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Research paper

Image analysis of lutrol/gelucire/olanzapine microspheres prepared by ultrasound-assisted spray congealing

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ABSTRACT

Nine systems were prepared containing Gelucire 50/13 and various amounts (9–18–36–45% w/w) of Lutrol F68 and F127 in the presence and in the absence of 10% w/w of olanzapine and formulated as a solid dispersion in the form of microspheres by ultrasound (US)-assisted spray congealing. Thermal analysis, using differential scanning calorimetry (DSC) and thermomicroscopy (HSM), suggested the presence of particles of reduced size of olanzapine precipitated inside the microspheres. The microspheres were also studied by means of electron microscopy (SEM) for their shape and aspect, by some image analysis parameters (fractal dimension) and using Energy-dispersive X-ray (X-EDS) and micro-Raman spectroscopy to qualitatively evaluate the composition of different points of the surface. The surface of the microspheres displayed a non-homogeneous distribution of the drug by the presence of wart-like protuberances, whose number increases as the Lutrol content of the systems increases. The same systems in the absence of US, obtained after cooling the molten mixtures, lack these structures and only a very few of them can be found. The blooming of the surface was hypothesized as related to crystallization or phase de-mixing or lipid component diffusion of the carrier mixture inside the cooling mass subjected to ultrasound vibration. Ultrasounds accelerate the physical changes concerning carriers and drug, outlining the importance of ultrasound to achieve stability for formulations of this type. The microspheres de-aggregate on contact with the dissolution medium and release the drug with a bimodal mode according to the Lutrol content.

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1. Introduction

A major task of the pharmaceutical technologist is to control the release of the drug from a formulation, intended in the broadest sense - to accelerate, retard, modulate, extend, and target the release of an active ingredient. This requires an in-depth understanding of the nature of the active substance to be formulated, as well as of the carriers and the technique of the preparation of the formulation. As a consequence, knowledge of the new materials offered by the pharmaceutical industry and their technological and physical characteristics must be continuously updated. The materials can provide interesting solutions to change the intrinsic nature of the active ingredient (hydrophilic/hydrophobic) and to direct the system drug/carrier towards the desired goal. Formulations containing newly structured excipients and carriers of unusual behaviour, such as cyclodextrins, co-polymers, surfactants, self-emulsifying systems, and liposomes, have thus recently been proposed. Similarly, recent techniques, such as ultrasound-assisted compaction and atomization [1–6], have been explored to modify the stability and behaviour at the release of the active agent.

The present paper is part of a work planned to study solid dispersions for the release of olanzapine [7], and to collect more results concerning the application of ultrasound atomization to formulate drug delivery systems [8–11].

The present systems were modelled into microspheres through the application of an ultrasound-assisted spray congealing process to molten mixtures. The excipients (Gelucire 50/13 and Lutrol F68 and F127) examined in this paper for the preparation of solid dispersions with olanzapine offer a range of the desirable properties considered above, especially for their solubilising or wetting capacity towards the active principle release: the Lutrols, in fact, enable the formation of polymer micelles in aqueous solution, and Gelucire 50/13 displays a high HLB value. The three selected solid

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carriers prove suitable for the formation of solid dispersions by the melt method, both for their low melting point and for the stability up to rather high temperatures, which does not necessitate a strict control of the temperature during preparation of the solid dispersion. They also allow the use of higher temperatures than those usually suggested to improve the solubility of the active ingredient in the hot-carriers of this type. In a preparatory work [7], preliminary to the present one, these individual carriers, as well as their binary and ternary mixtures, were proposed for the preparation of solid dispersions, with the aim of selecting systems which could best dissolve olanzapine in the molten state, and keep it dissolved or otherwise finely dispersed when the solid dispersion had solidified. However, it was not possible to obtain microspheres by the present US-assisted spray congealing technique [12] employing the Lutrols alone, while preparation was possible when a Gelucire associated with a Lutrol was present in the system. Due to the excessive presence in its composition of short chain fatty acids (C12 and C14), the initially proposed Gelucire 44/14 [7] proved unable to form microspheres. When the molten mixture was poured over the sonotrode, the low viscosity and melting point [13] of the drops could not be "modelled" into solid microspheres by the action of ultrasound; Gelucire 50/13, in which the fatty acid chains of the type C16–C18 prevail, behaves better for the present purpose. Consequently, the systems initially considered in the previous paper [7] have had to undergo a considerable modification, when their ability to be formulated as microspheres was considered and only a limited comparison was possible. Nine systems were thus prepared containing Gelucire 50/13 and various amounts (9, 18, 36, 45% w/w) of Lutrol F68 or F127 (in the presence or in the absence of 10% w/w olanzapine) and formulated both as solid dispersions and in the form of microspheres by ultrasound-assisted spray congealing. The various analyses carried out revealed interesting aspects that are briefly discussed in terms of image analysis, release and stability of the final systems, arising from application of ultrasound.

