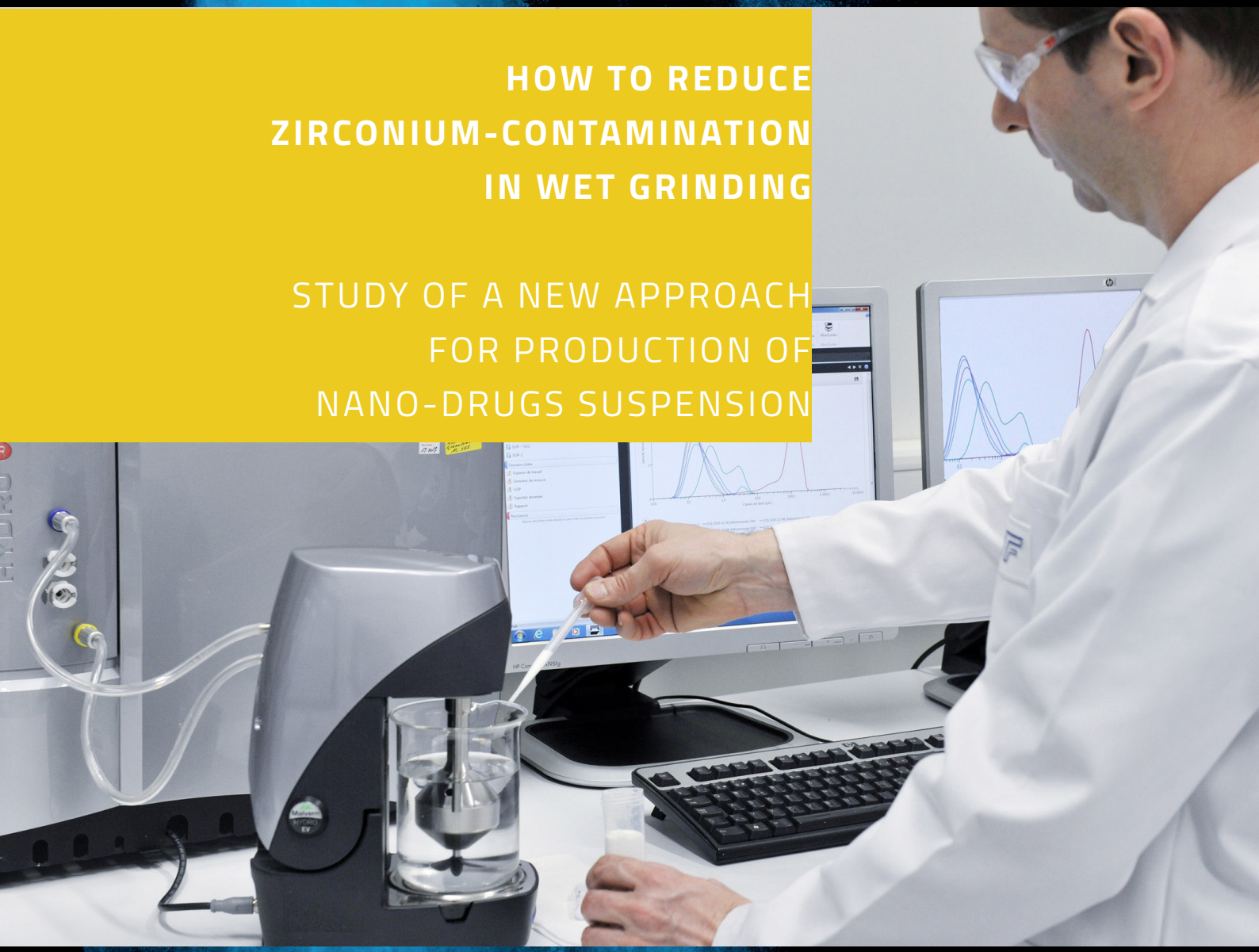
WHITE PAPER

FREWITT

HOW TO REDUCE ZIRCONIUM-CONTAMINATION IN WET GRINDING

STUDY OF A NEW APPROACH FOR PRODUCTION OF NANO-DRUGS SUSPENSION



WE CARE ABOUT MILLING

WWW.FREWITT.COM

INTRODUCTION

Top-down production of nanoparticle drug suspension is commonly done by wet stirred media milling (WSMM). In comparison to bottom-up approaches, WSMM offers many advantages for the production of poorly water soluble drugs, namely nanoparticles: capable of allowing high drug loading, organic solvent-free processing, continuous operation, as well as a capability of ease in scale-up[1].

