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Solid formulations by a nanocrystal approach: Critical process parameters regarding scale-ability of nanocrystals for tableting applications

Annika Tuomela [a,*], Timo Laaksonen [a], Johanna Laru [c], Osmo Antikainen [a], Juha Kiesvaara [c], Jukka Ilkka [d], Olli Oksala [e], Seppo Rönkkö [b], Kristiina Järvinen [b], Jouni Hirvonen [a], Leena Peltonen [a]

[a] Division of Pharmaceutical Chemistry and Technology, Faculty of Pharmacy, University of Helsinki, Helsinki, Finland
[b] School of Pharmacy, Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland
[c] Orion Pharma R&D, Formulation Research, Espoo, Finland
[d] Oy Medfiles Ltd., Kuopio, Finland
[e] Santen Oy, Tampere, Finland

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ABSTRACT

Nanocrystallization is among the foremost drug delivery platform approaches for the commercial development of poorly soluble drugs. There exists an urge to enable a universal shift of the production of the solid nanocrystal formulations from laboratory scale to industrially feasible scale. The success of any formulation development depends on its transferability to large scale manufacture. The objectives of the study were to increase the nanocrystallization batch size and to screen and optimize parameters for industrially feasible itraconazole (ITC) and indomethacin (IND) nanocrystal composition for tablet formulation. Thus, ITC and IND were transformed into nanocrystal suspensions, using an increased batch size of a wet milling process, freeze-dried, and further developed into both direct compression (DC) and granulated (G) tableting masses. According to the investigated powder and tablet properties (true density, flowability, dose uniformity, maximum upper punch force, crushing strength, dissolution and disintegration) and stability testings, it was clear that the amount of the nanocrystals in the solid tablet formulation is critical in order to fully utilize the benefits of the nanocrystals, *i.e.*, fast dissolution, and to produce high-quality tablets. The DC designs of both the model drugs with compositions including 40% of freeze-dried nanocrystalline drug powder outperformed the corresponding granulated tablets in all parameters after the stability surveillance.

1. Introduction

Drug nanocrystals play a significant and distinctive role in the current drug delivery technology platform and have laid foundation for broad utilization of the nanocrystal approch (Möschwitzer, 2013). Enhanced solubility and dissolution rate, improved bioavailability, safe dose escalation, elimination of food effects, and enhanced safety, efficacy and tolerability profiles are some of the numerous advantages of drug nanocrystals (Junghanns and Muller, 2008; Raghava Srivalli and Mishra, 2014). Additionally, drug nanocrystals with particle sizes below one micron propose an advantage of high drug loading due to the encapsulating of carrier-free nanoparticles, composing solely of the drug and stabilizer(s) (Junghanns and Muller, 2008; Merisko-Liversidge et al., 2003). In this ever emerging reign of nanocrystal technology, increasing resources are applied in the development of effective solid nanocrystal formulations. There exists an urge to enable a universal shift of the production of the solid nanocrystal formulations from laboratory scale to industrially feasible scale, because the success of any formulation development depends on its transferability to large scale manufacture (Raghava Srivalli and Mishra, 2014). However, there exist a limited number of studies about the up-scaling of nanocrystallization and their further processing into real-life applicable formulations.

Some research dealing with the up-scaling of various nanocrystallization approaches have been conducted, which have provided evidence about the successful change of the nanocrystal production scale. For instance, a method for controlled

* Corresponding author. Tel.: +358 50 3218789.
E-mail address: annika.tuomela@helsinki.fi (A. Tuomela).

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crystallization during freeze-drying was successfully converted suitable for large scale production, simultaneously resulting in a better product (de Waard et al., 2009). Furthermore, the traditional SmartCrystal combination technology has been up-scaled from lab to pilot scale, which provides foundation for the up-scaling of other nanocrystal approaches (Shaal et al., 2010). Also, the results of a technical feasibility study suggested the potential of combining static mixing and spray drying for large-scale continuous production of pharmaceutical nanocrystal formulations (Hu et al., 2011). The suitability of a precipitation–homogenization technique for large scale nanocrystal production has also been shown (Quan et al., 2011). Finally, by optimizing various parameters, wet media milling methods have been applied successfully at different scales (Ghosh et al., 2012; Niwa et al., 2011). Singare and co-workers (Singare et al., 2010) modeled thoroughly the parameters affecting a wet milling process with promising results regarding the scalability. However, no actual production of up-scaled batches was reported, which would have facilitated critical information about the real-life outcome. Wet milling is nevertheless the most utilized nanocrystallization technique and, evidently, there exist marketed solid nanocrystal formulations, *e.g.*, Rapamune®, Emend®, TriCor® (Junghanns and Muller, 2008), prepared by the wet milling. However, the number of these products is still relatively limited and there exists a need for additional information regarding the universal industrial feasibility and formulation development. The detailed evaluation of pharmaceutical processability properties of nanocrystal powders are still required for the development of the final solid dosage form.

