Nanonized itraconazole for the preparation of pellets by extrusion and spheronization

Matteo Cerea, Università degli Studi di Milano, Dipartimento di Scienze Farmaceutiche, via G. Colombo 71, 20133 Milano, Italy, matteo.cerea@unimi.it; **Franco Pattarino** Università degli Studi del Piemonte Orientale "A. Avogadro", Dipartimento di Scienze del Farmaco, Largo Donegani, 2/3, 28100 Novara, Italy, franco.pattarino@unipmn.it; **Evelyn Ochoa**, Università degli Studi di Milano, Dipartimento di Scienze Farmaceutiche, via G. Colombo 71, 20133 Milano, Italy, evemach09@gmail.com; **Andrea Foglio Bonda**, Università degli Studi del Piemonte Orientale "A. Avogadro", Dipartimento di Scienze del Farmaco, Largo Donegani, 2/3, 28100 Novara, Italy, a.foglio.bonda@gmail.com; **Luca Palugan**, Università degli Studi di Milano, Dipartimento di Scienze Farmaceutiche, via G. Colombo 71, 20133 Milano, Italy, luca.palugan@unimi.it; **Carlo Vecchio,** Pharmaceutical Technologies & Development, Via Comignago 2B, Revislate 28010 Veruno (NO) Italy, cavecch@tin.it

INTRODUCTION

Among different strategies that can be used for enhancing the dissolution rate of poorly soluble drugs, particle size reduction proved to give interesting results. Processes able to reduce the size of drug particles to the sub-micron range (typically 100-200 nm) allow a significant increase of the dissolution rate that could mean an ameliorated bioavailability. High pressure homogenization (HPH) has been successfully used for the production nanoparticles characterized by reproducible particle sizes and capable of generate stable nanosuspensions [1].

Pellets are interesting pharmaceutical innovative formulations that combine a high flexibility in the dosage form development and a significant improvement in terms of safety [2]. They are less susceptible to the variations in the gastric empty times thus minimizing intra- and inter-subject variability of plasma profiles. Pellets can also be employed for the preparation of fast release systems by layering the drug on the surface of inert cores for promoting the dissolution rate.

Even if nanotechnologies are a promising tool for the development of novel drug delivery systems with a variety of applications, the biggest challenge consists in the formulation of nanosized material in dosage forms that do not compromise their release performances.

The aims of the present work were i) to prepare a stable nanosuspension of a poorly soluble drug; ii) to obtain a versatile form of the nanonized drug that can be easily re-dispersed and handled; iii) to explore the possibility of producing fast disintegrating pellets by extrusion/spheronization loading a nanonized drug without compromising its dissolution performances.

Itraconazole (ITZ), an antifungal agent, characterized by a very low aqueous solubility, a poor oral bioavailability and high inter-individual variations in the plasma drug concentrations was chosen as the model drug.

EXPERIMENTAL METHODS

Nanonizing process

Nanosuspensions were prepared by a high-pressure homogenizer (HPH, Microfluidizer M-110L, Microfluidics, MA, USA). Preliminary trials, carried out using several stabilizing agents and surfactants in various amounts (0.5 to 2.0% w/w), and different homogenization conditions (pressure 3,000-18,000 psi, temperature 4-25°C, reprocessing times 10-40 minutes) allowed to identify the optimal setting of the nanonizing process. The obtained nanosuspension was subjected to spray drying carried out using a Spray-dryer (Mod. B-290, Buchi Labortechnick AG, CH) operating at 150°C (inlet temperature) with an air flux of 60 L/h at a spray rate of 15 mL/min.

Particle size analysis

The solid nanonized products were analysed by Zetasizer 3000HS (Malvern, UK) to determine the particle size. As a reference, micronized ITZ (as received by the manufacturer) was also analysed by a Mastersizer 2000 (Malvern, UK).

Pelletization process

Pellets containing 22% w/w ITZ were prepared by extrusion-spheronization. Different functional pelletization excipients were evaluated in order to prepare disintegrating pellets with acceptable sphericity. The final excipients composition of pellets selected for this study was Avicel PH101 33%, Kollidon CL 33% and Methocel E5 33% w/w. The excipients were granulated in mortar by adding the nanonized dry powder (ITZnanoDP) to the excipients mixture and wetted with water. Alternatively the wet masses were prepared introducing ITZ nanonized dry powder redispersed in water by 3 min sonication (ITZnanoLD) and used as the wetting liquid. Pellets containing micronized ITZ were also prepared by using the analogous procedures (ITZmicroDP and ITZmicroLD). When employing micronized ITZ, Tween 20 was added to the wetting solution for replicating the composition of nanonized systems (0.84% w/w based on the pellet composition). The wet masses were extruded using a radial screen extruder (Nica E4, GEA, B; screen size 1.0 mm). The extrudates were fed into the spheronizer (Nica S2-450, GEA, B) that operated at 700 rpm for 5 min. The wet pellets were dried in static oven at 40°C for 12 h (moisture content <5%).

Release study

Release tests were performed on powders and pellets in USP dissolution apparatus 2 (AT7, Sotax, CH; 100 rpm, 37.0±0.5°C, n=6) in SGF without enzymes (USP). Samples were withdrawn at fixed time points and spectrophotometrically assayed for the drug content.