However, this technology raises a challenging quality issue for the pharmaceutical industry: notably how to minimize and control the attrition of the grinding media (yttrium stabilized zirconium oxide beads) during the milling process. The ICH Guidelines Q3D and the newly enforced USP Chapter 232/233 set strict limits on elemental impurities in drug products. According to regulatory concepts, zirconium (Zr) presence ought to be reduced as much as possible, while the amount is to be quantified analytically and proven reliably stable during a robust manufacturing process. Several scientific publications [1,2,3,] studied the wear generation during drug production by WSMM and quantified the Zr generated under typical processing conditions.

We report herewith the investigation of a novel WSMM approach, drastically reducing 12-fold, the generation of Zr versus previously published studies of the same subject.

METHODS

Similarly to the published studies[1,2,3], a reference drug suspension system was used through all experiments: API (ketoconazole) at 10% w/w in DI was stabilized with 2.5% w/w non-ionic polymer (HPC) and 0.5% w/w anionic surfactant (SDS). Wet milling was done on a Frewitt NanoWitt with a milling chamber type 100 (working volume 140 ml) in silicon carbide, using a rotor/separator in zirconia. The milling chamber was filled with beads at a ratio of 60% v/v. Beads were sourced from 2 different suppliers, TOSOH Corp. Japan (type YTZ) and Sigmund Lindner GmbH, Germany (type ZY-P and ZY-E) and preconditioned prior to conducting the milling tests. All milling runs were carried out with bead size of 300 microns while using a rotor tip speed of 4.7 m/sec over a milling period of 120 minutes. Particle size distribution (PSD) of the drug suspension was measured by dynamic light scattering (DLS) and laser diffraction (LD). Elemental Zirconium was measured by inductively coupled plasma optical emission (ICP-OES).

RESULTS AND DISCUSSION

Impact of Processing Parameters on Zr Generation

The Table 1 summarizes the milling trials carried out under the different processing conditions tested. All runs reached a particle size d50 between 172 to 227 nm, and a poly dispersity index (PdI) between 0.14 to 0.18. Zirconium concentrations in ppm (micro g/g of API) were between 8 to 210 ppm. Before detailing further these results, we need to consider some global process aspects.

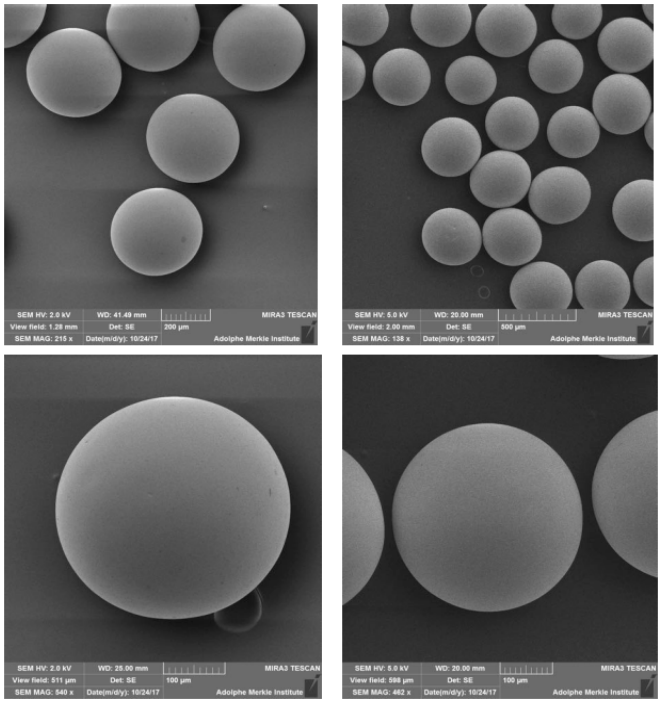


Figure 1. Beads before (l.) and after (r.) milling process

GLOBAL PROCESS CONSIDERATIONS

As mentioned, a paramount challenge for producing a drug substance by WSMM is the significant reduction of Zr. However one should not overlook the final objective of the WSMM process which is to produce nanoparticle drug suspensions for the purpose of developing a drug formulation, in order to enhance the bioavailability of an active pharmaceutical ingredient (API), primarily a BCS Class II type. Such drug formulation encompasses many aspects with prime consideration on the API nanoparticle suspension size and polydispersity (PdI). The PdI reflects the degree of homogeneity within the nanoparticle suspension and provides a critical quality attribute (CQA), ensuring the stability of the suspension system over time. This ensures a controlled release of the API, according to the drug formulation delivery mechanism and metabolic pathway. Consequentially, it is important to consider size & PdI requirements in conjunction with the objective of reducing the amount of Zr of the nanoparticle drug suspensions.

