Development of an Analytical Data Management System (ADMS) to Accelerate the Selection of a Suitable API Form Through Salt and Polymorph Screening

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Introduction

The aim of salt and polymorph screening is to lay the foundation for a successful and surprise-free development effort by exploring salt and polymorph formation feasibility, physicochemical and biopharmaceutical properties, and identifying forms at an early stage (1). Selection of a suitable form through salt and polymorph screening is a critical step that occurs between late drug discovery and early drug development phases, which has far-reaching effects on the ultimate efficacy, ease of manufacturing, and profitability of the final active pharmaceutical ingredient (API).

A delicate balance must be maintained between speed and risks when deciding which form to focus development efforts on. The decision process is complex, involving large quantities of chemical and physicochemical data from disparate sources that need to be evaluated—in a coordinated way—across multiple criteria. With the advent of high throughput screening (HTS) technology, scientists are being asked to explore even greater numbers of potentially developable forms than before. Nevertheless, the data evaluation and final decision must still be made in the same amount of time or faster. These pressures create a need for a physicochemical information management system to accelerate the selection process while facilitating the organization and analysis of the increased number of experiments being considered.

In this work, we discuss the acceleration of the API form selection by improving data management efficiency through state-of-the-art software systems. With such systems, real-time analytical data obtained from disparate instrument types are integrated into a single user-friendly interface. The implemented pilot Analytical Data Management System (ADMS) solution provides end users with significant capability for visualizing, processing, and comparing data across large groups of experiments, which ultimately facilitates decision making. Efficiency gains of 20% to 80% have been demonstrated for various steps in our workflow.

Salt and Polymorph Screening for API Form Selection

Figure 1 shows a typical salt and polymorph screening workflow. The key points indicated in the blue boxes correspond to the following general actions and goals:

- Discovery occurs via **HT Screening** and/or manual experiments with
  - Numerous solvent systems
  - Assorted salt forming agents
  - Various salt formation/crystallization conditions
- Characterization is refined in **Scale-Up Experiments** by using multiple analytical techniques like XRPD, Raman, NMR, elemental analysis, TGA, DSC, etc.
- **Best Candidate Selection** is finally performed based on different desirable and sometimes competing aspects:
  - Physical properties improvements: solubility, stability, packing density, etc.
  - Better manufacturing process: simpler, more robust, less costly, etc.
  - Enhanced patent protection, etc.

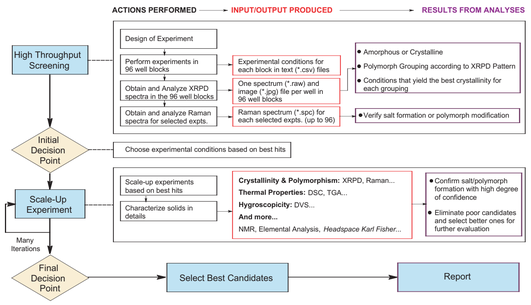
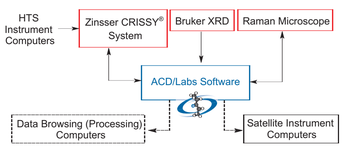


Figure 1 A typical workflow for salt and polymorph screening.

Other details on the actions, experimental output, and analyses of results for the HT Screening and Scale-Up phases are also described in Figure 1.

ADMS Pilot Evaluation Criteria

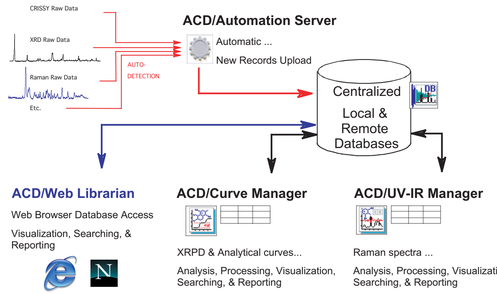
The first step of this study was to compile User Requirement Specifications (URS) for a working laboratory that is set up according to the workflow details in Figure 1. Schema A describes the required integration between the existing instrument and software systems and the ADMS. Critical network connections to the systems are shown as solid lines and secondary ones with dashed lines.



Schema A Connection between laboratory instruments and software with the pilot ADMS.

