Dissolution Market

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• Objective

- Dissolution - What is it?
- Market and Product Situation
- Carl Zeiss Offering
- System Packages
- Competition

• What is Dissolution

- Solid dosage form assays in the pharmaceutical industry
- Release profiles of tablets or capsules in an in-vitro system
- Test for measuring uniformity both within and between batches
- Correlation between the in-vitro and in-vivo for assessment of product performance

• USP 1 and 11 Methods

- Method 1 - Apparatus 1 using baskets
- Method 11 -Apparatus 11 using paddles
- Typically 3 to 4 time points for 1 hour test
- Analysis by manual, flow through to UV spectrometer or HPLC

• Market Review

- Many dissolution bath companies ie
  - Vankel, Pharmatest, Hanson, Distek, Logon
- Nearly all major spectrophotometer companies offer systems and software to link up to a bath
  - HP, PE, Varian, Beckman, Shimadzu, Hitachi, Unicam etc
- Same applies for HPLC suppliers

• Manual Methods

- Time consuming and tedious
  - Targeted for laboratory automation long time ago
  - Automated off-line chemical analysis systems available:
- Automated dissolution baths
  - Zymark Multidose, Pharmatest Auto Dis
    - samples then presented to spec via autosampler

•Automated spectrometer method

- Samples extracted by pump through tubing(1-2m)
- Filters used to remove particulates
- 8 cell programmmer with flow cells
- Calibration of flow and recovery needs to be checked regularly
  - These have inherent weakness:

• Disadvantages

- Blockage of tubing, wear and tear - cost and time
- Filters need to be regularly changed - cost and time
- Cell transport systems never the most reliable
- Calibration is a time consuming function

•Zymark - Zeiss System

- Automated filling of vessels with media
- Automated tablet dropping
- USP 1 and 11 apparatus
- Control of MCS Spectrometer
- Ability to do queued runs
- Automated cleaning of probe
- Automated cleaning of vessels

•Fibre optic probe method

- Readings directly in vessel with single probe - no extractive problems as with tubing and filters etc
- All readings receive same probe error ie pathlength, unspecified contamination
- Probe can be cleaned between measurements
- Carry over is greatly reduced

System Software

- NT operating system
- Security Level Access
- User friendly
- Secure
- Data written to NT server
- Automated Report Geberation

Business Advantages

- 293 dissolutions in 31 robot days
- Manual@4/day = 73 days. 15 working weeks
- 3 fold increase in productivity
- Payback for system < 2 years

Advantages with MCS 500

- Optimised fibre optic based system
- PDA detection for full spectrum analysis - robust calibration methods
- Modular units ie CLD cassette design
- Stable - MCS patented design
- Sensitivity

The Z-Dis-Mux System

A Multi-Channel Dissolution Monitoring System

Application

- Dissolution profiling of extended release formulations over 24-48 hours
- Fast release products also possible as time point intervals of 2 minutes can be achieved
- Aimed at Analytical and Pharm R&D groups involved in product enhancement and new formulation development

Advantages

- In-situ analysis via fibre optic probes - avoids problems related to extractive sampling i.e. filters and tubing
- Blank and standard readings taken during every cycle for higher accuracy
- All measurements and report generation are automatic freeing operator for other tasks

