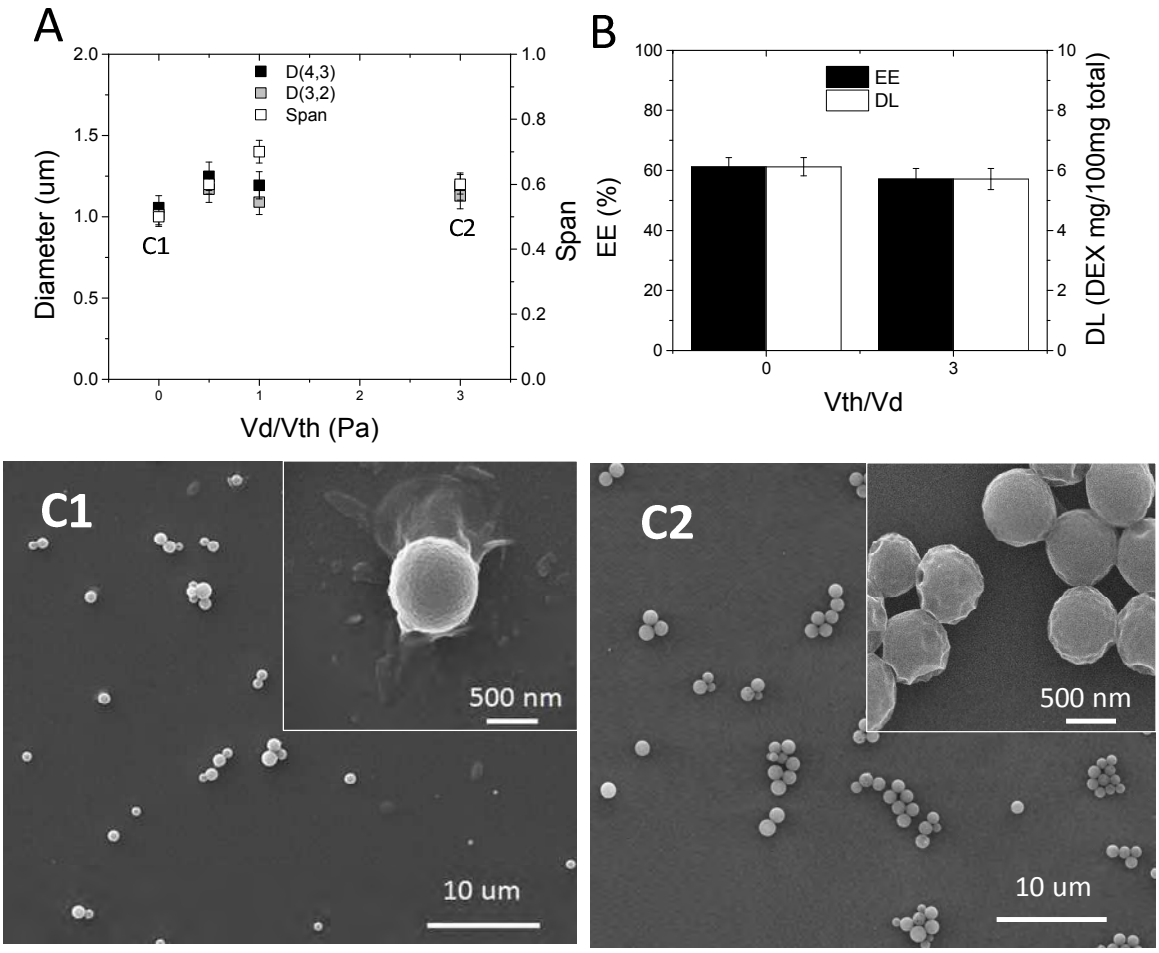

Figure 4. The effect of solidification velocity on A) particle size, particle-size distribution of particles, B) EE and DL (membrane emulsification/ solvent diffusion) and on particles morphology C) (Polymer: PLGA-PEG, Surfactant: Pluronic, Organic solvent: EA, PTM/Pc= 1.2, Shear stress: 2.48Pa). C1) SEM image of the particles PLGA-PEG particles produced with Vt/Vo =0. C2) SEM image of the particles PLGA-PEG particles produced with Vt/Vo =3.

In the present work, the production of PLGA-PEG particles as potential drug delivery vectors was assessed by using membrane emulsification/solvent diffusion method. The optimized operative conditions during the emulsification (DP flux = 12.84 $Lh^{-1}m^{-2}$, shear stress = 1.12 Pa) and the solidification steps (solvent= EA, Vd/Vth = 0) allowed to produce uniform particles (span = 0.62) with an average particle size of 1.25 μm and an EE of 61.22%. High throughput was achieved by

increasing the dispersed phase flux to 12.84 $Lh^{-1}m^{-2}$ in mild operative conditions (shear stress = 1.12 Pa) reducing at the same time the energy consumption ($3.96.10^5$ Jm^{-3}). EA resulted to be a valuable alternative solvent for PLGA particle production as being a greener solvent considering both green metric factors and toxicity compared to the use of DCM. The use of EA makes the particle production process more sustainable reducing the volume of water consumed and the amount of emulsifier used. This allowed also decreasing the economic impact of these components.

