An overview of automated systems relevant in pharmaceutical salt screening

Lokesh Kumar, Aeshna Amin and Arvind K. Bansal

Department of Pharmaceutical Technology (Formulations), National Institute of Pharmaceutical Education and Research (NIPER), Sector-67, Phase-X, S.A.S. Nagar, Punjab 160062, India

Modern drug discovery and development tools have evolved persistently to meet the demands of the highly competitive environment of the pharmaceutical industry. This has introduced high-throughput methodologies in various stages of drug development. Salt screening is an integral part of the preformulation stage of drug development and is increasingly being adapted to 'high-throughput experimentation' (HTE), to shortlist the potential salt(s) for a comprehensive biopharmaceutical characterization at the scale-up stage. The selected salt form may then be forwarded to the next stage of drug development. This review provides an overview of 'high-throughput experimentation' methodology for selection of an optimal drug salt candidate.

Recent years have witnessed the pharmaceutical industry continually evolve with respect to the ways in which experimental data is generated, gathered, and analyzed, improving the efficiency and rate of early discovery success [1]. Novel high-throughput tools have affected various facets of pharmaceutical research and are being increasingly relied upon to reduce the risk of failure in drug discovery and development. The early development phase has been typified by the pharmaceutical scientist performing a limited number of experiments, due to constraints of availability of compound and limited analytical capabilities. Limited availability of data can put a lot of pressure at the decision-making phase and also increase the chances of obtaining problematic results in later stages of development, thus, underlining the need for a comprehensive 'high-throughput experimentation' (HTE) process.

The initial drug development phase invariably involves a significant contribution from the pharmaceutical research group for preformulation profiling of the potential drug candidate. Assessment of aqueous solubility, permeability, hygroscopicity, and stability profile of the compound forms the backbone of these efforts. Salt screening can be an invaluable tool to modify these biopharmaceutical properties, should there be problems with them, without changing the structure of the drug candidate [2–4]. Salt form can affect the solubility, permeability, hygroscopicity, and processability of an ionizable drug candidate; thereby providing an effective means to balance the requirements of bioavailability, stability, manufacturability, and patient compliance [5,6]. The fact that an estimated 50% of drug molecules used in medicinal therapy are administered as salts, somewhat justifies the extensive early efforts to find optimal salt formulations [2]; thus qualifying salt selection as one of the most important activities that critically affect the successful development of a drug candidate.

Salification (salt formation) constitutes an acid/base reaction, involving either a proton transfer or neutralization reaction [7], wherein, a drug candidate forms strong ionic interaction with an oppositely charged counterion. The presence of charged groups in the drug and counterion lead to an intermolecular coulombic force of attraction, which, if maintained through crystallization, generates a salt form [8]. Numerous counterions are available to the pharmaceutical scientist for the preparation of salts, which include common acidic counterions like hydrochloric, sulfuric, and acetic acids for basic drugs, and alkaline counterions like sodium, potassium, and magnesium for acidic drugs [6]. Diclofenac, a nonsteroidal anti-inflammatory drug, has three currently marketed salt forms: sodium, potassium, and diethylamine; wherein the former two have improved solubility (9.7 and 4.6 mg/ml for diclofenac sodium and potassium, respectively) over

Corresponding author: Bansal, A.K. (akbansal@niper.ac.in)

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2007.08.002

free diclofenac acid [~0.02 mg/ml solubility, BCS (Biopharmaceutical Classification System) class II drug], the latter is designed to have better skin penetration, thereby permitting its use an effective topical anti-inflammatory agent [9–11].

Owing to a significant impact on drug development, the salt selection process is increasingly being integrated with HTE, for rapid selection of potential salt candidate(s) [12]. Availability of a wide spectrum of counterions, crystallization conditions, and the need to analyze numerous physicochemical parameters encourages automation of salt selection. HTE allows a large number of parallel small-scale experiments, thereby easing the material demand; facilitating a more objective selection of compounds for the next stage of drug development [13].

High-throughput experimentation in salt selection

The objective of any salt screening procedure is to identify the most suitable salt form for development and generally involves a two-tiered approach, wherein the 'essential criteria' of crystallinity, hygroscopicity, solubility, and stability are examined at the first tier. Progressively time-consuming and labor-intensive experiments, involving 'desirable criteria' such as the absence of polymorphic variability and ease of synthesis/formulation development, are conducted at the second tier. A tiered approach allows the systematic elimination of nonoptimal salt forms, thus reducing experimental effort and cost [14].