A first pilot ADMS prototype was built to meet core requirements using off-the-shelf software from ACD/Labs—ACD/Curve Manager—with some custom programming involving macros and some executables. The pilot ADMS was then evaluated by the intended users against the original URS.

In a second step, the URS was expanded to incorporate more advanced requirements and modified with the insight gained from the first pilot. As shown in Schema B, additional ACD/Labs' software components were added to the pilot in order to meet the new set of requirements. This second pilot adds the ACD/UV-IR Manager, ACD/Automation Server and ACD/Web Librarian and software capabilities to the original ACD/Curve Manager pilot with some additional custom programming.



Schema B ACD/Labs software description for expanded pilot ADMS.

The final evaluation criteria included:

1. **Flexibility**: Sufficient adaptability to meet the pharmaceutical company's form selection needs, present and future, is required.
2. **Harmonization**: Ability to incorporate various types of analytical data in a single interface.
3. **Automation**: Capability to upload, organize, and process data automatically in real time from various instrumental computers.
4. **User Friendliness**: Must enable users to process, view, search, and create reports in a way that facilitates and accelerates the form selection process.
5. **Information Retrieval and Visualization**: Must ensure ease of use and speed of retrieval and comparison of data.
6. **Web Access**: Ability to share and visualize data via a Web browser.
7. **Knowledge Base**: Must facilitate the ability to archive, extract, and leverage knowledge from previous studies.

Performance of the Pilot ADMS

Data Unification, Flexibility, and Harmonization:

The pilot ADMS systems allowed us to load multiple types of data from selected experimental data and results into a single database. A list of the various required data types that were incorporated in the database is given in Table 1. Three methods were used to incorporate analytical data into a centralized system:

1. User data entry
2. Direct uploading of instrument data such as plots, tables.
3. Web links, capable of launching external applications.

Data compiled in a single database facilitates retrieval evaluation, reporting, and archival processing. The extensive support of a wide variety of analytical and chemical data underscores the ability of this system to evolve and adapt to changing needs.

- **Raw data generated in HTS experiments**
  - **CRISSY Automation Platform (one Excel file, * .CSV)**
  - **XRPD (96 or less Bruker DIFFRACT Plus *.raw files and corresponding well image *.jpg files) and *PolySnap***
  - **Raman (96 or less Kaiser Optics *.spc files)**
- **Scale-up samples or selected samples in HTS experiments**
  - *** XRPD**
  - *** NMR**
  - *** TGA/DSC**
  - *** Solubility**
  - *** SEM image**
  - *** *Particle size analysis***
  - *** Raman and UV/IR**
  - *** Elemental analysis**
  - *** DVS**
  - *** Dissolution Test**
  - *** *Polysnap***
  - *** *HPLC***
- **General file types which may need to be stored in database**
  - *** Image files**
  - *** IsisDraw; ChemDraw**
  - *** Microsoft office**
  - *** Excel spreadsheet**
  - *** ASCII text file**

Green: user input **Blue: data plot or image** **Brown: a link**

Table 1 List of data types considered in the URS for the salt and polymorph screening.

Removing the HTS Data Upload Bottleneck by Automation:

The application of HTS technology can cause workflow bottlenecks due to large volumes of data created in a short time. Time can be saved and errors reduced if data is automatically collected and organized with minimal human intervention. The upload capabilities are summarized in Figure 2.

Routine data handling task could be managed efficiently as follows:

- User involvement was minimized with a customized Basic program and ACD/Labs group custom macro capabilities to load and process multiple input files at a time.
- User involvement was removed in the expanded pilot ADMS by using ACD/Automation Server to perform the tedious data collection task:
  - *.csv files from the Zinsser CRISSY Automated Dispenser
  - *.raw spectra and *.jpg image files from the Bruker XRPD
  - *.spc spectra files from the Kaiser Raman instrument

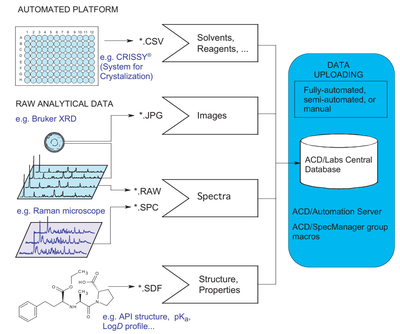


Figure 2 Transferring HTS data to the pilot ADMS *.