2. Experimental part

2.1. Materials

Olanzapine was a gift of pharmaceutical grade (Montefarmaco OTC, Bollate-Milan, Italy): the sample was crystallized for purification by cooling an anhydrous ethyl acetate solution that allows crystallization of the unsolvated form of this drug: its thermogram fits that of a commercial sample (m.p. 197 °C). Lutrol F68, Lutrol F127 and Gelucire 50/13 (PEG-32glyceril palmito-stearate – m.p. 50 °C; HLB 14) were obtained as gift samples from Gattefosse (Saint-Priest, France) at the highest purity available.

2.1.1. Preparation of physical mixtures

Nine physical mixtures were prepared containing Gelucire 50/13, Lutrol F68 or Lutrol F127 in the relative percentages shown in Table 1; olanzapine was added at the constant 10% w/w of the total amount. Some samples of these mixtures were also prepared for comparison in the absence of olanzapine.

Table 1
Weight per cent composition of the systems (1–9).

Systems	1	2	3	4	5	6	7	8	9
Gelucire 50/13	81	72	54	45	81	72	54	45	90
Lutrol F68	9	18	36	45					
Lutrol F127					9	18	36	45	
Olanzapine	10	10	10	10	10	10	10	10	10

2.1.2. Preparation of the solid dispersions

Each mixture was heated on a hot plate and, due to thermal stability of drug and carriers, heating could continue until complete dissolution of the drug, to obtain a homogeneous starting system for the spray congealing process. When present, the drug was added to the molten mixture, thus obtaining its dispersion into the carriers as a function of their mutual affinity. The molten mass was divided into two parts.

One part was stored in a freezer at −20 °C for two days; then milled, sieved and stored in a desiccator over silica gel. Throughout the paper these systems are referred to as *dispersions*.

Another part was poured on the horn of the ultrasound device, previously heated at 70 °C: the liquid mass is divided by ultrasound energy into small droplets, which solidify in the form of microspheres on cooling during free fall (1.5 m) down to a suitable container, collected and sieved, and stored at ambient temperature in a desiccator. Throughout the paper these systems are referred to as *microspheres*.

2.1.3. Dimensional analysis

Dimensional analysis of the microspheres was performed using a vibrating sieve Octagon Digital (Endecotts Limited, London, UK) to evaluate the influence of the drug loading, but also of the nature of the carrier on the particle size distribution of the final microspheres in the presence or in the absence of the active agent.

2.1.4. Scanning Electron Microscopy (SEM)

The morphological characteristics of the microspheres were observed by Scanning Electron Microscopy.

Image analysis of the particles was carried out using a SEM (Philips XL30, Eindhoven, Netherlands) at 10 kV accelerating voltage that used special software (Image® Pro Plus) to calculate the coordinates (x, y) of the particle boundary through the digitization of the particle image obtained by SEM. These coordinates are then used to calculate size parameters, such as projected area, perimeter, mean diameter, and shape parameters, such as shape factor (s), aspect ratio (a) and heterogeneity. The shape factor (s) provides information about the shape of the particles; for a circular particle, the shape factor is 1, while in the other cases s is <1. In fact: $s = 4\pi$ [area/(perimeter)^2]. The aspect ratio (a) is 1 for a round and square particle, while it is higher or lower than one unit for elongated particles. All these parameters were calculated by analysing at least 20 particles for every sample (200 μm < x < 355 μm).

A second SEM (EVO50EP Carl Zeiss AG, Jena, Germany) was used to obtain photomicrographs of the microspheres: the particles were observed without coating, working in VP mode at approximately 90 Pa in chamber and using a 20 kV accelerating voltage, before taking the image. An X-EDS (Energy Dispersion Spectrometry) spectrum was taken from the surface of the particles showing the main elemental composition of the area itself.

2.1.5. Differential scanning calorimetry (DSC)

Thermograms were obtained with Mettler equipment (Greifensee, Switzerland: FP 80HT control unit, FP 85TA cell furnace and FP 89 control software). Samples of about 10 mg were accurately weighed and analysed in pierced Al crucibles in the range of 40–300 °C, at a heating rate of 10 °C min^{-1}. To compare the thermal behaviour of the systems, the temperature of the peak was preferred to the melting onset temperature, as in a previous paper [7]. The heating and cooling times were strictly respected to ensure reproducibility of the results in fresh and aged systems.

2.1.6. Thermomicroscopy (HSM)

Hot-stage microscopy was carried out by means of a Mettler FP 82HT hot plate (Greifensee, Switzerland), coupled to an Olympus BH-2 optical microscope, equipped with a photographic recorder

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