HTE adopts a similar 'tiered approach', using a multiwell format, wherein a compound passes through designated platforms to screen for 'essential criteria', followed by 'desirable criteria' of salt selection (Figure 1). HTE allows a diversity of experimental conditions [15], to evaluate a number of compounds in a controlled and repeatable manner (http://www.tessella.com), thus enabling a better understanding of the underlying physicochemical process based on the knowledge generated from a large number of experiments on a diverse set of compounds [16]. The technique can also provide comprehensive patent coverage (patent clustering) through the complete

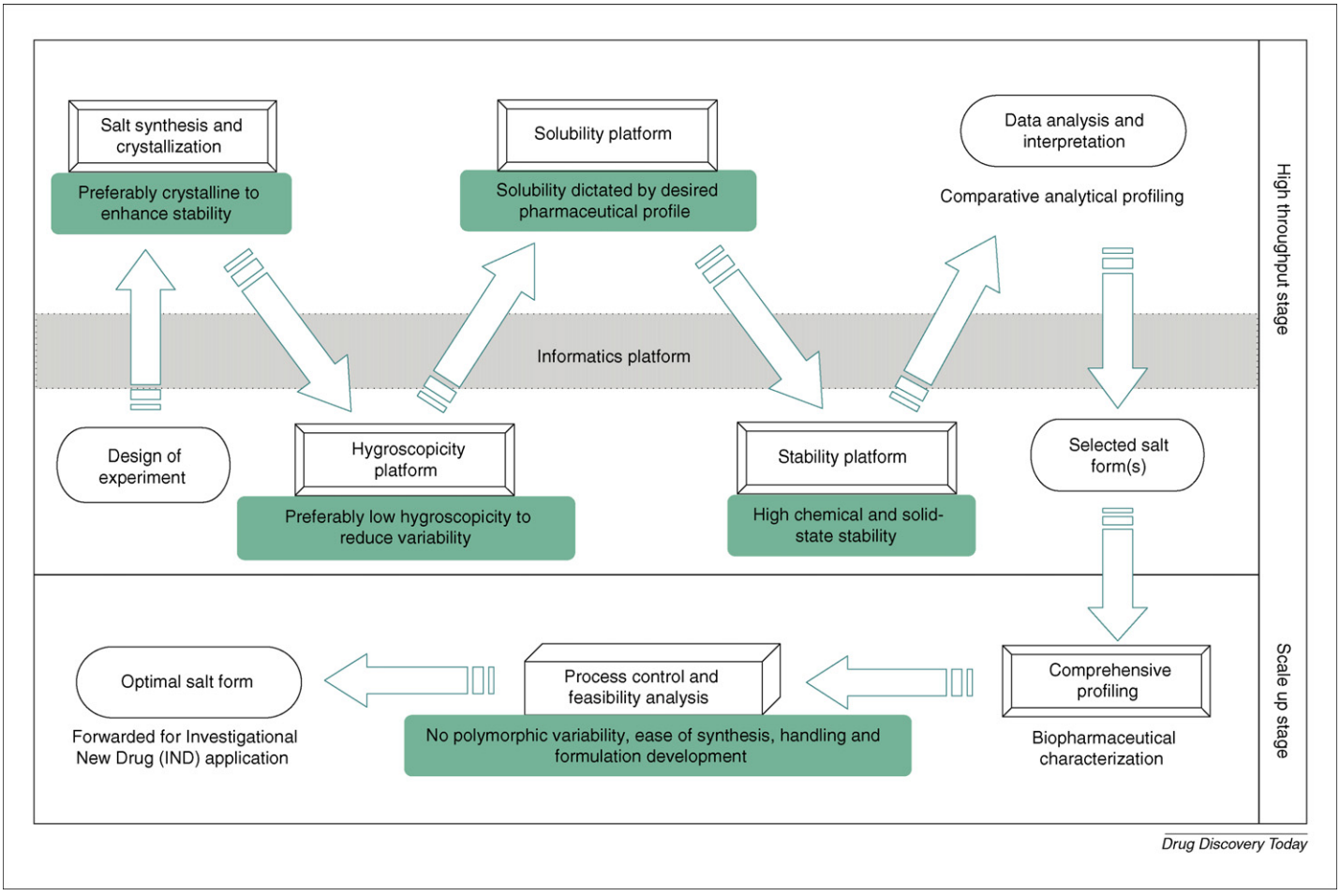

FIGURE 1

Stages of high-throughput salt selection showing an interface with the scale-up stage of salt screening. Each high-throughput stage is interlinked through the informatics platform. Stages depicted with double lined box indicate essential criteria and the cuboidal box shows desirable criteria of salt selection, with the preferable parameters depicted in the underlying green shaded area. The informatics platform generates experimental design for crystallization, hygroscopicity, solubility, and stability platforms, and evaluates the analytical profile generated, to shortlist the potential salt(s). The initial 'salt synthesis and crystallization' station includes a reaction platform for salt and counterion reaction, a crystallization platform for solvent recrystallization, and a solid form screening platform for initial solid form screening using X-ray diffraction, Raman, thermal, and chromatographic methods. Salt candidate(s) pass through the various stages of high-throughput salt selection (in the direction of the arrows indicated), to scale-up stage for extensive biopharmaceutical characterization, proceeded by an assessment of desirable criteria to finalize the optimal salt form.

profiling of a compound, reducing the chances of generic competition (http://www.avantium.com).