User-Friendliness and Improved Information Retrieval and Access:

The single centralized database increases information access. A wide selection of structural, spectral, analytical, and text query tools as well as interactive browsing and data selection functionalities help ensure that information can be found in a relatively facile manner. Figure 3 shows two powerful ways of visualizing data in which large array of data can be presented in an intuitive interface. In Figure 3a, all data associated with the selected sample are shown through a Web browser. In Figure 3b, the database Table view is shown which is useful for reviewing and comparing data from different experiments.

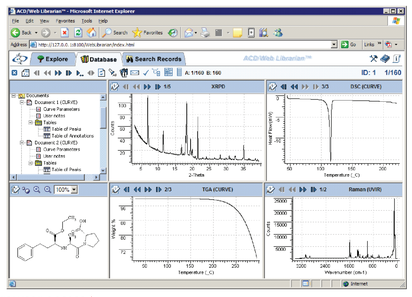


Figure 3a Web browser access *.

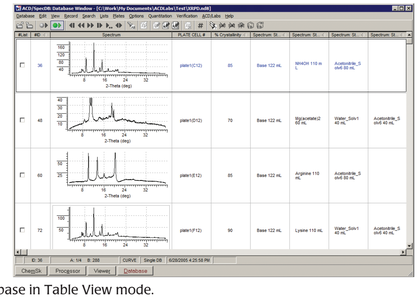


Figure 3b Database in Table View mode.

Faster HT Screening Evaluation and Ergonomic Customization:

Data evaluation and final decision as to the API form selection must be made quickly. The ability to create task-focused custom data layouts for the database windowpane and templates for the report editor helps accelerate data review and comparison. These templates and forms help hide extraneous data and highlight relevant ones. Collecting all the information in one window further avoids the need to constantly switch from one place to another to review different aspects of the same sample. It also helps create reports quickly that can be exported to Microsoft® Office applications.

Figure 4 shows a database custom display layout created to make HT Screening data evaluation and review easier. The evaluation window includes:

- Friendly navigation with clickable well plate positions
- Color-coded wells according to selected key parameters, e.g., crystallinity, salt forming agent, polymorph
- Ability to collect all relevant data in one window: plots, well plate images, XRPD spectrum, reaction conditions, % crystallinity, and polymorph forms

It is easy to create new layouts or to reorganize existing ones. Ultimately, the display flexibility offered by the software directly supports faster and smarter evaluation and decision making.

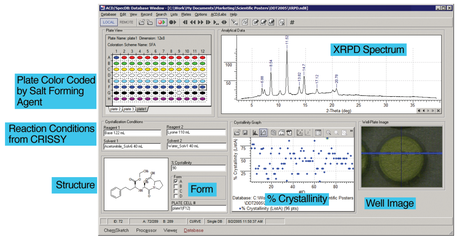


Figure 4 Example of a custom evaluation window (screen view) created for HTS *.

Further features are especially useful for HT Screening Data evaluation:

- The ability to display (analyze and annotate) different types of spectra with experimental conditions in the same processing window is useful for in depth evaluations
- Several sample data can be collected in a single window as a series to help the evaluation
- A fully adjustable sliding zoom window allows detailed comparisons of particular regions in a spectral series or synchronized windows.

Fostering Salt and Polymorph Knowledge Base Creation: Knowledge bases can be created dynamically. The generalized access to data helps ensure high data quality through greater chances of having more than one independent reviewer.

Conclusion

To meet the User Requirement Specifications (URS) related to data management for salt and polymorph screening, a pilot ADMS was implemented using off-the-shelf software from ACD/Labs: ACD/Curve Manager, ACD/UV-IR Manager, ACD/Automation Server, and ACD/Web Librarian. With some customization, the needs set forth in the pilot project were met within the scope of a typical HT Screening workflow and user experiences.

Suggestions for future improvements include interface and customizability enhancements as well as the addition of specific capabilities to enable or facilitate the form selection workflow.

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References

1. P. Heinrich Stahl, Camille G. Wermuth (Editors), *Handbook of Pharmaceuticals Salts, Properties*, Selection and Use. Verlag Helvetica Chimica Acta, Zuerich (2002).

* For illustration purposes only: to protect proprietary data, a generic structure (Enalpril Maleate) is shown.

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