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Research paper

Critical parameters involved in producing microspheres by prilling of molten lipids: From theoretical prediction of particle size to practice

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ABSTRACT

The aim of this work was to identify the key parameters which influence the running of the prilling process with lipid material from the initial melting to the formation of solid microspheres. The microsphere size would essentially result from break-up at the Rayleigh–Weber's wavelength which mostly depends on the liquid properties (mass density, surface tension and dynamic viscosity). After molten liquid extrusion through the nozzle, the cooling rate is very fast and the instantaneous temperature of the liquid jet decreases rapidly of 0.2–0.3 °C during the duration of the droplet formation (1–2 ms). This leads to no significant modification of the physical characteristics of the lipids and only a very slight change in the dynamic viscosity. Consequently, no significant effect on the optimal wavelength λ_W and on droplet formation can occur. However, coalescence of liquid droplets has been observed during their fall, probably caused by turbulence into the air column, leading to a minor population of larger microspheres.

1. Introduction

Interest in multi-particulate drug delivery systems for oral administration has noticeably increased in recent years. In such dosage forms, the pharmaceutical substances are usually incorporated in a solid dispersion divided into a number of independent small particles resulting in multiple-units drug dose which indeed facilitates the achievement of controlled or delayed release oral formulations. Compared to conventional monolithic dosage forms, these systems provide flexibility of blending, limit the risk of dose dumping and ensure better reproducibility of drug bioavailability. This mainly arises from gastric emptying less dependent on the state of nutrition, higher degree of dispersion in the digestive tract and less absorption variability [1]. Furthermore, as these dosage forms consist in very small particle dispersions, they enable the improvement of the treatment compliance for patients with difficulties to swallow like young children [2] or elderly people.

It is worth noting that some drawbacks caused by the physicochemical properties of any active pharmaceutical ingredients (API) can be circumvented by its incorporation in a multi-particulate delivery system, depending on the choice of the excipient used to form the API solid dispersion. In this respect, lipids deserve special attention since they have been demonstrated to be matrix components particularly effective in enhancing absorption and bioavailability of drugs with poor water-solubility [3] beside other advantages from taste masking [4] to modulated release of drugs [5,6]. Among the numerous technologies which have been implemented to produce micron-sized particles from lipids, spray congealing also called spray chilling or spray cooling [7], hot-melt extrusion [8] or supercritical-CO_2-based technology [9] have the advantage of not resorting to the use of volatile organic solvents. In the present work, we were interested in the alternative and innovative technology of prilling which has been successfully applied to lipid materials according to a solvent-free methodology without the need for preliminary formation of an emulsion [10].

Generally speaking, prilling processes are based on a mechanical dispersion of a liquid through pressure-controlled injection in a cooling fluid after apart breaking into droplets by a vibrating nozzle device. This technology has been shown especially suitable to immobilise microorganisms or entrap bioactive substances in polymeric beads being formed by fall of a mixed host-polymer liquid formulation into an appropriate polymer gelling solution [11–13]. Recently, pharmaceutical applications have been developed in order to control the drug release [14–16] or targeting the drug delivery [17].

Beside sol–gel process, prilling can be conveniently applied to fusible materials [18]. In the pharmaceutical field, lipids are quite

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Nomenclature

C_p	specific heat capacity of molten lipid (kJ/kg °C)
d_d	droplet diameter (m)
d_j	jet diameter (m)
d_n	nozzle diameter (m)
f	friction factor
g	acceleration due to gravity (9.81 m/s^2)
h	heat transfer coefficient (W/m^2 °C)
K	loss coefficient
L_c	characteristic length (m)
P	pressure (Pa)
Q_m	mass flow (kg/s)
S	section area (m)
v	velocity (m/s)
μ	dynamic viscosity (Pa s)
ρ	density (kg/m^3)
σ	interfacial tension (N/m)

Subscripts

a	air
c	crystallisation
d	droplet
e	connection element
f	friction
i	initial
j	jet
n	nozzle
t	tank
y	elementary segment
E	external disturbance
W	Rayleigh–Weber