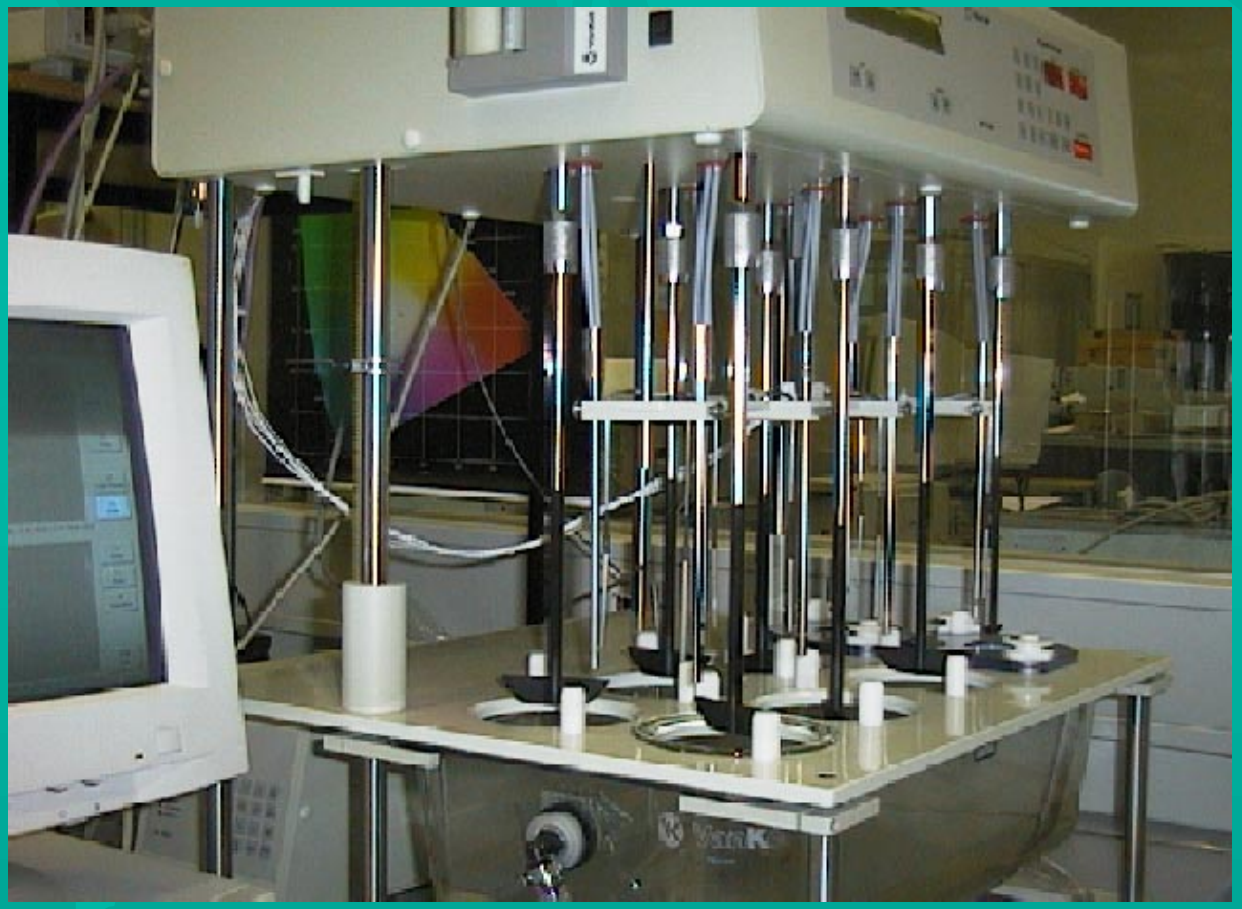
System Configuration

- VanKel 8 vessel bath with autotemp controller and manifold for USP 1 or 2 methods
- Dicon Multiplexer
- 1/4 in diameter probes with 2 m fibres from Hellma or CST
- MCS 551 UV Spectrometer
- Zeiss labView Z-Dis-Mux software

MCS 551 UV Spectrometer with Dicon Multiplexer

Vankel Bath with manifold

Side view of Vankel with manifold and attached F/O probes with temperature sensors



Front view of Vankel, 6 vessel positions and two for blank and standard on extreme right

