Prosimy cytować jako: Inż. Ap. Chem. 2016, 55, 1, 22-23

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Emulsions as precursors for structurized inhalable microparticles

Introduction

Dry emulsions are powders obtained by spray drying of oil-in-water (O/W) emulsions. In such powder particles, the oil droplets are dispersed and encapsulated inside the solid matrix of water soluble substances. Separation of oil droplets from outer environment can delay the degradation and oxidation of lipophilic compounds dissolved in organic phase. In addition, such formulations are much more physicochemically stable than ordinary emulsion [*Christensen et al., 2002*]. Dry emulsions are widely used in food, cosmetic and pharmaceutical industry. They may be also proposed as carriers of water-insoluble drugs delivered by inhalation therapy which is the main motivation of this research.

The main objective of this study was to investigate the possibility of obtaining dry emulsion particles with the characteristics proper for the inhalation drug carrier, that is, adequate size and aerosol properties [*Gradoń and Sosnowski, 2014*].

Experimental

Materials

Lactose monohydrate, used as a matrix for oil droplets encapsulation, was purchased from *POCh* (Poland). Soy bean oil, L-leucine, used as a powder dispersibility enhancer, and sodium caseinate, used as an emulsifier, were purchased from *Sigma-Aldrich* (USA). Solutions and reemulsions were prepared using water purified by reverse osmosis (*Puricom, USA*).

Preparation and characterization of precursor emulsions

80 ml of lactose aqueous solution (10% or 20%) containing 4% of sodium caseinate and 1 g of L-leucine was homogenized with soy bean oil at 95:5, 90:10 and 80:20 ratios (v/v). Homogenization was carried out for 3 minutes at 24 000 rpm using an *Ultra Turrax* homogenizer (*IKA,* Germany). Obtained O/W emulsions were then characterized for size distribution of oil droplets by *Spraytec* diffraction spectrometer (*Malvern Instruments*, UK) equipped with the wet-cell. Experimental set-up is shown in Fig.1. Emulsion aliquots (300 µl) were injected to the stream of pure water continuously pumped through the cell mounted in the path of laser beam. The dispersion was automatically sensed by the optical system allowing determination of droplet size distribution (measuring period: 30 s, sampling rate: 1 Hz). Experiments for all emulsions were triplicated and the results were averaged over time. Obtained size distributions were further characterized by volume median diameter Dv(50) of the oil droplets.

Preparation of powder (dry emulsion)

Powder was obtained by spray drying of O/W emulsions in *Mini Spray Dryer B-290* (*Büchi*, Switzerland). The emulsion was pumped at volumetric rate of $5 \cdot 10^{-8}$ m^3/s (3 cm^3/min) to the atomizing nozzle (diameter 0.7 mm) fed by compressed air with rate of $2.33 \cdot 10^{-4}$ m^3/s (14 dm^3/min). The inlet temperature of drying air (flowrate: 0.01 m^3/s) was set at 150°C. Produced powders were separated in the high performance cyclone and collected in the product container.

Characterization of dry emulsions particles

Obtained dry particles were characterized in scanning electron microscope (SEM, model *TM1000, Hitachi*, Japan) after coating with 20 nm layer of gold (K550x *Sputter Coater, Quorum Technologies*, UK). Size distribution of aerosolized powder particles was determined using aforementioned *Spraytec* spectrometer after

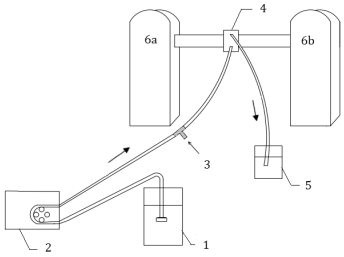

Fig. 1. The experimental set-up for determination of droplet size in O/W emulsions. 1- vessel with a pure water, 2- peristaltic pump, 3 - sample injection point, 4 -wet measurement cell, 5 - waste collection beaker, 6a - *Spraytec* laser emission unit, 6b – *Spraytec* laser detection unit

powder dispersion in the commercial inhaler (*Aerolizer, Novartis*, Switzerland). In this case the spectrometer was operated in a dry mode, and it was connected to the inhalation chamber and the vacuum pump. Aerosol generation was obtained by drawing the airflow at the rate of 100 dm^3/min which is recommended for this inhaler . The measurements were time-averaged (measuring period: 500 ms, sampling rate: 1 kHz) and triplicated for each type of powder. The volumetric median diameter Dv(50) was derived to characterize the particle size.

