New cascade impactor software

CITDAS Version 3.00 Wibu offers new options for processing cascade impactor deposition data

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Processing deposition data in a standardized form, an important requirement for the pharmaceutical industry, presents a major task since the various phases of product development, stability testing, and batch release generate significant amounts of data. Each of these steps necessitates deposition data processing to confirm product performance and robustness. Copley Inhaler Testing Data Analysis Software (CITDAS) allows rapid and standardized processing of cascade impactor deposition data for all of the commonly used types of impactors and for a range of operating conditions.

The latest release, CITDAS Version 3.00 Wibu, builds upon the success of the Version 2.00 Wibu and represents the first update since 2004. All of the key features that have made the software so successful and widely used have been retained, and the highly anticipated new release introduces features that can increase data processing rates and expand the scope of data interrogation

Expansion to nebulizer data

CITDAS has always allowed standardized data processing for the operating conditions of four alternative impactor devices; Andersen Cascade Impactor (ACI), Multi-Stage Liquid Impinger (MSLI), Marple-Miller Impactor (MMI) and the Next Generation Impactor (NGI). Since the first release of CITDAS in January, 2001, the development team has focused the needs of users working with Metered Dose Inhalers (MDIs) and Dry Powder Inhalers (DPIs). The original software's data processing did not encompass the flow rates now used for nebulizer testing with the NGI.

Now, Version 3.00 Wibu has extended the range of data processing to include the NGI at operating flow rates between 15 – 30 L/min [1], so calibration data is automatically selected across the operating range 15 – 100 L/min, allowing users working with nebulizers to benefit from this useful tool.

Fine particle dose/fraction groupings

The new version of CITDAS includes a key new feature that provides users with the ability to define up to five fine particle dose/fraction groupings, with each group defined by a range of either impactor stage or aerodynamic particle diameter. Therefore, in addition to reporting fine particle dose values, the software now can routinely subdivide the reported delivered dose into five populations. CITDAS determines the new dose populations by interpolation, as it does most other calculations, which means that users can confidently process both log-normal and multimodal particle size distributions.

The new groupings feature comes with a host of data integrity checks to ensure that all values reported precisely represent the input data. For example, on occasions when interrogation of the data would be inappropriate, e.g., in size ranges where no cumulative drug mass exists, new features in the software report limit of detections (LOD) accordingly. Also, to facilitate the introduction of the fine particle dose/fraction groupings, Version 3.00 Wibu has enhanced calculation precision to ensure that the effect of compound errors is minimal.

Performance of Calculation

In accordance with USP 31 and Ph. Eur. 6.0, CITDAS uses cumulative drug mass and % cumulative drug mass data to determine values for Mass Median Aerodynamic Diameter (MMAD), Geometric Standard Deviation (GSD), and Fine Particle Dose (FPD). The stages used for evaluating particle size distributions are shown in Table 1.

The developers used twelve lognormal input distributions (Table 2) to verify the calculation performance

Table 1

Stages used to evaluate particle size distributions

ACI	Filter to Stage 0 (inclusive)
MSLI	Stage 5/Filter to Stage 2 (inclusive)
MMI	Filter to Stage 2 (inclusive)
NGI	MOC to Stage 1 (inclusive)

Table 2

Lognormal input distributions used to verify calculation performance

MMAD (µm)	0.5			1.0			3.0			5.0		
GSD	1.3	1.5	2.5	1.3	1.5	2.5	1.3	1.5	2.5	1.3	1.5	2.5

during the input/output verification of CITDAS Version 3.00 Wibu. Each of the "superfine," "fine," "medium," and "coarse" distributions was tested at a GSD of 1.3 (i.e. a very narrow distribution), 1.5, and 2.5. Over the operating flow rate of each of the four impactors, CITDAS Version 3.00 Wibu reported MMAD to within ± 0.2% of input values and GSD to within ± 0.5% (Table 3).