In order for the development process to be successful, a detailed characterization of process parameters, design and choice of equipment, development of a robust formula including effective excipients and satisfactory stability surveillance results, are all required (Raghava Srivalli and Mishra, 2014). The nanocrystal approach may benefit the companies also due to the possibility of a product line extension offered by the FDA for the already existing drug formulations (Raghava Srivalli and Mishra, 2014; Singare et al., 2010). Nanocrystals offer flexibility of both up-scaling and down-scaling, which is a great advantage during manufacture process (Van Eerdenbrugh et al., 2009). The objective of this study was to increase the size of nanocrystal production batch, and to screen and optimize parameters for industrially feasible nanocrystal composition for tablet formulation. The aim was to achieve therapeutic doses and realistic tablet dimensions. An essential question was to investigate the maximum amount of freeze-dried nanocrystal drug powder possible to be included in a tablet. Thus, two poorly soluble model compounds, itraconazole (ITC) and indomethacin (IND) were transformed into nanocrystal suspensions, using an increased batch size of a wet milling process (Liu et al., 2011; Sarnes et al., 2013, 2014; Tuomela et al., 2014), freeze-dried and further developed into direct compression tableting masses or wet granulated into micro-granules for tableting. The direct compression and granulated tableting designs were used to model and to optimize the formulation compositions and the process parameters regarding feasible tablet dosage forms.

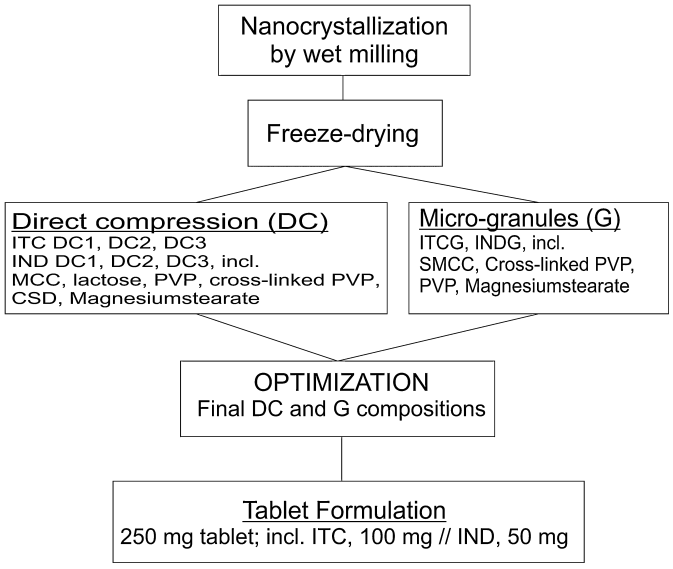

Fig. 1. The schematic illustration of the production phases of the nanocrystal formulations.

Table 1
The compositions of test formulae (w/w%) of the ITC and IND nanocrystal formulations for direct compression (ITC; DC1, DC2, DC3 // IND; DC1, DC2, DC3), the final ITC and IND DC compositions (fDC), the ITC (ITCG) and IND (INDG) nanocrystal granulation formulas for 250 mg tablets, and the physical mixtures (PM) (Section 2.6).

Composition (w/w%)	DC1[a]		DC2		DC3		ITCG[a]	INDG[a]
	ITC	IND[b,c]	ITC[c]	IND[b]	ITC[b]	IND[b]		
Freeze-dried NPS	**18**	**40**	**40**	**60**	**71**	**75**	**73**	**57**
MCC	41	29	29	19	11	9		
Lactose monohydrate	30	20	20	10	7	5		
PVP	5	5	5	5	5	5	3	3
Cross-linked PVP	5	5	5	5	5	5	5	5
CSD	0.5	0.5	0.5	0.5	0.5	0.5		
SMCC							18.5	34.5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

[a] Compositions of the PMs, where NPS replaced with bulk ITC/IND.
[b] Therapeutic dose included.
[c] fDC compositions.

2. Materials and methods

2.1. Materials

Itraconazole (ITC) and indomethacin (IND), used as model compounds, were generously provided by Orion Pharma Oy (Espoo, Finland). Poloxamer 407 (F127, Kolliphor® P, Sigma–Aldrich Chemie GmbH, Steinheim, Germany), poloxamer 188 (F68, Kolliphor® P, Sigma–Aldrich Chemie GmbH, Steinheim, Germany), microcrystalline cellulose (MCC, Avicel PH-102, (Ø ~ 100 μm) FMC International, Cork, Ireland), silicified microcrystalline cellulose (SMCC, Prosolv HD 90, Penwest Pharmaceuticals Co., Patterson, N. Y., USA), polyvinylpyrrolidone (PVP, povidone, Kollidon K25, (Ø ~ 50–250 μm) BASF Co., Ludwigshafen, Germany), lactose monohydrate (Pharmatose® 80 M (Ø ~ 200–800 μm) DMW International, Veghel, the Netherlands), cross-linked povidone (cross-linked PVP, Kollidon CL, (Ø < 250 μm) BASF Co., Ludwigshafen, Germany), colloidal silicon dioxide (CSD, Aerosil® 200 M, Orion Pharma Oy, Espoo, Finland) and magnesium stearate (Orion Pharma Oy, Espoo, Finland) were used in the preparation of the nanocrystal formulations and the negative control, *i.e.*, physical mixture. Ethanol (96 v/v%, Altia Oyj. Rajamäki, Finland), methanol (HPLC grade, VWR International, Leuven, Belgium), hydrochloric acid aqueous solution (0.1 M, HCl, VWR International, Fontenay-sous-Bois, France), phosphate buffer (0.2 M, KH_2PO_4 and NaOH, Riedel-de Haën GmbH, Seelze, Germany), acetonitrile (ACN) (HPLC grade, VWR International, Pennsylvania, USA), ortho-phosphoric acid (85 v/v%, Sigma–Aldrich Chemie GmbH, Steinheim, Germany) and trifluoroacetic acid (Sigma–Aldrich Chemie GmbH, Steinheim, Germany) were used in the characterization of the nanocrystal formulations. Water used throughout the study was ultra-purified Milli-Q®-water (Millipore SAS, Molsheim, France).