HTE involves screening of potential salt candidates using designated experimentation platforms that are interlinked with an informatics platform to control the experiments. A salt form successfully needs to fulfill the criteria of crystallization, hygroscopicity, solubility, and stability platforms, in the order mentioned, to be eligible for a comprehensive examination at the scale-up stage.

Informatics platform

A major challenge in drug development, further complicated by HTE, involves management of the enormous amounts of data acquired during solid form screening that require collation in a proper manner for easy traceability and analysis [17]. Development of modern software with sophisticated modeling capabilities has addressed this challenge by enhancing data management efficiency [18]. Modeling software (Table 1) is available for salt and solid form screening that forms the backbone of the informatics system, designing the relevant experiments, instructing the automation hardware to perform the required operations, and analyzing and interpreting the results.

High-throughput salt synthesis and crystallization

Discovery and characterization of all the potential salt and/or solid forms of a compound allow the selection of a form having the appropriate balance of critical properties for development [15]. Therefore, synthesis of a series of potential salts is generally initiated during the preformulation program. Traditional salt synthesis involves mixing the ionizable compound with appropriate counterion(s) to generate a crude salt precipitate followed by recrystallization to a pure solid, which requires significant input in terms of time and quantity of compound, thus making it a cumbersome process. Conversely, in HTE (Figure 1), the entire process, involving addition of potential drug candidate (~1–10 mg/well) and counterion, dispensing of crystallization solvents, equilibration, and filtration of mixture, dispensing aliquots of filtrates, cooling, removal of aliquots for solubility measurement, and removing the supernatant, is automated, thereby improving the efficiency [22,23]. In HTE, salt synthesis and crystallization stations typically involve a 'reactor platform' for drug and counterion reaction, a 'crystallization platform' for solvent recrystallization, followed by a 'solid form screening platform' for spectral/chromatographic characterization of the generated salt forms.

TABLE 1

Informatics tools used for high-throughput salt selection

Organization	Software solution	Comments
Symyx (http://www.symyx.com)	Library studio®	Designing of combinatorial arrays
	Spectral studio®	Viewing and sorting Raman spectra
	Impressionist®	Automation of predetermined process
	Epoch®	Dilution, data acquisition, and storage
	Polyview®	Searching and retrieving data stored during experiment, grouping XRD spectrum
	Data Browser	Library access to produce reports
	Polymorph reporting tool™	Reporting software [19,20]
Transform pharmaceuticals (http://www.transformpharma.com)	ARCHITECT™	Experiment design
	INFORM	Experimental design for array of solvents
Tessella (http://www.tessella.com)	EMS	Data management
	THERM™	Experiment design
ACD labs (http://www.acdlabs.com)	Chemanalytics™	Data management
	SpecManager	Spectral & chromatographic data processing and databasing
RPD Tools (http://www.rpdtool.com)	SpecFlash	Automated data evaluation, visual screening of generated results
	SpecAnalyser	Spectral modeling, statistical analysis
Accentus (http://www.drugresearcher.com)	CrystalGEM™	*In silico* predictive computational and experimental model
Zinsser analytic (http://www.zinsser-analytic.com)	Zinsser Designer	Design of experiment
	Navigator™	Control of experiment
	WinRun	Experiment scheduling
Avantium (http://www.avantium.com)	Chemometric & statistical tools	Design of experiment
Anachem (http://www.reactarray.com)	Peak tracker	Control of stability studies
	RDM	React Array™ Data Manager
PANalytical (http://www.panalytical.com)	X'Pert Data Collector	Central control module
	X'Pert Industry	Diffraction data interpretation
Barr *et al.*	PolySNAP	Matching and analyzing powder diffraction patterns [21]
Hammond *et al.*	Grid-based molecular modeling	Drug/counterion binding prediction, crystal packing [18]

Reactor platform

Reactor platform involves dispensing the potential drug candidate as a solution in multiwell plates/tubes along with aqueous or organic solutions of counterions (at equimolar or other defined ratios), followed by removal of solvent to yield a crude solid salt that is forwarded for solvent recrystallization. Alternatively, salt synthesis and crystallization may be performed simultaneously by utilizing different counterions in one Cartesian coordinate and the recrystallization solvent in other coordinate of the multiwell plate/tube [6,20]. Control of the reactor platform is mediated by the informatics platform, assuring a meticulous performance of desired conditions with set variables.

Crystallization platform

Because of time and material constraints, manual crystallization techniques provide limited data, thereby yielding the possibility of errors in critical solid form selection [15]. This was evident in the case of ritonavir, where the subsequent discovery of a less soluble form II two years after market entry caused failure of dissolution specification, forcing an eventual withdrawal of the formulation from the market [23]. High-throughput crystallization systems have overcome these problems, permitting rapid and comprehensive solid form screening with small amounts of material. Although high-throughput crystallization is not a foolproof method, it can provide useful information regarding the selection of the most stable polymorphic form.