As with the previous versions of CITDAS, the software reports GSD only for a particle size distribution if the distribution is determined to be lognormal within ± 1 standard deviation of the Mass Median Aerodynamic Diameter (MMAD). CITDAS calculates whether or not to report GSD by performing a linear regression upon the cumulative % undersize plot (log-Probit scale) between the Probit (+5) values 4 and 6. If the R2 coefficient for the regression exceeds the user defined value (default value is 0.95), the program reports GSD; otherwise, the value for GSD appears as "NA."

Evaluation of the reported values of FPD using the twelve distributions (Table 2) was performed for six size-ranges over the operating flow rates of the four impactors (Table 4). Accuracy in the interpolation of FPD depends on the total cumulative drug mass, where the total cumulative drug mass is calculated by summation of the drug mass collected on the stages presented in Table 1. During verification, the difference in the input and output data fell within 1.0% of total cumulative drug mass divided by the number of doses sampled for the ACI and NGI. Further testing determined values of 2.1% for the MSLI and 1.7% for the MMI (see Table 5). For calculation values of FPD less than or equal to 5µm, the respective values fell to 1.0% for the MSLI and 0.4% for the ACI, NGI, and MMI.

Table 3

Summary of MMAD and GSD errors relative to actual value

	MMAD		GSD	
	Min	Max	Min	Max
ACI	99.8	100.2	99.6	100.5
MSLI	99.9	100.2	99.6	100.2
MMI	99.8	100.2	99.7	100.4
NGI	99.8	100.2	99.7	100.4

Table 4

Size ranges evaluated

	Size range (µm)					
ACI	0-1	1-2	2-3	3-4	4-5	≤5
MSLI	0-1.7	1.7-2	2-3	3-4	4-5	≤5
MMI	0-1	1-2	2-3	3-4	4-5	≤5
NGI	0-1	1-2	2-3	3-4	4-5	≤5

Data integrity checks

When interrogation of the data is inappropriate, Version 3.00 Wibu reports LOD (limited of detection) for fine particle dose and fraction (when defined by size) if:

a) Values are associated with a cumulative drug mass of less than 2%.

b) Fewer than three stages have a cumulative drug mass >1%.

c) Group results (when defined by size) use a specification that is captured by a) or b).

In addition, Version 3.00 Wibu reports "NA" (not applicable) for mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) values when:

a) >50% of the cumulative drug mass is deposited on the lowest impaction stage (filter/MOC).

b) Fewer than three stages have a cumulative drug mass >1%.