Paddle shaft, F/O probe and temperature sensor

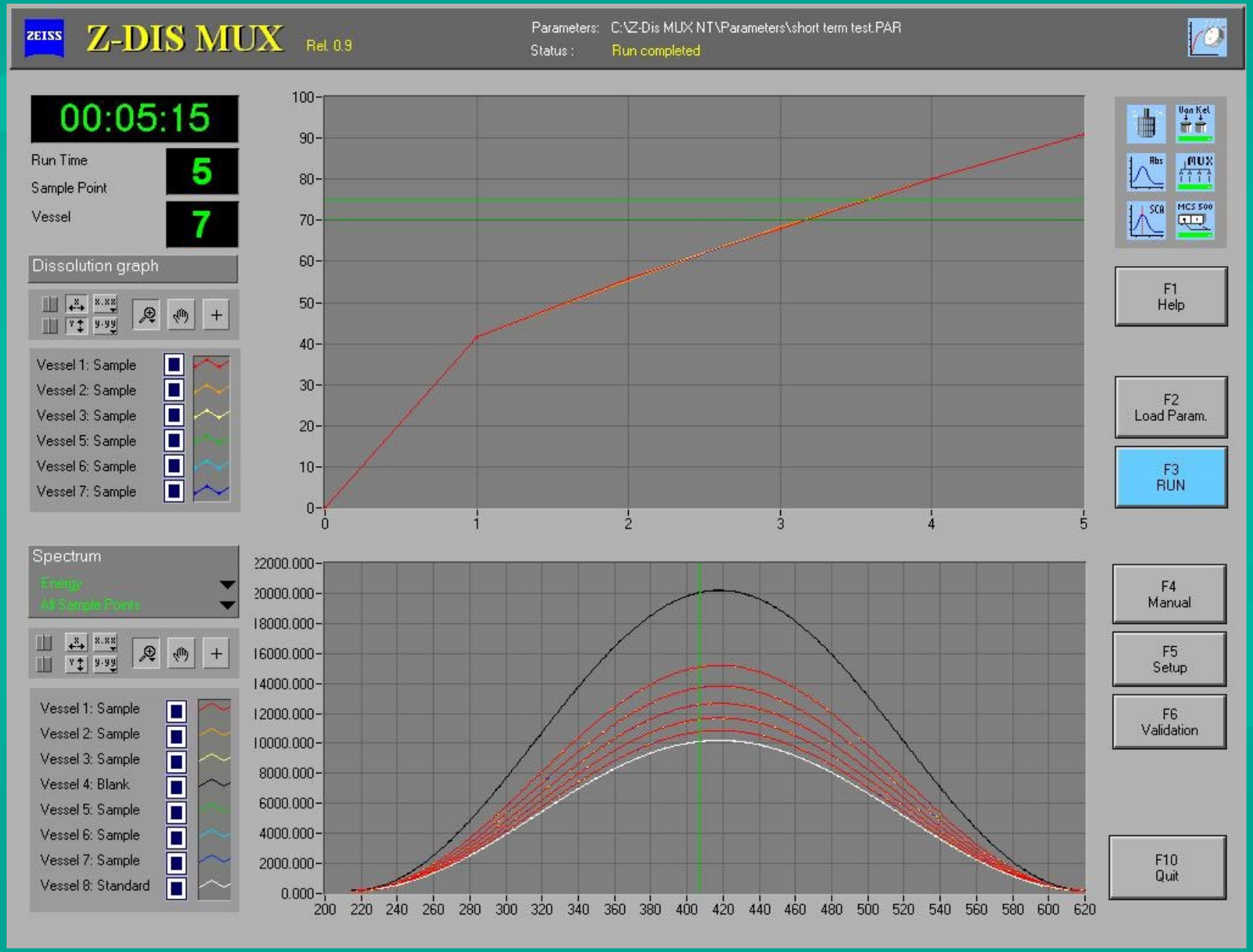
Operation

- Vankel bath prepared for paddles or baskets
- Vessels manually filled with media
- All probes lowered for Interchannel Calibration
- 2 standards placed in vessels 4 and 8 for system suitability check
- Standard in vessel 4 replaced with blank solution
- System ready for run