At the crystallization platform, the crude precipitate generated from the reactor platform is subjected to crystallization, using a variety of solvent and crystallization conditions. Formation of a solid is described as a 'hit', and the success rate may range from 10 to 100% depending upon the type of experiment and process mode(s) used. Removal of solvent may be accomplished by passive (e.g. air drying) or active (e.g. vortex/vacuum drying) evaporation. Occasionally, evaporation may be promoted by the addition of an antisolvent to induce precipitation or by passing a slow stream of nitrogen gas over the sample [15]. Solid formation may be observed by an inverted or birefringence microscope.

Around one-third of organic substances show crystalline polymorphism and a further one-third are capable of forming hydrates and solvates [24]. Screening for crystalline salts is, therefore, generally coupled with initial screening for polymorphs, hydrates, and/or solvates of salt candidates. Solvents with diverse properties are used to generate a solvent matrix that may improve the chances of screening all the possible salt and polymorphic forms [25]. Parameters, including solvent polarity, degree of supersaturation, crystallization temperature, cooling rate, and presence of impurities/additives, are carefully optimized [24]. A more comprehensive evaluation of polymorphism may be undertaken at the scale-up stage.

Different crystallization platforms/technologies are utilized for high-throughput salt and polymorph screening. Crystal 16™ (Avantium, The Netherlands) (http://www.crystal16.com) is a medium-throughput polymorph and salt screening technology that performs 16 parallel crystallization experiments, in addition to providing an estimate of solubility using turbidity measurements [26]. Transform pharmaceuticals, USA (http://www.transformpharma.com) has developed the 'CrystalMax' crystallization technology; having an array of discrete tubes with a capacity of up to 10,000 crystallizations per week. Symyx, USA (http://www.symyx.com) has produced the Universal Substrate™ that assists the removal of crystals for analysis, along with the provision for *in situ* optical measurement during crystal formation. Zinsser analytic, Germany (http://www.zinsser-analytic.com) has developed an automated sample preparation platform CRISSY® to automate the necessary steps for extensive crystallization, using different solvents, temperatures, concentrations, agitation, and pH. This platform is increasingly being used in crystallization experiments and has the provision for precise gravimetric distribution of powder, liquid handling, and crystallization at controlled temperature with agitation, concentration, evaporation, and pH measurement. Table 2 shows some of the drugs that have been subjected to high-throughput salt screening.

Solid form selection platform

Identification and characterization of solid-state forms at an early stage, using appropriate analytical methodology, is an essential prerequisite in the development of solid dosage forms, both from the scientific as well as regulatory point of view [31]. Most HTE techniques utilize multiple analytical methods to screen the crystalline salts generated at a crystallization platform, wherein an evaluation by Raman spectroscopy, melting point, powder X-ray diffraction (PXRD), and high-pressure liquid chromatography (HPLC) is undertaken.

TABLE 2

Drugs subjected to high-throughput salt screening

Drug	Information obtained	Refs
Naproxen	Identification and characterization of eight crystalline salt forms of naproxen	[27]
Sulfathiazole	Identification and characterization of 10 crystalline salt forms with varying melting point depending upon the counterion type and stoichiometric ratio	[28]
Tamoxifen	Citrate and fumarate salts screened for scale-up stage, novel insight on prediction of stoichiometry, and potential polymorphism	[16]
Sertraline HCl	Identification and characterization of 18 crystalline salt forms	[12]
Caffeine	Identification and characterization of different salt forms of caffeine	[27]
Trazodone HCl	Tosylate salt as a potential candidate for prolonged action or suspension type formulation	[29]
Ephedrine	Identification and characterization of seven crystalline salts	[30]

High-throughput salt screening has been effectively applied to a number of drugs to deduce valuable information for shortlisting potential salt candidate(s) that may be further examined extensively to select an optimal salt form.

Raman spectroscopy provides vibrational spectroscopic information, complementary to that obtained from infra-red analysis, with more sensitivity and can probe the lattice vibrations associated with a molecule in its crystalline state [32]. It is a useful tool for rapid polymorph and salt selection, as the technique provides both physical as well as chemical information [33]. For example, in solid-state characterization of salbutamol salts, characteristic Raman shifts were observed, indicating that the choice of salt form affected the molecular nature of the drug, with obvious changes in its physicochemical properties [32].