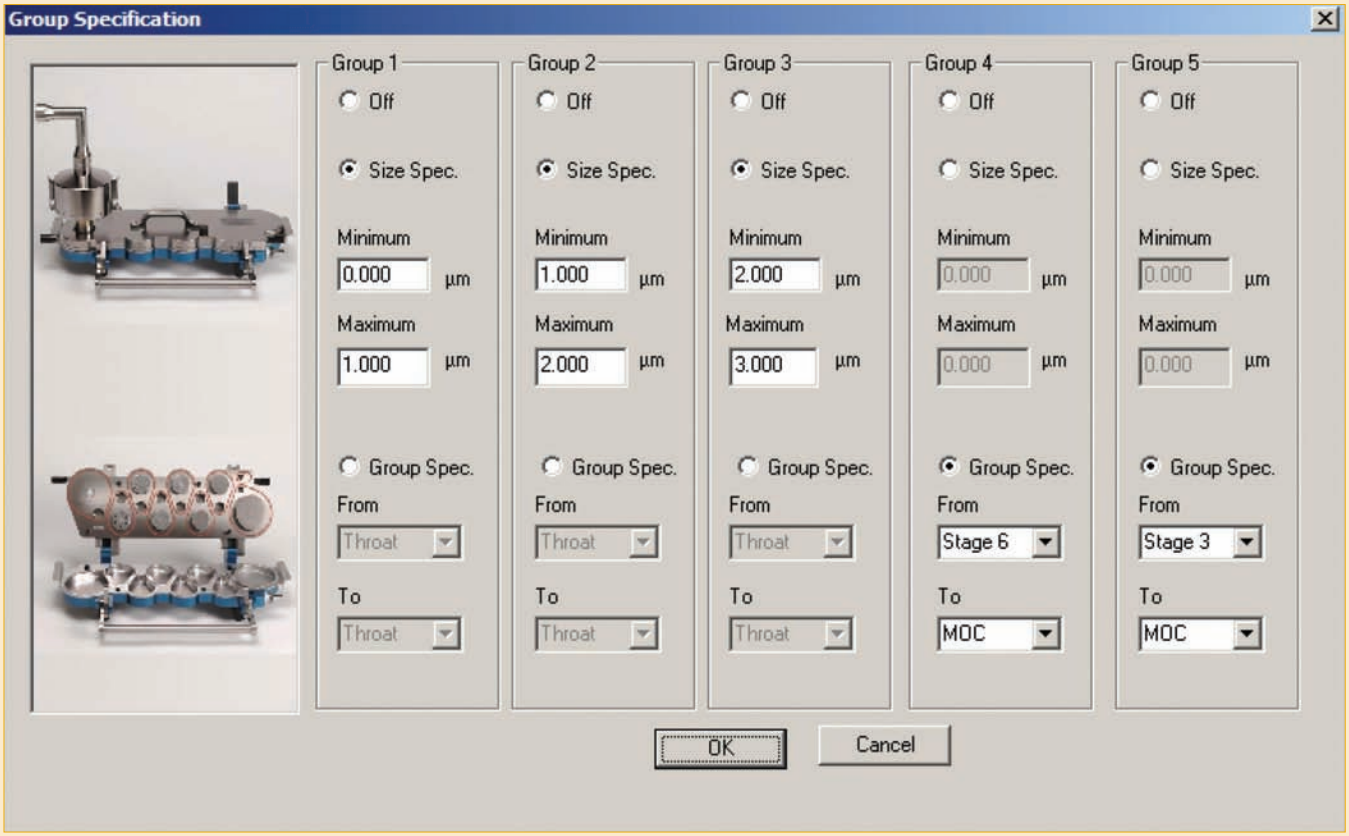
The introduction of these data integrity checks ensures that CITDAS output is always representative of the input data.