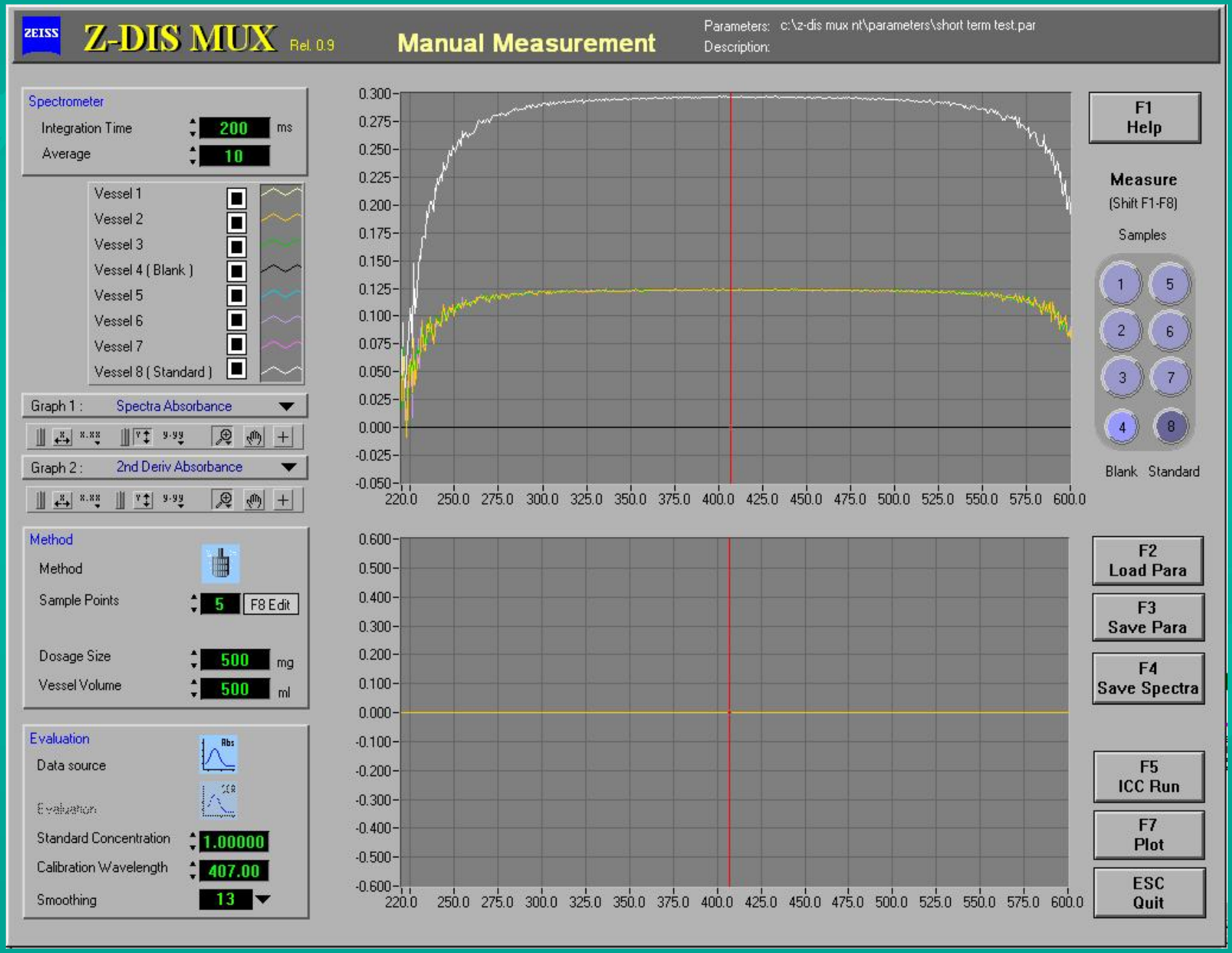
Z-Dis-Mux Software - main features

- LabView programme under NT linked to client network for data storage and printout of reports
- Security access and password protected
- Validation screen for testing and checking status of Vankel, Dicon and MCS hardware
- Automatic and manual operation
- Automatic Interchannel Calibration with bubble detection
- Absorbance data can be viewed in Aspect software

