Production of particles used to inhalation process and controlled release of drugs
Proceedings of European Congress of Chemical Engineering (ECCE-6)
Copenhagen, 16-20 September 2007

Production of particle powder for inhalation process and controlled release of drugs

A. Karolina Kula, B. Tomasz Ciach, C. Krzysztof W. Szewczyk

Faculty of Chemical and Process Engineering,Warsaw University of Technology,Warynskiego 1, 00-645Warsaw, Poland

Abstract

Obtaining particle powders used for controlled release of drugs through atomization processes – EHDA and spray drying, has been presented in this paper. Polymer and paracetamol solutions in organic solvents have been sprayed and obtained particles have been collected. The size and morphology of collected particles have been analyzed. The influence of solvent type, polymer additives on particle morphology, as well as drug release rate have been demonstrated.

Keywords: EHDA, spray drying, controlled release, paracetamol, polycaprolactone

1. Introduction

A controlled delivery and release of drugs have recently become an intensively developed field of pharmaceutical activity. The purpose behind controlling the drug delivery is to achieve more effective therapies while eliminating the potential for both under and overdosing. Other advantages of using controlled delivery systems can include the maintenance of drug levels within a desired range, the concentration monitoring, the accidental effects decrease, and optimal use of the drug.
One of the methods of controlled drug delivery occurs when a polymer, either natural or synthetic, is combined with a drug or another active agent in such a way that the active agent is released from the material in a predesigned manner.
Two atomization processes have been used to obtain particle powders used for controlled release of drugs – electro hydro dynamic atomization (EHDA) and spray drying process (SDP). Both methods allow to produce small monodisperse particles at complex, porous or hollow structure. Polymer and paracetamol solutions in organic solvents have been sprayed and obtained particles have been collected.
In electrostatic atomization a liquid to be atomized has been supplied to a nozzle connected to the high voltage power supply, whereas for spray drying the power supply has been replaced by the high pressure supply. In both methods the particles could be dried also by hot air. The obtained particles have been collected in a

different way, on smooth plate connected to the opposite voltage power supply or in a cyclone, respectively.
The size and morphology of collected particles have been analyzed. The influence of solvent type, polymer additives on particle morphology, as well as drug release rate have been demonstrated.

2. Materials

As an active agent paracetamol (Acetaminophen, $C_8H_9NO_2$) was used. This is an easily accessible drug with analgesic and antipyretic properties. It has been purchased from Fluka. Polymer – polycaprolacton, medical grade 20kDa, was a gift from Solvay. Solvents applied in the experimental work were purchased from POCH distributor. They were of analytical grade. All the chemical substances were used without further purification or other processing.
In the experiments different mass fraction solutions of paracetamol and polymer/paracetamol mix in organic solvents were used.

3. Methods

Two different apparatuses have been constructed: for electro hydro dynamic atomization and for spray drying. Solutions have been sprayed and obtained particles have been collected. The size and morphology of collected particles have been analyzed using electron microscopes: LEO 1530 CBW PAN and Philips XL40 – CLK KGP. A drug release rate has been analyzed as well.

Electro Hydro Dynamic Atomization - EHDA

An idea of electrostatic atomization is to supply a liquid to be atomized by a nozzle connected to the high voltage power supply (HV-1). Beneath the nozzle there is a ring shape electrode connected to the second high voltage power supply (HV – 2) – operated at lower – intermediate voltage. It stabilizes a process of atomization. In front of the nozzle a discharge electrode is placed. The scheme of EHDA process is shown in Fig 1. The process propeller is a potential difference. In the electrostatic field a droplet hanging beneath the nozzle changes its shape to conical, and if the voltage difference is suitable, a liquid filament is ejected from a cone apex. This liquid jet breaks up to the mist of droplets (Fig. 2).

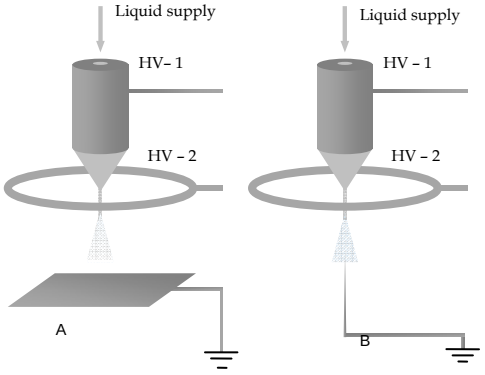


Fig. 1. Scheme of EHDA process
a - with grounded collecting plate; b – with grounded electrode needle.