Powder rehydration and secondary emulsions characteristics

Adequate aliquots of produced powders were resuspended in water in order to obtain emulsions with the same concentration of components as in the initial emulsions which had been used as precursors for spray drying. Size distribution measurements of oil droplets were performed according to the procedure used for primary emulsions.

Results and discussion

Volumetric median droplet diameter Dv(50) in emulsions with lactose concentration of 10% and 20% are shown in Figs 2 and 3, respectively. The median size of oil droplets in primary emulsions increases with the increasing content of oil phase: from approximately 1.5 µm to almost 2.5 µm in case of 10% lactose, and from 2 to 5 µm for 20% lactose content in emulsion. Similar, although less apparent effect of change in Dv(50) of droplets, is observed in secondary O/W emulsions obtained by powder rehydration. Moreover, it can be seen that for higher lactose concentration, the median diameter of oil droplets is also higher, probably due to increased viscosity of the continuous (aqueous) phase which impairs the effectiveness of mechanical emulsification. This effect is apparent both for the primary and secondary emulsions, but again it is more evident in the precursor formulation.

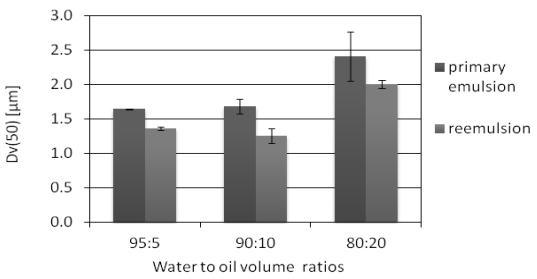

Fig. 2. Volumetric median diameter of oil droplets in 10% lactose primary emulsions and in emulsions reconstituted from the corresponding powder (Error bars represent the standard deviation)

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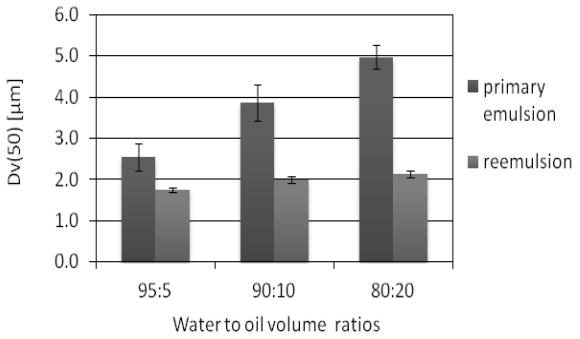

Fig. 3. Volumetric median diameter of oil droplets in 20% lactose primary emulsions and in emulsions reconstituted from the corresponding powder (Error bars represent the standard deviation)

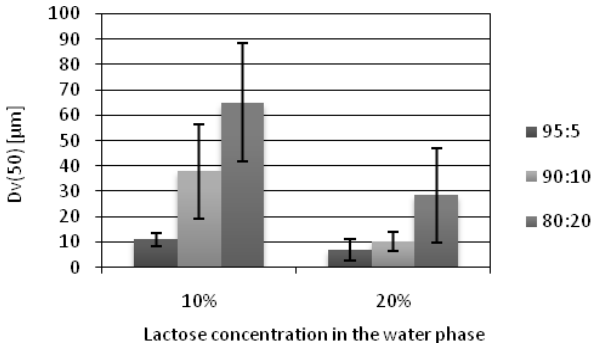

Fig. 5. Volumetric median diameter of aerosol particles for different compositions of primary emulsion used as a precursor in powder production (Error bars represent the standard deviation)

Secondary emulsions prepared by the powder rehydration are characterized by lower sizes of oil droplets than the initial emulsions (median diameter: 1÷2 µm vs. 1.5÷5 µm, depending on the composition) what suggests that additional disintegration of oil droplets occurs in the atomizing nozzle of the dryer due to high hydrodynamic stresses during spraying.