For melting point determination, recrystallized material may be fed to a thermal chamber with an image scanning device, wherein, the crystals can be heated at a predetermined rate. The device provides an optical signal for each sample and can monitor any associated morphological change. A change in birefringence pattern at the melting point may be assessed for melting point determination [34]. Birefringence microscopy can also give an indication of the crystallinity of the potential drug candidate, that may be further evaluated by PXRD, considered a gold standard for solid-state analysis in the pharmaceutical industry [35]. Each solid form produces a characteristic PXRD pattern that can be used as a fingerprint for that particular solid form. In salt screening as well, PXRD can indicate the crystallinity and polymorphic stability of the salt form. During initial synthesis, PXRD can also provide information regarding the completion of salt formation. Salt form(s) have a characteristic PXRD pattern, different from that of the corresponding potential drug candidate and the counterion. If salt is not formed, or is disproportionate to the individual components, it will have a diffraction pattern equivalent to the sum of the diffraction patterns of the drug and counterion. However, the method has limitations in cases of nonsolid nature of counterions like hydrochloric acid, and multiple polymorphism of drug candidate, where acquisition and/or interpretation of diffraction patterns become complicated [13].

PANalytical, The Netherlands (http://www.pananalytical.com) has a range of automated X-ray powder diffraction models including X'Pert PRO MPD with an automated sample changer, and can process hundreds of full scans every day for salt screening. Initial solubility information can be obtained by HPLC analysis of the supernatant left in the crystallization mixture. For a thorough investigation of pH and temperature-solubility profiles, generated salts are evaluated at the solubility station.

Solid forms may be classified into groups, depending on the similarity coefficients of data acquired from various techniques, giving an indication of the number and type of crystalline forms suitable for further screening. Once potential forms are shortlisted, they may be forwarded for hygroscopicity profiling at the hygroscopicity station.

High-throughput hygroscopicity study

Pharmaceutical solids frequently show a propensity to interact with water molecules, leading to absorption of moisture in their bulk structure or adsorption on their surfaces. Such a behavior can critically affect many pharmaceutical properties such as purity, solubility and chemical stability, density, surface area, powder flow, compactability, and crystal form [36,37]; thereby necessitating its evaluation during selection of a suitable solid form. Conventionally, compounds may be classified as nonhygroscopic, slightly hygroscopic, moderately hygroscopic, or very hygroscopic, on the basis of percentage weight gain during exposure to defined humidity conditions at specified temperature [38].

In high-throughput mode, a hygroscopicity measurement apparatus may be utilized, whereby automatically weighed amounts of sample (typically 5–10 mg) are placed on a sample holder and subjected to known constant relative humidity and temperature (http://www.vanha.physics.utu.fi/industrial/equipment.html). By determining the sample weight as a function of time and relative humidity/temperature of the ambient air, hygroscopic behavior of the sample can be studied. Alternatively, dielectric measurement of the sample kept on a substrate (having probes for dielectric measurement) in controlled humidity conditions can be undertaken. Raman spectroscopy measures hygroscopicity as a function of spectral changes during moisture absorption [27]. Dynamic vapor sorption (DVS) analyzers also determine hygroscopicity profiles using a very small sample (~3 mg), and provide both qualitative, as well as quantitative, information on the water uptake. It can be coupled with other analytical techniques, for example NIR (near infra-red) spectrometers, under a range of humidity environments (http://www.assainternational.com), or a Raman probe to determine the spectral changes with moisture uptake [39]. Similarly, automatic sorption test system SPS11 (Health Scientific, U.K.) can perform hygroscopicity profiling of 11 compounds simultaneously, with high precision and reproducibility, using a few milligrams of sample (http://www.projekt-messtechnik.de/Sps11_details_e.html).

High-throughput solubility study

Aqueous solubility at different pH with buffers is one of the most important physicochemical properties that significantly affects oral absorption and, consequently, bioavailability [8]. This is especially relevant in the case of poorly soluble drugs, where aqueous solubility may become the limiting factor for oral absorption, acting as a 'show stopper' if solubility is less than 10 μg/ml [40]. Therefore, early assessment of solubility of drug candidates is vital for their further development. This has led to development of high-throughput methods for rapidly weeding out the solid forms with undesirable solubility profiles.

After an initial assessment of hygroscopicity, the selected salts are subjected to automated solubility determination. Analysis of the supernatant during the recrystallization process gives a preliminary idea of the solubility of the salt form [20]. However, a detailed analysis of solubility, including solubility in different solvents, pH-solubility profile and temperature-solubility profile, is performed separately at the solubility platform. A number of techniques may be utilized for high-throughput solubility determination (Table 3).

During solubility screening, accurate dispensing of solid into the solubility station, in predetermined quantities of solvent is essential. Techniques like Powdernium® (Autodose, SA), REDI® (Zinsser analytic, Germany), and Flexiweigh™ (Mettler Toledo, IL) provide an automated means for dispensing powders with diverse physicochemical properties [41].