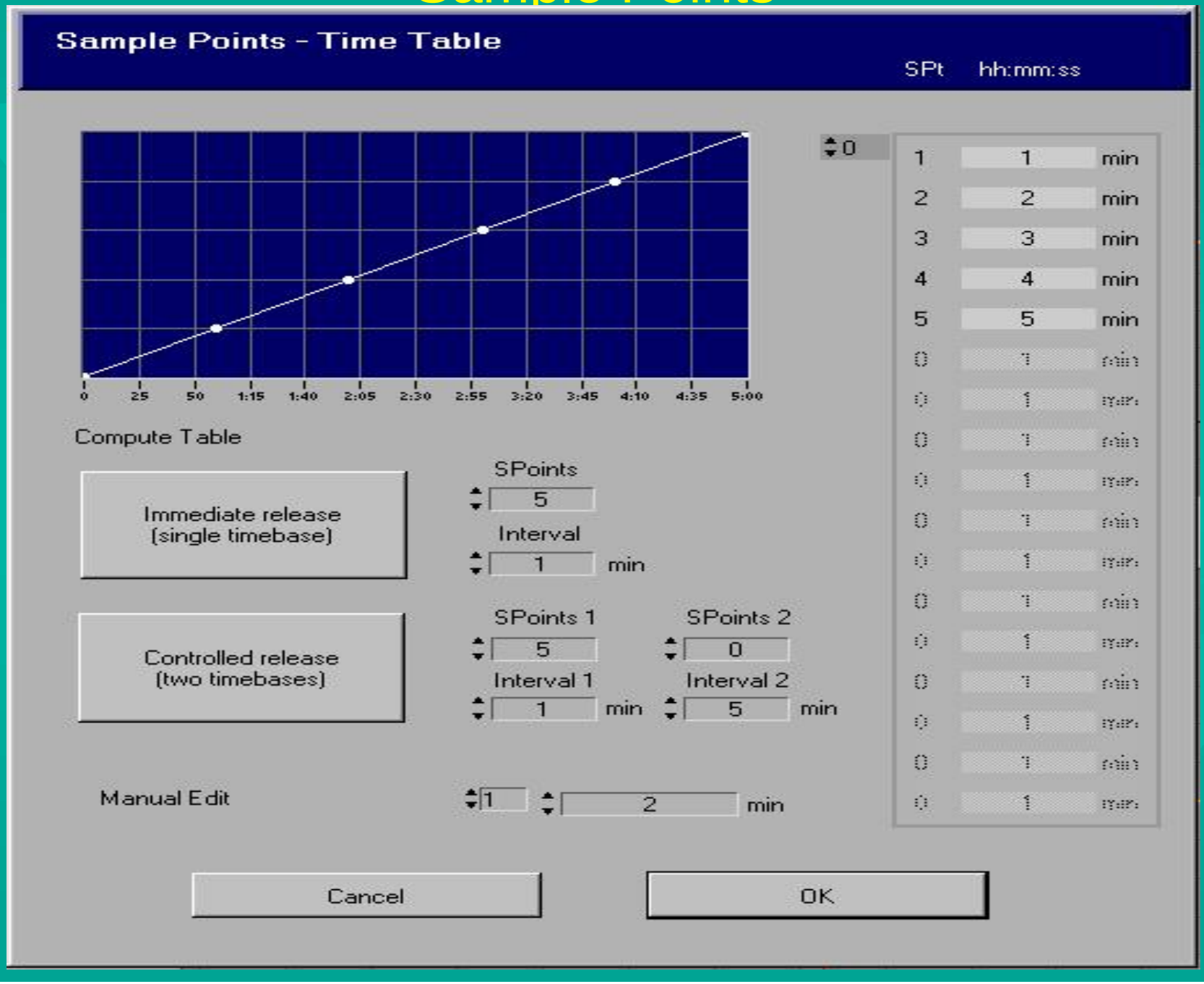
Automatic Dissolution Run Screen



Manual Screen



Sample Points



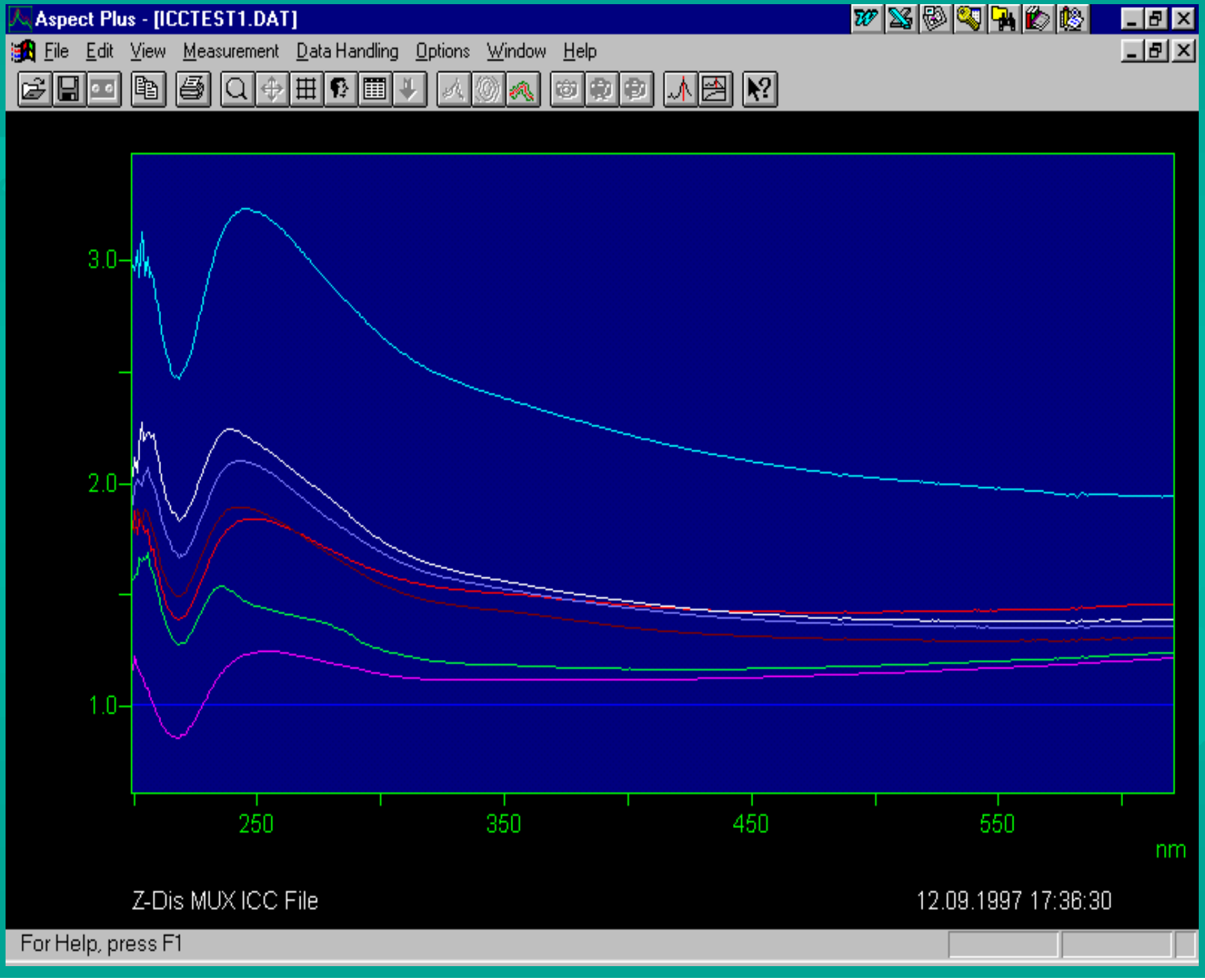
Interchannel Calibration(ICC) - Why

- 8 probes via 8 different channels of multiplexer will have different transmission characteristics i.e. level of counts will vary for a fixed integration time
- Multichannel system must be normalized before any measurements otherwise false absorbance readings will be generated as we are comparing difference in energy of measurement channels with a reference channel
- A pathlength correction factors also need to be applied for accurate quantitative measurements as required for dissolution

ICC - How

- All vessels positions, including blank and standard are filled with media solution. The ICC runs automatically through the following steps:
  - Acquires energy curve set to 80% of the ADC for each channel and storing the given integration times
  - The lowest integration time found is then used to set identical conditions for each channel(avoids any saturation) and each energy curve is reacquired
  - The channel with highest number of counts is then selected as the reference to which all energies are corrected. ICC curves computed are a function of wavelength
  - ICC can be tested by running all channels again and the resulting energy curves should be identical
  - Bubble detection warning is raised if the determined integration is too high

ICC Curves


Aspect Plus - [ICCTEST1.DAT]
File Edit View Measurement Data Handling Options Window Help
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For Help, press F1

Selling Strategy

- System uses standard, off the shelf, hardware components
- Proven , stable, reliable spectrometer designed for fibre optics
- State of art software and easy to use
- Pfizer reference(undergoing validation)
- Potential clients only to be handled on a project basis until a demo plan can be addressed