Example SEM micrographs of obtained dry emulsions particles are presented in Fig. 4. These results show that particles are polydisperse with the size in the range of 1÷10 µm. Such size make them potentially suitable to be carriers of inhalation drugs *[Gradoń and Sosnowski, 2014]*. No significant differences in particle morphology for different precursor composition are observed. Particles, especially larger ones, are deformed and have corrugated surface. Some empty particles, sometimes with the additional voids in the shell (indicated by an arrow in Fig. 4A), are also detected.

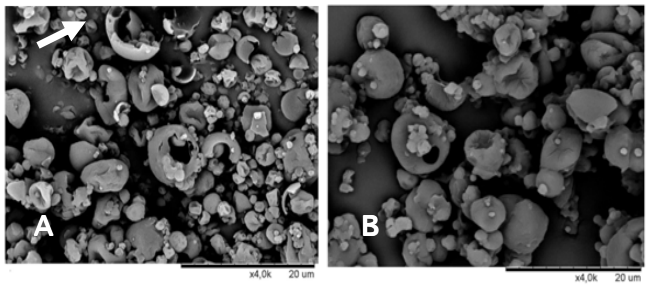

Fig. 4. SEM pictures of powders obtained by spray drying of emulsions with 80:20 water to oil ratio and A) 10% and B) 20% lactose concentration in the aqueous phase. Scale bar - 20 µm.

Powder dispersibility results represented by the volumetric median diameter of the aerosolized particles are shown in Fig. 5. Particles produced from O/W emulsions containing 10% of lactose are characterized by higher values of Dv(50) than particles obtained from emulsion containing 20% of lactose (size range 10÷65 µm for the first case and 6÷28 µm for the latter case, depending on water to oil ratio). Based on these results it is seen that aerosolized particles are larger than powder particles visible at the SEM pictures. It suggests that aerosol generated from powders contain mainly particles agglomerates, so powder resuspension in the tested inhaler is insufficient to obtain the desired amount of respirable particles.

Decrease in powder dispersibility with the increase of oil content in the primary emulsions was observed for both lactose concentrations in the aqueous phase. This effect may be attributed to the increase in interparticulate interactions in powders due to higher amount of oil at particles surface, which leads to formation of larger and more durable agglomerates.

Large standard deviations of median particle diameter in the majority of examined powder samples additionally prove their poor aerosolization properties, and eliminate their applicability as carriers of drugs delivered by inhalation (potentially too high dose variability). Regarding the average particle size of aerosolized particles and moderate standard deviation, only 95:5 emulsions can be considered as promising precursors of inhalable powders.

Conclusions

The idea of preparation of multicomponent powders as candidates for carriers of inhalable drugs has been tested using spray-drying of O/W emulsions with two different concentrations of lactose as matrix material. Oil-to-water ratio was shown to have strong influence on the properties of obtained powders, especially regarding their properties to be effectively aerosolized in the typical inhaler available on the market. Produced particles of dry emulsions have a geometric diameter of few micrometers which is the proper size for the inhalation drug carriers. Particles are non-spherical and have corrugated surface what reduce their aerodynamic diameter. Although all these features makes them potentially convenient for aerosol therapy, the results of powder dispersibility measurements showed that particles form durable agglomerates, which do not break up during aerosolization in the tested inhaler. Therefore, aerosol particles formed from powders are too large to penetrate deep parts of the respiratory system. Additionally, size distribution of aerosol particles is poorly reproducible what is unacceptable in case of pharmaceutics products. That makes the majority of examined powders unsuitable for aerosol therapy. The results of this study indicate that only powders containing the smallest amount of oil in the dry mass can be considered suitable for the pulmonary drug administration in terms of particle size and dispersibility in air. Planned further research in this area will test if such particles influence properties of the air/liquid interface of the lungs by interactions with constituents of the pulmonary surfactant.

LITERATURE

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Gradoń L., Sosnowski T. R. (2014). Formation of particles for dry powder inhalers *Adv. Powder Technol.* 25, 43-55. DOI:10.1016/j.apt.2013.09.012

Work financed by National Science Centre (Poland) - project No. 2014/13/B/ST8/00808