FreDrive-Lab NanoWitt
High performance bead mill for the particle size range D50 to 50nm

COMPARISON WITH PREVIOUS STUDIES

Taking into consideration the need to produce nanoparticle drug suspensions with PSD of d50 50-300 nm and PdI < 0.2 (mid-value window for a moderately poly- dispersion[4]), we compared the analytical values of Zr elemental impurities of our trial runs with the published data[2,3].

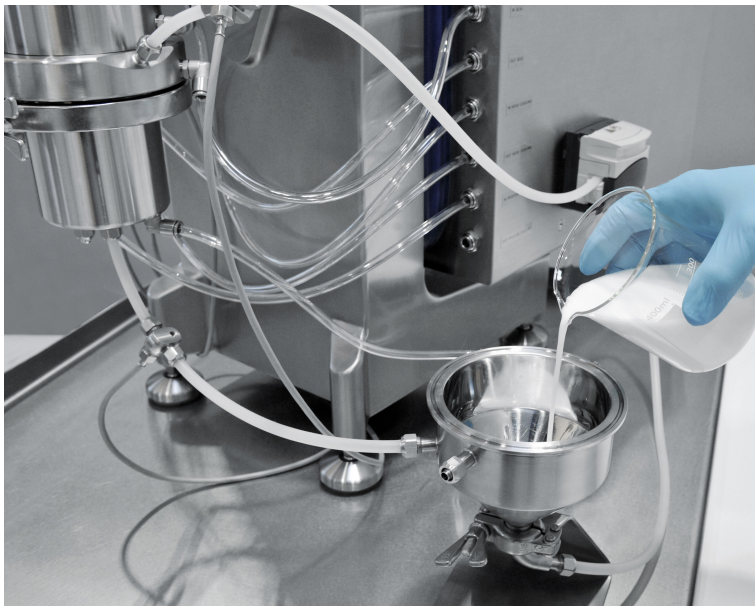
Trials	Beads size µm	Beads ratio volume % (bulk vol)	Milling time Min	Tip Speed m/sec	Particle size d50 nm	Particle size PdI	Zr level µg Zr/g drug ppm
Investigation of novel WSMM							
TS (YTZ)	300-400	60	120	4.7	215	0.16	8
TS (YTZ)[A]	300-400	60	120	4.7	219	0.15	8
SL (ZY-E)[B]	300-400	60	120	4.7	219	0.18	75
SL (ZY-E)[AB]	300-400	60	120	4.7	227	0.17	174
SL (ZY-E)[B]	300-400	60	180	4.7	172	0.16	83
SL (ZY-P)	300-400	60	120	4.7	203	0.14	66
SL (ZY-P)[A]	300-400	60	120	4.7	217	0.16	210
Published data [2]							
TS (YTZ)	100	80	D	12	150	0.13[C]	98
TS (YTZ)	200	80	D	12	160	0.17[C]	109
SL (ZY-P)	70-120	80	D	12	150	0.13[C]	346
SL (ZY-P)	150-250	80	D	12	180	0.21[C]	389
SG	100	80	D	12	150	0.13[C]	443
SG	200	80	D	12	180	0.18[C]	316
Published data [3]							
1	800	67.5	360	11.7	169	0.158	1004
2	400	67.5	360	11.7	137	0.114	832
3	200	67.5	360	11.7	120	0.246	453
4	100	67.5	360	11.7	97	0.272	307
5	50	67.5	360	11.7	95	0.241	47
6	50	67.5	120	14.7	94	0.228	36
7	50	90	120	14.7	93	0.250	70
8	50	90	120	14.7	88	0.269	83
9	50	67.5	360	11.7	77	0.272	24
10	50	90	120	14.7	72	0.338	56

A: New beads used without preconditioning
B: ZY-E new replacement version of ZY-P formerly available and tested in previous publication (ref. 2)
C: PdI estimated based on published data of the study (ref. 2)
D: Milling done until reaching a specific energy of 7.2 kJ/kg API

TABLE 1

From the published data set ref. 2 (section 2 of Table 1), all results were used as comparison base (Zr values between 98 to 443 ppm) and only 2 results (Zr values between 832 to 1004 ppm) of the published data set ref. 3 (section 3 of Table 1). As a result, the lowest Zr value that matched PSD/PdI criteria is 98 ppm.