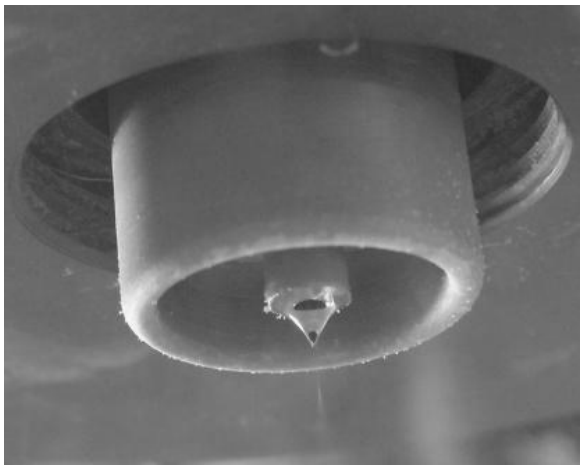


Fig. 2. A nozzle with a liquid cone jet and mist of droplets.

The set – up consists of electro hydro dynamic atomization apparatus, two high voltage (+) power suppliers, a high voltage (-) power supplier, a syringe pump, an air supplier, an air filter, an air heater, a thermometer and a rotameters (Fig. 6a).
The apparatus consists of three main modules: top – a nozzle and a ring operated at intermediate voltage; mid – a cylindrical glass tube; bottom - grounded collecting plate, a scrapper and a discharge electrode.
As a precursor for the production of drug loaded particles, a solution of drug, sometimes with addition of polymer, is supplied to the spraying nozzle via syringe pump. To obtain particles, voltage and liquid flow rate should be fixed in such way that the system has operated in the cone – jet mode. Typical map of the stable EHDA operation for 5% paracetamol solution in isopropyl alcohol is shown in Fig. 3. It is a function of ring voltage and the liquid flow rate, all other parameters are constant.
The spray is stable in the area inside presented curves. A stable jet is presented in Fig. 2.

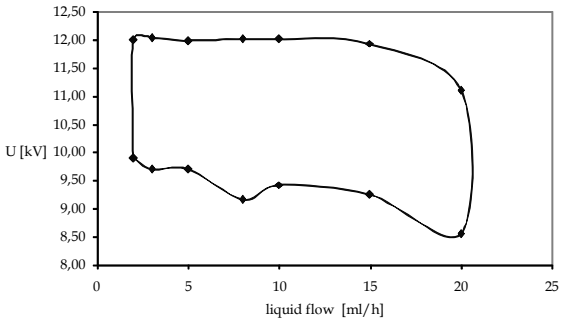


Fig. 3. A stability map of the EHDA, cone diameter 1.6 mm, nozzle voltage 16 kV
5% paracetamol in isopropyl alcohol

Spray Drying Process - SDP

The second apparatus was a spray drying apparatus. An idea of spray drying is to supply a liquid to be atomized to a nozzle connected to the high pressure. The scheme of SPD process is shown in Fig 4., and the nozzle module is shown in Fig. 5.
Liquid blown off from the inner tube is shared by the air flow from the outer one. The shear makes fine mist.

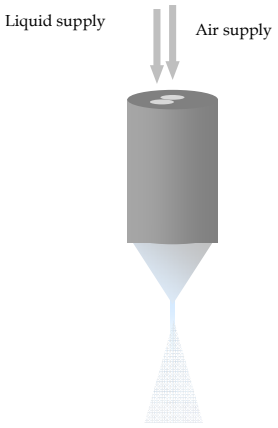


Fig. 4. Scheme of SDP process

Fig. 5. A nozzle module in SPD

The set – up consists of a spray drying apparatus, a cyclone, a syringe pump, an air supplier, an air filter, an air heater, a thermometer and two rotameters (Fig. 6b).
Such as EHDA, a solution of drug, sometimes with addition of polymer, has been supplied to the spraying nozzle via syringe pump. Additional air supplier has been connected to dry the particles and to simplify their collection.