A comparison with the literature

Recent works on the production of PLGA-PEG particles by emulsification-solvent diffusion method is analysed in this section with the aim to demonstrate the sustainability of the manufacturing method used in the present work. The use of membrane-emulsification in the preparation of PLGA particles has been previously reported [50–53] however; the greenness of this process has not been measured.

Energy density and process throughput obtained in the present work are compared with data calculated from previous works in which membrane-based processes [50,53] and also conventional emulsification methods [7,9,49] have been used during PLGA particle production (Table 2). Considering the similar physicochemical properties of PLGA and PLGA-PEG polymers [49], literature data about PLGA particles manufacturing were used for the comparison according to the availability of all the information required for throughput and energy density calculations (see supplementary materials section).

One of the frequently mentioned advantages of membrane emulsification over conventional emulsification methods is the lower energy density requirement[54]. The concept of energy density has been previously applied to compare different mechanical emulsifying processes[54,55]. The

comparison illustrates that, given equal energy densities, different emulsifying equipment (rotor-stator systems, ultrasound systems, high-pressure homogenizers and membrane emulsifiers) produces very different droplet sizes. In membrane emulsification, particles with a mean diameter approximately equal to were produced with an energy density in the range of 10^3-10^6 Jm^{-3} which is 1-2 orders of magnitude smaller than in high-pressure valve homogenizers[54]. In the present work, we compared the energy density required for the production of PLGA particles by using different mechanical emulsifying processes. The comparison illustrates that only the pulsed back-and-forward method allowed decreasing effectively the energy density respect to the other conventional emulsification methods. It is well known that higher energy densities are needed to produce smaller droplets[54,55]. For that reason, results obtained in the present work by using the pulsed back-and-forward method are more relevant if we consider that the mean particle size (1.25 μm) is significantly smaller that the size reported by other membrane emulsification methods (60-120 μm) [50] or by conventional emulsification methods (15-80 μm) [15,56,57]. Slightly smaller particles (mean particle size = 0.4-0.6 μm) with high throughput (3 10^{-7} m^3s^{-1}) were produced by using the sonicator in the emulsification step but with a significant increase in the energy consumption (from 10^5 Jm^{-3} by using pulsed-back-and-forward membrane emulsification to 10^8 Jm^{-3} by using a sonicator). [40] Pulsed back-and-forward membrane emulsification appears to be an alternate valuable method with low energy consumption (3 orders of magnitude lower) respect to other membrane emulsification methods of operation for the production of particles in the same range of sizes[53] although the process throughput was one order of magnitude lower than those associated with the conventional emulsification methods.

Table 2. Comparison between the membrane emulsification/solvent diffusion process and processes described in the literature

		MEMBRANE EMULSIFICATION			CONVENTIONAL EMULSIFICATION METHOD			
		Present Work	Ho et al, 2013 [53]	Gasparini et al, 2008 [50]	Kim and Martin, 2006 [58]	Gu and Burgess, 2015 [15]	Park et al, 2009 [56]	Goodfriend et al, 2016 [57]
Chemical Composition	Polymer	PLGA-PEG	PLGA	PLGA	PLGA	PLGA	PLGA	PLGA
	Drug	DEX	curcumin	N/A	DEX	DEX	DEX	DEX
	Solvent	EA	Chloroform	DCM	DCM/Acetone	DCM	DCM	Tetrahydrofuran
	Surfactant	Pluronic F127	PVA	PVA	PVA	PVA	PVA	Pluronic F127
	Dispersed Phase/Continuous Phase ratio	0.20	0.10	0.07	0.20	0.20	0.10	1.00
	Total Volume (mL)	30.00	6.60	160.00	180.00	137.00	330.00	10.00
Emulsification Process	Membrane	SPG Membrane D_p= 1um	Silicon nitride membrane D_p= 2um	Metallic membrane D_p= 40um	-	-	-	-
	Emulsification Device	Cross-Flow pulsed back-and-forward	Cross-Flow	Stirred	Sonicator (Fisher 500)	T 25 digital ULTRA-TURRAX homogenizer	Magnetic stirrer	Vortexed stirrer
	Throughput (m3 s-1)	$1.32*10^{-08}$	$2.20*10^{-08}$	$1.33*10^{-07}$	$3.00*10^{-07}$	$2.00*10^{-07}$	$5.50*10^{-07}$	$5.56*10^{-09}$
Formulation Properties	Mean Particle size (um)	1.25	2.30	60.00	0.40–0.60	15.00	20.00	50.00
	EE %	61.20	32.00	N/A	79.00±5.00	70-95	N/A	60.00
	DL %	6.16	2.00	N/A	13.00±3.00	10	N/A	N/A
Energy Consumption	Energy density (Jm-3)	$3.96*10^{-05}$	$2.29*10^{-08}$	$2.25*10^{-08}$	$2.00*10^{-08}$	$1.60*10^{-09}$	$1.09*10^{-08}$	$2.52*10^{-08}$
Green Analysis	sEF	5.90				0.71		
	cEF	591.35				313.17		
	% cEF litd	1.00%				0.23%		
	% solvent + water	98.84%				99.45%		
Economic Analysis	Polymer Price (Euros/g product)	50.00	50.00	50.00	50.00	50.00	50.00	50.00
	Drug Price(Euros/g product)	34.50	34.50	N/A	86.25	70.38	3.45	215.63
	Total Cost (Euros/g product)	97.09	106.09	52.14	155.35	121.73	56.56	265.68