Dimensionless numbers

N_v	viscosity number
We	Weber number
Oh	Ohnesorge number
Re	Reynolds number

designated due to their moderate melting temperatures, well-recognised biocompatibility and ability to incorporate other chemical compounds [19,20]. Contrarily to the gelling process, the procedure used for lipids is devoid of solvent and does not require a drying step to achieve solid particles. The lipid blend is indeed melted to get a homogenous liquid which then serves as solvent or suspension medium of the API to be formulated. The extrusion throughout vibrating nozzles divides the fluid mixture in micron droplets which are then rapidly cooled and solidified during their fall in a cold airstream. The obtaining of solid micron-sized particles with regular spherical shape and uniform size distribution tightly depends on the flow conditions before and during the extrusion process. These have to be properly adjusted as a function of the physical properties of the lipid blend used. Once the drops are generated, the conditions of cooling are also crucial and must comply the thermal behaviour of the lipids as we have already shown in a previous study [10].

The aim of this work was to identify the key parameters which influence the running of the prilling process from the initial melting to the formation of solid microspheres and which are related to the physicochemical characteristics of the lipid material. For this purpose, five commercially available lipid excipients which differ in their composition were studied. On the basis of a theoretical approach depicting the different steps of the process, we attempted to evaluate to what extent the rheological and consequent fluid mechanics properties of the lipids in their liquid state can be predictive of the final particle size, and how this last can be modulated by the thermotropic behaviour of the lipids as well as by the trajectory of the droplets during their fall in the cooling air column.

2. Materials and methods

2.1. Materials

Imwitor®491 (90% min. glyceryl monostearate, 66–77 °C melting temperature range) and Cutina®HR (hydrogenated castor oil, 83–88 °C melting temperature range) were purchased from Sasol (France). Speziol®GDB (mixture of glyceryl mono-, di- and tribehenate, 65–77 °C melting temperature range) and Speziol®L2SM (90% min. of a mixture of stearic acid and palmitic acid, 55–59 °C melting temperature range) were obtained from Cognis (France). Gelucire®50/13 (mixture of mono-, di-, and tri-glycerides enriched with mono- and diacyl-poly(ethylene glycol), 46–51 °C melting temperature range) was supplied from Gattefosse S.A.S. (France).

2.2. Prilling equipment and operating conditions

The industrial device (designed by Synetude, Chambéry, France) consists of a pressurised stainless steel tank of 10 L (2.5 bar maximal pressure) equipped with a temperature-controlled heating device (150 °C maximal temperature) and connected to the prilling head through a thick walled heated silicone tubing (Fig. 1). A sieve (40 μm-mesh) was placed before the prilling head which contains the nozzle. Due to its circular geometry and its small thickness compared to the pipe diameter, the later belonged to the "sharp edged orifice" class. The ratio between orifice (200 μm) and inside pipe diameters was 0.15. This nozzle was fixed on a round

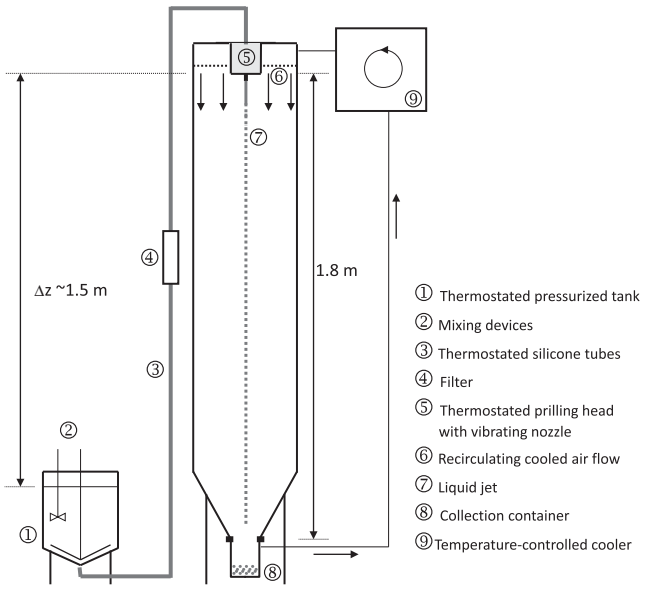

Fig. 1. Schematic configuration of the prilling process and pilot plant device (not a scale).