High-throughput stability study

A drug candidate is required to maintain its properties throughout its shelf life, necessitating an early evaluation of its stability behavior

TABLE 3

Techniques for high-throughput solubility determination

Organization/inventor	Technique	Description
Symyx (http://www.symyx.com)	Automated solubility determination platform	Ninety-six-well library format, wide range of solvents, HPLC-UV determination, rapid and precise measurements, up to 192 compounds a week, pH solubility, temperature solubility, pK_a, log *P*/log *D* determination
Zinsser analytic (http://www.zinsser-analytic.com)	Turbidity-based solubility determination	UV determination, turbidity probe measurement [42]
	SuSy	Microplate solubility measurement for 24, 48, or 96 samples
Bruker Optics (http://www.rpdtool.com)	SpecScreen xHTS	Solubility and chemical stability, temperature-solubility profile
Anachem (http://www.reactarray.com)	Reactarray™	Equilibrium solubility, wide analyte concentration range
Nanostream (http://www.nanostream.com)	Nanostream CL	High-throughput low volume liquid chromatography
pION (http://www.pion-inc.com)	pH-metric technique	Intrinsic-solubility and pH-solubility profile, pK_a profiling, three to five compounds a day, wide dynamic range, FDA recognized
Tan *et al.*	Automated solubility assay	Ninety-six-well library format, HPLC-UV determination, up to 192 compounds in a week [43]
Chen *et al.*	UV plate reader	Multiwavelength determination, thermodynamic solubility [44]
Chen and Venkatesh	Miniaturized device	Equilibrium solubility (aqueous and nonaqueous) [45]

A number of automated techniques for high-throughput solubility analysis are available to pharmaceutical scientist, that can provide intrinsic and/or apparent solubility in a wide range of solvents, at varying conditions of pH and temperature.

during preformulation profiling, with possible elucidation of underlying pathway of degradation. A properly delineated stability study helps in the appropriate selection of a stable salt and/or solid form [46], as well as the design of long-term stability studies.

Conventional stability studies involve a considerable manual sampling element and is tedious and subject to errors that may make the data less valuable. Automated instruments, on the other hand, are capable of handling a large set of experiments simultaneously, under a variety of degradation conditions, rapidly and efficiently with minimal errors. In automated stability studies, all compounds are subjected to the same general workflow for degradation [19]. These systems have an in-built capacity for retrieval, sampling, and testing of compounds from environmental chambers, by plate movements across the instrument stations (http://www.rpdtool.com). A number of methods may be utilized for automated stability testing (Table 4).

Automated excipient compatibility systems allow rapid identification of the compatibility of a drug candidate with various excipients, both in solid and solution states. Symyx has developed an extended core module (XCM), a robust flexible robotic platform

TABLE 4

High-throughput methods for stability testing

Organization/inventor	Technique	Description
Symyx (http://www.symyx.com)	Automated stability platform	pH-stability profile, automated stress testing under a variety of environmental conditions (temperature, humidity, light), and chemical exposure (acid, base, peroxide, free radicals, or other oxidizers)
	Excipient compatibility model	Automated testing of solid and solution samples, stability at various temperature, humidity, pH, light, and exposure in varying duration
Anachem (http://www.reactarray.com)	ReactArray™ instrumentation	Stability studies, excipient compatibility testing, automated sample uptake, dilution, and transfer to HPLC
Bruker Optics (http://www.rpdtool.com)	SpecScreen xHTS	Automated stability studies, spectra acquisition and data evaluation of liquid, suspended and solid test samples, small sample volumes (50 μl to 10 ml)
Fermier *et al.*	Automated stability analysis	Isothermal and nonisothermal stability, user-defined temperature profile and sampling period [48]
Fermier *et al.*	High-throughput stability station, HPLC modification	Simultaneous 96 samples and multiple assay conditions, automatic sample preparation and storage in autosampler for required time and temperature, pH-stability profile in physiological medium, forced degradation and excipient compatibility testing [46]
Di *et al.*	Automated solution stability, HPLC modification	pH-stability profile, stability in physiological fluids, forced degradation studies, compatibility studies [49]
Sims *et al.*	Automated multisample analysis	Accelerated drug excipient compatibility [50]
Wyttenbach *et al.*	High-throughput screening statistical design	Automated degradation, 0.1 mg of sample per data point [51]

Stability testing is nowadays subjected to high-throughput profiling in order to increase the throughput in pharmaceutical research and development. High-throughput stability analysis can provide an initial assessment of stability of a potential drug candidate at varying conditions of temperature, pH, humidity, light, and chemical exposure.

with a common software and hardware platform that allows full integration of a variety of modular components. It is capable of determining solubility, developing liquid formulations, as well as performing stability studies [47].

Symyx enabled the selection of a highly stable and highly soluble salt form for the liquid formulation of a commercial drug marketed as a hydrochloride salt that showed poor solubility in desired neutral aqueous conditions. The study provided stability and solubility profile as a function of pH, counterion, cosolvent, and complexing agent to select a salt form showing adequate solubility and stability [19].