Green metric factors obtained for the method developed in the present work were compared with the same data calculated for the method described by Gu and Burgess [15]. This paper was the only one that included data referred to both emulsification and solvent diffusion steps, while other papers analysed in this section only referred to the emulsification step [50,53,56–58] sEF and cEF resulted to be quite similar and the most important difference was attributed to the amount of polymer and drug used. The ratio between sEF and cEF values (% cEF litd) is a helpful indicator for relative solvent usage and thus waste reduction potential. The low % cEF litd value (lower than 1%) and the relative value of solvent and water percentages higher than 95% indicated that, solvents (organic solvent and water) are the most utilized material in the production of polymer particles via emulsification and solvent diffusion.

Similar analysis previously conducted in the pharmaceutical field confirms the higher contribution of solvents to the cumulative PMI. The relative value of solvent and water percentages associated with the production of active ingredients from a survey of several pharmaceutical companies was estimated to be 88% by the Pharmaceutical Roundtable[57]. In contrast, the results for the commercial route show a lower relative value of solvent and water percentage solvent of 78%[58]. Anyway, the environmental impact of the solvent depends on the environmental factor and the solvent type as previously discussed.

Solvents used for the production of PLGA particles included in Table 2 are DCM [50,56,58] and chloroform [53]. Both, Chloroform and DCM have been classified as Class 2 with a permissible concentration of 60 ppm for Chloroform and (lower than that allowed for DCM) [59]. EA is classified as a Class 3 solvent and then it results a greener solvent respect to the solvents previously used in PLGA particles production. EQ-factor (environmental quotient factor) was proposed as a valuable extension of E-factor in order to consider the toxicity of materials and it is obtained by multiplying the E factor with an arbitrarily assigned unfriendliness quotient, Q. However, the magnitude of Q is

currently debatable and difficult to quantify and this hampers the correct assessment of a green analysis. [60] Several general purpose solvents, [22] analyzing the most conventional solvents taking into account the European regulation concerning the 'Registration, Evaluation, Authorisation and Restriction of Chemicals' (REACH) and the recommendations of pharmaceutical industry solvent selection guides identified EA as recommended/preferred solvent while Chloroform and DCM as undesirable.

The economic analysis performed demonstrates that the cost of the microparticles was 97.09euro/g of particles produced. It is important to point out that in the calculation only the raw material costs are included, however, the calculation helps to identify the components influencing most significantly the cost of particle production. Main cost components result to be the polymer (51.15%) and the drug (35.45%) as reported also in previous works [15,50,53,56–58].

About the formulation properties, it is notable that EE and DL for DEX encapsulation previously reported in Table 2 were close to those obtained in the present work. This indicates that the encapsulation efficiency is not correlated with the emulsification method used. EE and DL are highly dependent on the polymer and drug initial amounts, surfactant type, concentration and solvent type[15,49]. A low initial amount of drug used in the present work (1 mg L^{-1}) is responsible for a lower EE obtained respect to other data reported in Table 2 (EE = 70%, initial drug concentration = 6.66 mg L^{-1} [58] and 44.93 mg L^{-1} [15]).

The simplicity and versatility of the membrane emulsification method combined with the use of green solvents hold much promise for the development of a sustainable chemical manufacturing industry. Considering that a broad spectrum of micro-nanostructured materials with predictable and controllable sizes, different chemical compositions, morphologies, and functionalities can be produced by using the proposed method, membrane-based technologies result the best green process choice.

Associated content

Full details about the intensification analysis (mass balance, economic, green analysis and energy consumption) of the described process are provided in the Supplementary Information.

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TOC/Abstract graphic and Synopsis

Polymeric particles production with high yield, minimized solvent and energy consumption and reduced waste by membrane emulsification.