The first section of Table 1 reports our test results for all tests (duplicated) and done with beads of 300 microns. The Zr values range from 8 to 210 ppm. To assess the impact of preconditioned beads; milling runs were done with and without for the 3 types of beads. No change of Zr value was reported for TS YTZ whereas SL ZY-E showed



an increase of 132 % if not preconditioned (75 to 174 ppm) and SL ZY-P an increase of 218 % (66 to 210 ppm). Extending the milling time by 50% (120 min to 180) with preconditioned SL ZY-E resulted in a Zr increase of 11 % (75 to 83). Compared with beads preconditioned similarly to published studies[2,3] the Zr values were 8 ppm for TS YTZ, 75 ppm for SL ZY-E and 66 with SL ZY-P. Comparing strictly on the bead types with the lowest published data set ref. 2, our results for TS YTZ are 8 ppm vs 98 ppm and for SL ZY-P 66 ppm vs 346 ppm. As mentioned previously, the zirconium generated during the milling process can be reduced by optimizing the processing conditions and selecting the beads offering the best performances in terms of wear resistance and efficiency.

Considering these process conditions, the system under evaluation in our study uses very low tip speed and low bead ratios compared to published data (4.7 vs 12 m/s ; 60% vs 80%) in order to achieve the expected PSD, PdI and milling time. When comparing Zr generated by using the most performing beads (TS YTZ), this translates into a value of 8 ppm, which is 12 X lower than the best published data[2,3] (98 ppm).

The radical reduction of Zr impurities reported in our study opens up new opportunities for the WSMM technology. An extensive process characterization of this novel approach is currently under way with partners in the pharma industry.

We would like to acknowledge the sound support of the following Swiss research institutes in our investigational work: Federal Polytechnical School of Lausanne (EPFL), University of Applied Sciences (HES-SO/Wallis), Adolf Merkle Institute (AMI).

CONCLUSION

The results of our investigation of a novel wet stirred media milling (WSMM) system shows a significant, 12-fold reduction factor of the zirconium (Zr) generated during milling versus the published studies on the same subject. To make results comparable; a similar drug suspension system processing methodology, final d50 size, PdI, and analytical techniques were used in our study, as in the previously published studies. The WSMM system investigated is a recently developed wet nano milling equipment (NanoWitt from Frewitt SA) with a proprietary, patented configuration that increases the milling efficiency and homogeneity, while curtailing the attrition between zirconium beads. Generation of Zr, as elemental impurities in a drug product, is currently a major issue and drawback for the broader acceptance of drug nano-suspensions produced by WSMM.

REFERENCES

1. Li M, Azad M., Dvé R. Bilgili E., Nano-mil ling of drugs for bioavailability enhance ment : a holistic formulation-process perspective, Pharmaceutics, 8, 1- 39 (2016).
2. Juhnke, M., Märtin D., John E., Generation of wear during the production of drug nano-suspensions by wet media milling. Eur. J. Pharm. Biopharm. 81, 214-222 (2012).
3. Li M., Yaragudi N., Afolabi A., Bilgili E., Sub-100 nm drug particle suspensions prepared via wet milling with low bead contamination through novel process intensification, Chem. Eng. Sci. 130, 207-220 (2015)
4. Malvern Instrument Ltd., White paper DLS, (2017)

After peer and committee review, this white paper, entitled Investigating a novel Approach to drastically minimize Zirconium Contamination during the Production of Drug Nano-Suspensions by wet stirred Media Milling , has been Accepted for Poster presentation at the 2018 AAPS PharmSci 360 to be held November 4-7, 2018 in DC.

Contact:

Christian Rhême
R&D Manager

Frewitt SA
Route du Coteau 7
CH-1763 Granges-Paccot / Switzerland
Phone: +41 (0) 26 460 74 00
c.rheme@frewitt.com
www.frewitt.com