Table 5

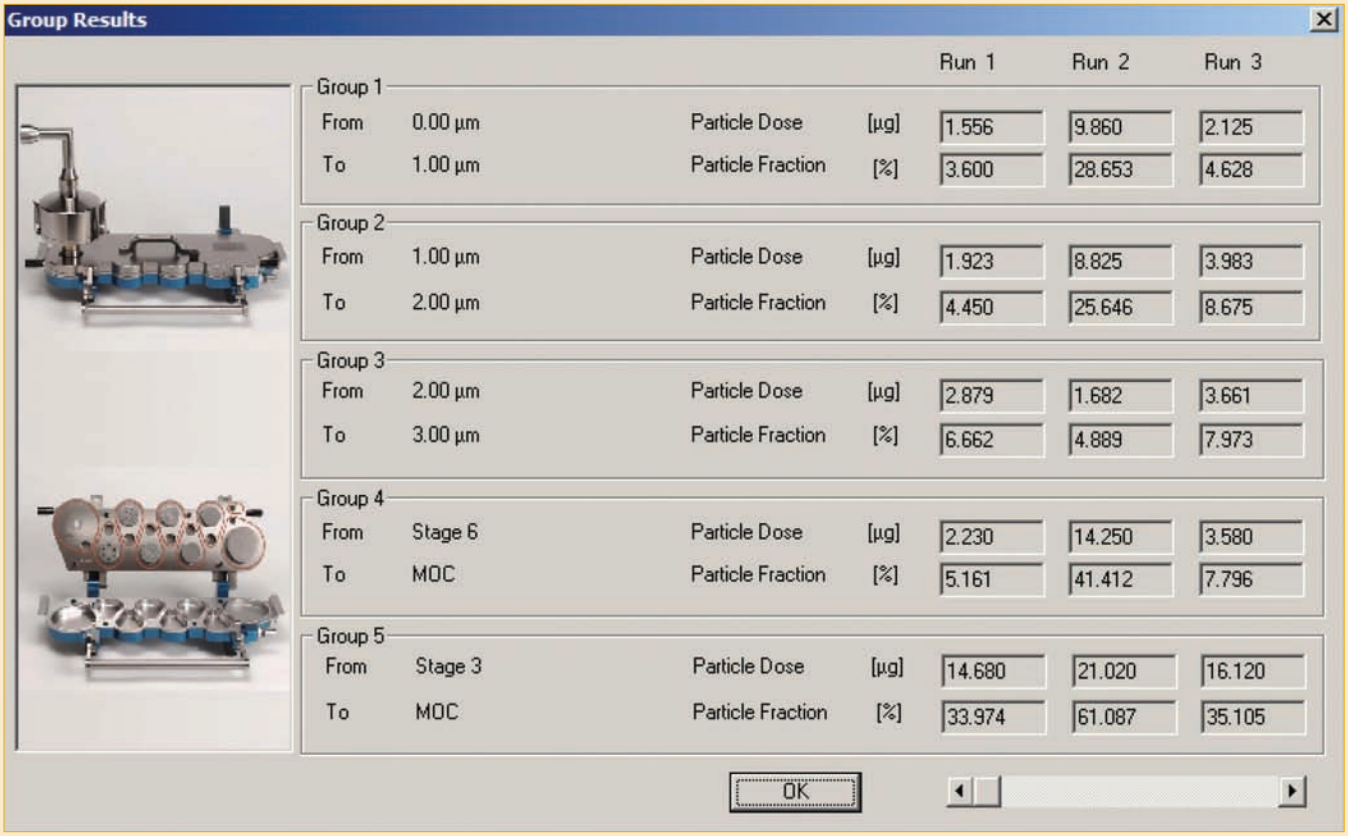
Summary of FPD errors

	Residual per dose relative to cumulative drug mass (%)			
	FPD by size range		FPD ≤5µm	
	Min	Max	Min	Max
ACI	-0.6	+1.0	-0.1	+0.4
MSLI	-2.1	+1.7	-0.2	+1.0
MMI	-0.9	+1.7	-0.1	+0.4
NGI	-0.6	+1.0	-0.2	+0.4