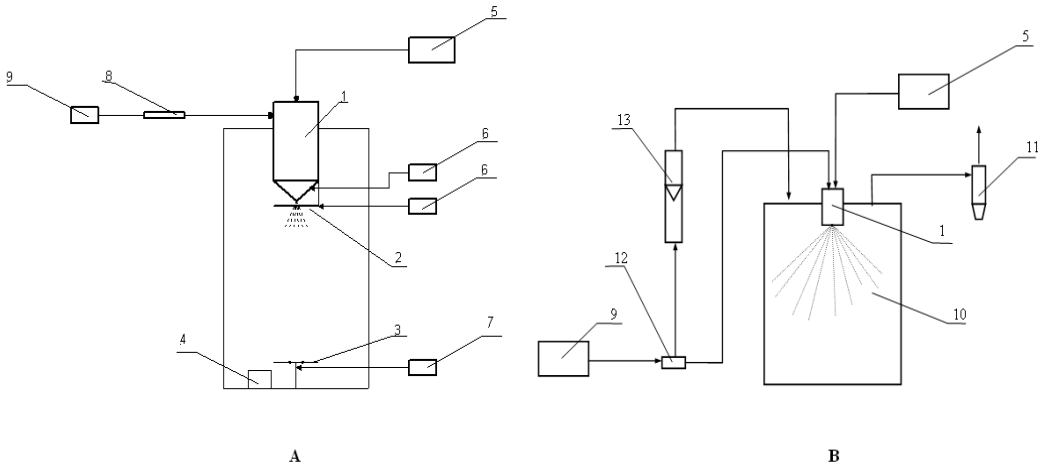


Fig. 6. A scheme of set – up: a – EHDA; b – SPD.

1 – a nozzle, 2 – a stabilizing ring, 3 – grounded collecting plate with a scrapper a discharge electrode, 4 – collecting box, 5 – a syringe pump 6 – high voltage (+) power supplier, 7 – high voltage (-) power supplier, 8 – an air heater, 9 – an air supplier, 10 – a drying chamber, 11 – cyclone, 12 - T-connection, 13 – rotameter.

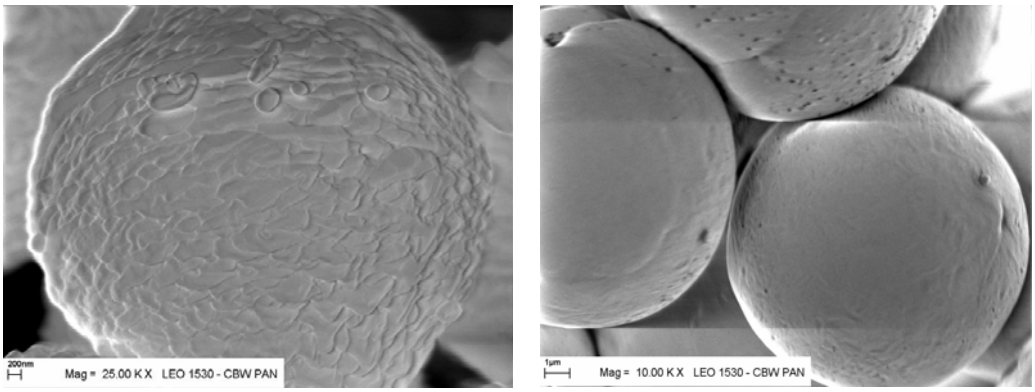
Drug Release

The experiment of paracetamol release from polymer and non – polymer particles has been conducted. To avoid rinsing particles away, a powder was closed in the a kind of pin. This sealed membrane piece was immersed in phosphate buffered saline (PBS)

with small addition of NaN_3 to prevent bacteria growth, at 37ºC. Drug concentration in the solution was estimated by spectrophotometer Biomate3, at λ=242 nm.