Scale-up studies

High-throughput salt screening shortlists potential salt candidates that are forwarded for comprehensive biopharmaceutical screening at the scale-up stage. Finally, a combination of high and 'medium to low throughput' experimentation would conclude the process of salt screening. During the scale-up stage, larger samples (10–50 mg) of potential salts would be comprehensively characterized by various analytical techniques, including birefringence (crystallinity), Raman (salt formation, solid-state stability, and polymorphism), PXRD (crystallinity, polymorphism, and polymorphic stability), differential scanning calorimetry/thermogravimetric analysis (purity and solid-state stability), nuclear magnetic resonance spectroscopy (salt formation, purity, and stoichiometry), and DVS (hygroscopicity and solid-state stability). Processing parameters, such as flow properties, corrosivity, and handling, as well as crystallization scale-up experiments such as crystal size optimization, crystal morphology, environmental impact of solvent, and economic considerations are also evaluated [52]. After the scale-up stage, the salt form possessing optimal properties, with least variability, may be chosen for further development to Phase I (toxicological studies) of drug development.

Limitations of high-throughput experimentation in salt form screening

In spite of their enormous potential in salt form screening, HTE techniques are beset with disadvantages, including generation of a vast amount of data and creating difficulty with data handling and interpretation. In complex situations, including 'multiple polymorphism', the large scale of operation makes it difficult to reproduce the results, leading to possible failures (http://www.solvias.com). Also, the small sample input, as well as uncontrolled particle size, may provide suboptimal data [13], which may introduce error in practical situations [15]. In certain cases, including complex crystallization experiments, experimental space may also be too large to be explored (http://www.avantium.com). This underlines the importance of coupling 'medium- to low-throughput' experiments with the initial high-throughput procedure, which may help to negotiate the limitations of HTE, deducing useful information regarding optimal salt form selection.

Conclusion and future prospects

HTE is becoming an indispensable part of drug development, and is frequently applied to most of its stages, including the preformulation stage. Because of its critical effect on biopharmaceutical properties, salt form selection is vital to the development of a potential drug candidate. A properly designed HTE process can select a suitable salt form in a rapid and efficient manner, thereby accelerating the overall drug development process.

The process of salt selection is being continuously upgraded, due to the painstaking initiative of numerous companies specializing in instrumentation for pharmaceutical processes. With continuous development of technology, the future shall witness better management of the 'critical' salt selection process.

References

1 Li, M.S. and Kerns, E.K. (2000) LC/MS applications in drug development. *Mass Spectrum Rev.* 18, 187–279

2 Wermuth, C.G. and Stahl, P.H. (2002) Introduction. In *Handbook of Pharmaceutical Salts: Properties, Selection and Use* (Stahl, P.H. and Wermuth, C.G., eds), pp. 1–7, Wiley–VCH

3 Brittain, H.G., ed. (2002) *Polymorphism in Pharmaceutical Solids*, Marcel Dekker Inc.

4 Datta, S. and Grant, D.J.W. (2004) Crystal structures of drugs: advances in determination, prediction and engineering. *Nat. Rev. Drug Discov.* 3, 42–57

5 Anderson, B.D. and Conradi, R.A. (1985) Predictive relationships in the water solubility of salts of a nonsteroidal anti-inflammatory drug. *J. Pharm. Sci.* 74, 815–820

6 Bastin, R.J. *et al.* (2000) Salt selection and optimization procedures for pharmaceutical new chemical entities. *Org. Process Res. Dev.* 4, 427–435

7 Berge, S.M. *et al.* (1977) Pharmaceutical salts. *J. Pharm. Sci.* 66, 1–19

8 Bhattachar, S.N. *et al.* (2006) Solubility: it's not just for physical chemists. *Drug Discov. Today* 11, 1012–1018

9 Connor, K.M.O. and Corrigan, O.I. (2001) Preparation and characterisation of a range of diclofenac salts. *Int. J. Pharm.* 226, 163–169

10 Raumer, V.M. *et al.* (2006) Polymorphism, salts, and crystallization: the relevance of solid-state development. *Chem. Today* 24, 41–44

11 Fini, A. *et al.* (1996) Factors governing the dissolution of diclofenac salts. *Int. J. Pharm.* 4, 231–238

12 Remenar, J.F. *et al.* (2003) Salt selection and simultaneous polymorphism assessment via high-throughput crystallization: the case of sertraline. *Org. Process Res. Dev.* 7, 990–996

13 Stephenson, G.A. (2005) Applications of x-ray powder diffraction in the pharmaceutical industry. *Rigaku J.* 22, 2–15

14 Morris, K.R. *et al.* (1994) An integrated approach to the selection of optimal salt form for a new drug candidate. *Int. J. Pharm.* 105, 209–217

15 Morissette, S.L. *et al.* (2004) High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids. *Adv. Drug Deliv. Rev.* 56, 275–300

16 Kojima, T. *et al.* (2006) Crystalline form information from multiwell plate salt screening by use of Raman microscopy. *Pharm. Res.* 23, 806–812

17 Lowry, S. *et al.* (2006) Integrating a Raman microscope into the workflow of a high-throughput crystallization laboratory. *J. Assoc. Lab. Automat.* 11, 75–84