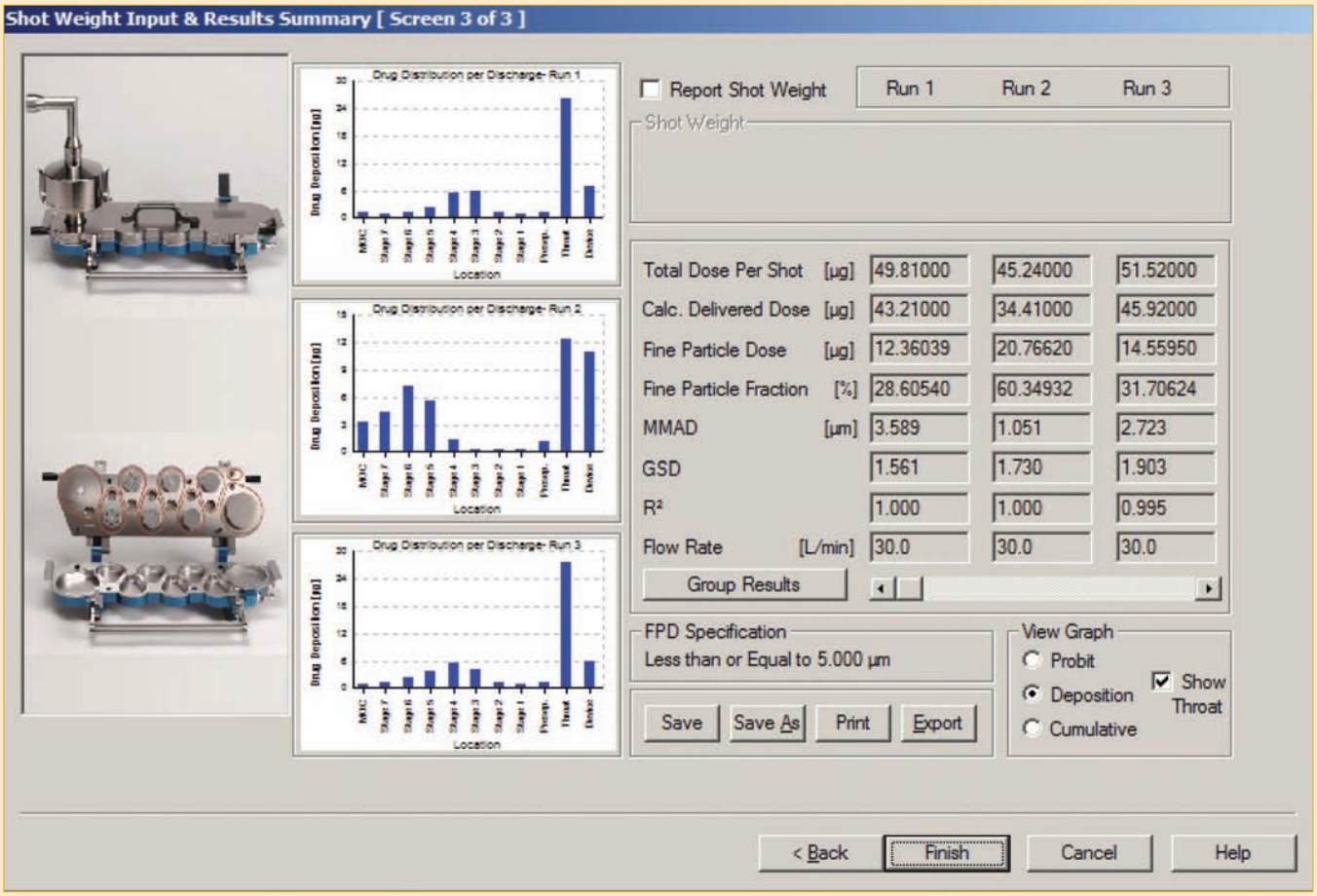
Groupings can be defined by aerodynamic diameter or impactor stage



Group results can be viewed onscreen



Results summary screen— up to 12 runs can be processed in each file



Importation of Comma Separated Value/Variable (CSV) files

The "import CSV file" function provides a powerful new feature with the potential to enable CITDAS to link up with other applications and allows files exported from CITDAS in CSV format to be modified/edited and re-imported. Use of this function with appropriate verification of data integrity following importation introduces the potential to streamline data input into CITDAS, potentially reducing manual data entry requirements.

Other new features

The new version of CITDAS now has five printout types that allow the user to present data in a variety of formats, including European Pharmacopeia format, United States Pharmacopeia format, Graphical Summary, the Tabulated Summary, and Group Results. In addition, the tabular summary printout now includes raw input data, allowing direct cross-checking of output data against raw input data on the same printout. Further user control of data appearance is provided by the ability to select the number of decimal places for seven different input/output parameters.

Users can now scroll right at data entry to view new calculations that include "Mean/dose," "SD/dose," and "%RSD/dose." Mean values for up to 12 runs can also now be printed separately. Mass balance calculations on USP and Ph.Eur. print-outs have also been expanded beyond the USP/Ph.Eur. requirement of 75%-125% to include ranges of 80%-120% and 85%-115% to meet FDA requirements.

CITDAS V3.00 Wibu runs on Microsoft Windows XP home, Windows XP, and Windows VISTA operating systems. With its host of new features, this version of CITDAS provides additional versatility without changing the original's simplicity of operation.

References

1. Marple V., Roberts D., Mitchell J., (2004) 'A proposal for the use of the next generation pharmaceutical impactor (NGI) at flow rates between 15 and 30L/min.' Respiratory Drug Delivery IX. Davis Healthcare International Publishing, River Grove, IL, 701–703.

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