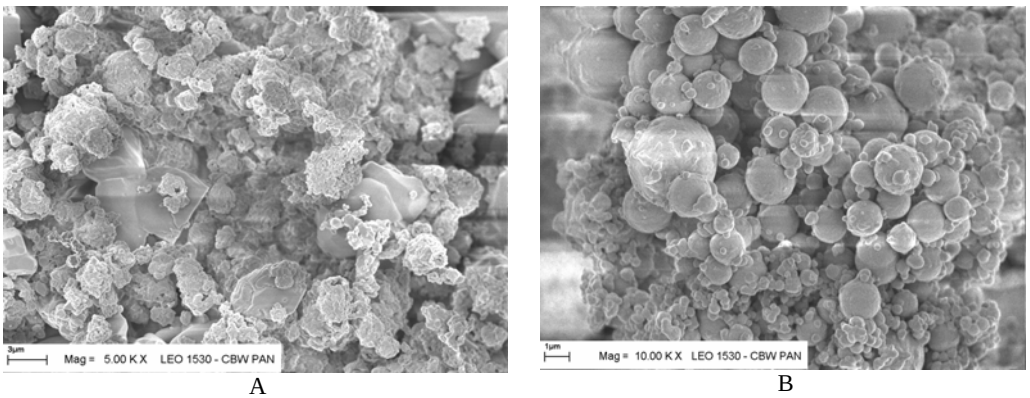
4. Results

The particles from 3% and 7% paracetamol solutions in organic solvents, as well from polycaprolacton with paracetamol solutions, have been collected.
The structure of obtained particles is different. If the paracetamol solution has been sprayed, the particles are porous and consist of nanocrystals of paracetamol on the particles surface, as it can be seen in Fig. 7a, for EHDA, and Fig. 8a, for SDP. If polymer with a drug was dissolved, the particles obtained from such a solution are solid – Fig. 7b (EHDA) and Fig. 8b (SDP). It should be mentioned that the presence of cavities inside particles is hard to be revealed.
EHDA gives a narrow distribution of a particle diameter, whereas SDP gives more wide. Both methods give particles range 10 μm.



A B

Fig. 7. Particles obtained with EHDA method: a - from the 7% paracetamol solution in isopropyl, b - from the paracetamol - polycaprolacton solution in isopropyl alcohol/dichloromethane



A B

Fig. 8. Particles obtained with SD method: a - from the 7% paracetamol solution in isopropyl, b - from the paracetamol - polycaprolacton solution in isopropyl alcohol/dichloromethane

The drug release rate from the particles is shown in Fig. 9. The constant rate of paracetamol release from produced particles has been observed The addition of polymer results in deceleration of release rate.

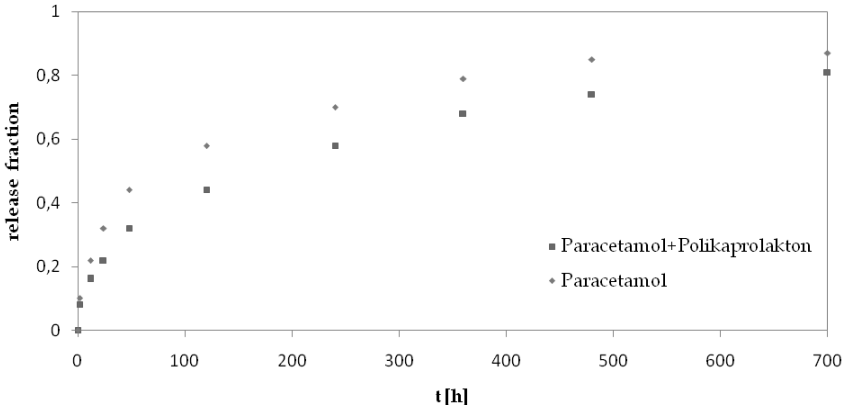


Fig. 9. Drug release from the particles.

5. Conclusions.

These two atomization methods, electro hydro dynamic atomization and spray drying, have been used to produce small monodisperse particles for drug delivery purposes. The size, the morphology, and the structure of particles produced in the both set – ups depend strongly on the solvents properties and polymer addition. The rate of particles production by spray drying is higher than the electro hydro dynamic atomization. The drug release rate from particles has been constant and has depended on a polymer addition.

References

Ciach, T., (2004*) Chemical and Process Engineering* (in Polish), 25, 795 – 801.
Ciach, T., (2006) *International Journal of Pharmaceutics*, 324, 51 – 55.
Ciach, T., Wang, J., Marijnissen, J.C.M., (2001) *J. Aerosol Science*, s32, 1001.
Ding L., Lee T., Wang C. – H., (2005) *Journal of Controlled Release*, 102, 395 - 413.
Lefebvre, A.H., *Atomization and spray*, Taylor & Francis (1989).
Orzechowski, Z., Prywer, J., *Atomization of liquid* (in Polish), WNT, Poland (1991).
Xie J., Lim L.K., Phua Y., Hua J., Wang C.-H., (2006) *Journal of Colloid and Interface Science*, 302. 103–112
Xie J., Marijnissen J.C.W., Wang C.-H., (2006) *Biomaterials*, 27, 3321 - 3332.