Measurement and Identification of Foreign Particles in a QbD Environment - Streamlining with Effecient Analytical Methods

O. Valet and M. Lankers, rap.ID Particle Systems GmbH, Berlin, Germany

Dedicated Approach for Foreign Particles

filtr.AID

Sample Preparation

The special filtration and sample preparation equipment and the controlled filtr.AID filters minimized the amount of time for cleaning of the equipment and resulted in the quick establishment of a low blank value.

Single Particle Explorer

Database

Enumeration

Substance	All particles	Size distribution [µm]					
		2 - 5	5 - 10	10 - 25	25 - 50	50 - 100	larger 100
All particles	6516	2368	1976	459	846	660	207

ID Raman

Identification

Use of the LPE streamlined method development, directly verifiying ideal active and carrier dissolution parameters with integrated Raman spectroscopy.

Substance	All particles	Size distribution/ µm					
		2 - 5	5 - 10	10 - 25	25 - 50	50 - 100	larger 100
Polystyrene	270	58	36	20	0	20	20
Polymorphine	154	29	2	56	0	59	4
Polyvinyl acetate	59	146	22	12	34	7	7
Talcum	26	17	7	9	21	10	0
Protein	291	97	0	27	24	44	14
Analyzed	800	347	65	124	79	140	45
All particles	6516	2368	1976	459	846	660	207

ID Result for Lactose.

Identifying Control Points of a Dry Powder Inhaler Formulation

Process Environment

Formulation — Active 1, Active 2, Lactose

Delivery Device — Part A, Part B, Part C

For three of the major components of the inhaler, different methods of particle extraction were established. This was also validated with the ISO 16232 approach.

Delivered Dose

As an example, several parts of a dry powder inhaler formulation were measured separately. For each part, an FP assessment method was developed and validated In the validation step the linearity, robustness, repeatability and intermediate precision were tested according to the ICH parameters.

Particle Counting Results after Method Development Qualification of Components and Parts of a Dry Powder Formulation and the Device

Substance	Amount (mg)	Size Distribution (µm)						
		All particles	>=2	>=5	>=10	>=25	>=50	>=100
Active 1	33	2264	1550	345	267	81	17	4
Active 2	39	1999	1634	224	89	48	4	0
Lactose	507	6516	3524	1475	978	357	174	8
Part A	1 Piece	1668	988	415	197	48	17	3
Part B	1 Piece	1352 1	6345	4215	1987	635	287	52
Part C	1 Piece	1595 8	7865	4486	2450	784	325	48
Delivered Dose	7 Actuations	678	485	117	52	19	4	1

The Analytical Method leads to the right Decision

In the development of the Design Space for enumeration and identification of foreign particulate matter, possible factors affecting measurement results must first be considered.

Development

Routine QC

LPE High Throughput Raman spectroscopy enables quick root cause and the elimination of source of foreign particles directly after enumeration without further sample preparation.

Root Cause

Design Space

Enumeration Development Batches

Stability Trend

No

Control Space

Specification for NDA

Enumeration

No — OOS/ OOT — Yes