RESULTS AND DISCUSSION

The results of preliminary tests conducted on nanosuspensions prepared with various surfactants (SLS, Tween 20 and 60, Span 20 and 80, Cremophor ELP) and different suspending polymers (HPMC, poloxamer 407, Lutrol F127, CMC, HEC) led to identify the most promising formulation and most effective set of HPH conditions. A nanonized ITZ dispersion, characterized by acceptably small particles size and good physical stability was obtained starting from micronized ITZ (25% w/w) in water added of Tween 20 (1% w/w) using HPH at 18000 psi for 40 minutes operating at 4°C. The nanonizing process produced particles with a mean diameter of 456 nm, about 20 times lower than that of the starting micronized material (mean diameter 8.9 µm) (Fig. 1). The nanosuspension was spray dried for enabling an easy handling and for increasing the formulation possibilities of the drug. The dried powder was dispersed in water by sonication for 3 min and a stable nanosuspension was obtained. The particle size of the original nanosuspension was only slightly affected by the drying and dispersing processes (mean diameter 677 nm).

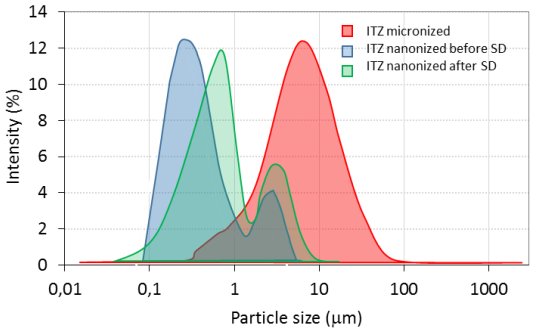

Figure 1: Particle size distribution of nanonized ITZ before (blue) and after (green) spray drying and micronized (red) itraconazole powder.

The results obtained from the dissolution tests, carried out on nanonized and micronized ITZ dry powders (ITZnanoDP and ITZmicroDP respectively), indicated that the reduction of the particle size increased the dissolution rate: in particular, an evident increase has been observed when the dried powder of nanonized ITZ was redispersed in water (5 mg/mL) (ITZnanoLD) before the test (Fig. 2).

The pellet composition was set up employing micronized and nanonized ITZ using Kollidon CL as disintegrating agent, Methocel E5 as hydrophylic binder and Avicel PH101 as spheronizing aid. In Fig. 3, the release profiles of ITZ from the pellets are reported. The release profiles from pellets containing nanonized or micronized ITZ were significantly different (f_2 values range between 34 and 40). The pellets ITZnanoLD gave the highest release rate: after 30 minutes, the pellets formulated with ITZnano released 58.7% of ITZ, while only 40.8% of drug was released from pellets prepared with ITZmicro. At the end of the test (120 min), the pellets containing nanonized ITZ released 72.6% drug compared to 53.2% with pellets prepared with micronized ITZ.

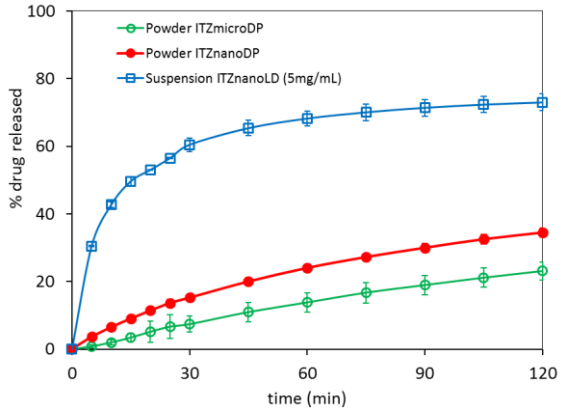

Figure 2: Dissolution profiles of ITZ powders with different particle sizes and ITZ nanonized dry powder re-dispersed in water (5 mg/mL).

Comparing the pellets prepared with the drug as powder with those obtained using ITZ re-suspended in water, the release profiles resulted not substantially different (f_2 parameter value 65.5 for pellets ITZnanoLD vs. pellets ITZnanoDP and 69.6 for pellets ITZmicroLD vs. pellets ITZmicroDP).

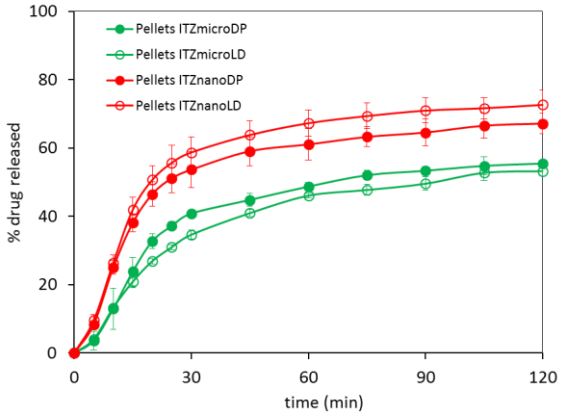

Figure 3: Dissolution profiles obtained from pellets prepared with ITZmicro and ITZnano dry powders (DP) or liquid dispersion (LD).

CONCLUSIONS

The study demonstrated that HPH is effective in the particle size reduction: the nanonization of a poorly soluble drug such as ITZ in the presence of a surface active agent increased its dissolution rate. Fast disintegrating pellets were obtained by extrusion/spheronization with the nanonized ITZ, and ameliorated release performances were observed in comparison with systems containing the drug as micronized powder.

REFERENCES

1. Salazar, J.; et al., Process optimization of a novel production method for nanosuspensions using design of experiments (DoE), Int. J. Pharm, 420, 395 (2011)
2. Pharmaceutical Pellettization Technology, I. Ghebbre-Sellassie Editor, Marcel-Dekker Inc., Drugs and the Pharmaceutical Sciences, Vol. 37, 1989