18 Hammond, R.B. *et al.* (2006) Grid-based molecular modeling for pharmaceutical salt screening: case example of 3,4,6,7,8,9-hexahydro-2*H*-pyrimido (1,2-a) pyrimidinium acetate. *J. Pharm. Sci.* 95, 2361–2372

19 Carlson, E.D. *et al.* (2005) Automated integrated forced degradation and drug-excipient compatibility studies. *J. Assoc. Lab. Automat.* 10, 374–380

20 Carlson, E.D. *et al.* (2003) An integrated high throughput workflow for pre-formulations: polymorph and salt selection studies. *Pharmachem* 1, 10–15

21 Barr, G. *et al.* (2004) *PolySNAP*: a computer program for analysing high-throughput powder diffraction data. *J. Appl. Cryst.* 37, 658–664

22 Higgins, J.D. and Rocco, W.L. (2003) Pharma preformulation—a stop along the drug development highway. *Today's Chemist at Work* 12, 22–26

23 Morissette, S.L. *et al.* (2003) Elucidation of crystal form diversity of the HIV protease inhibitor ritonavir by high throughput crystallization. *Proc. Natl. Acad. Sci.* 100, 2180–2184

24 Mirmehrabi, M. and Rohani, S. (2005) An approach to solvent screening for crystallization of polymorphic pharmaceuticals and fine chemicals. *J. Pharm. Sci.* 94, 1560–1576

25 Gu, C.H. *et al.* (2004) Grouping solvents by statistical analysis of solvent property parameters: implication to polymorph screening. *Int. J. Pharm.* 283, 117–125

26 Birch, M. *et al.* (2005) Towards a PAT-based strategy for crystallization development. *Org. Process Res. Dev.* 9, 360–364
27 Carlson, E.D. *et al.* [Symyx Technologies] Apparatuses and methods for creating and testing pre-formulations and systems for same. *USP6939515*
28 Gardner, C.R. *et al.* (2004) Application of high throughput technologies to drug substance and drug product development. *Comput. Chem. Eng.* 28, 943–953
29 Ware, E.C. and Lu, D.R. (2004) An automated approach to salt selection for new unique trazodone salts. *Pharm. Res.* 21, 177–184
30 Desrosiers, P.J. (2004) The potential of preformulation. *Mod. Drug Discov.* 7, 40–43
31 Byrn, S. *et al.* (1995) Pharmaceutical solids: a strategic approach to regulatory considerations. *Pharm. Res.* 12, 945–954
32 Bugay, D.E. (2001) Characterization of solid-state: spectroscopic techniques. *Adv. Drug Deliv. Rev.* 48, 43–65
33 Findlay, W.P. and Bugay, D.E. (1998) Utilization of Fourier transform–Raman spectroscopy for the study of pharmaceutical crystal forms. *J. Pharm. Biomed. Anal.* 16, 921–930
34 Carlson, E.D. *et al.* [Symyx Technologies] Polymorph characterization. *EP1467205A1*
35 Balbach, S. and Korn, C. (2004) Pharmaceutical evaluation of early development candidates ''the 100 mg-approach''. *Int. J. Pharm.* 275, 1–12
36 Zografi, G. (1988) States of water associated with solids. *Drug Dev. Ind. Pharm.* 14, 1905–1926
37 Ahlneck, C. and Zogafi, G. (1990) The molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state. *Int. J. Pharm.* 62, 87–95
38 Callahan, J.C. (1982) Equilibrium moisture content of pharmaceutical excipients. *Drug Dev. Ind. Pharm.* 8 (3), 355–369
39 Gift, A.D. and Taylor, L.S. (2007) Hyphenation of Raman spectroscopy with gravimetric analysis to interrogate water–solid interactions in pharmaceutical systems. *J. Pharm. Biomed. Anal.* 43, 14–23
40 Lipinski, C.A. *et al.* (1997) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.* 23, 3–25
41 Kane, N.R. *et al.* (2004) A System for dispensing sub-milligram doses of active pharmaceutical powders for early stage solubility assays. *J. Assoc. Lab. Automat.* 9, 218–227
42 Dinter, C. *et al.* (2005) Automated solubility determination using a customized robotic system and a turbidity probe. *J. Assoc. Lab. Automat.* 10, 408–411
43 Tan, H. *et al.* (2005) An automated screening assay for determination of aqueous equilibrium solubility enabling SPR study during drug lead optimization. *J. Assoc. Lab. Automat.* 10, 364–373
44 Chen, T.M. *et al.* (2002) Evaluation of a method for high throughput solubility determination using a multi-wavelength UV plate reader. *Comb. Chem. High Throughput Screen.* 5, 575–581
45 Chen, X.Q. and Venkatesh, S. (2004) Miniature device for aqueous and non-aqueous solubility measurements during drug discovery. *Pharm. Res.* 21, 1758–1761
46 Fermier, A.M. *et al.* (2002) Automation of chemical reaction kinetics and product distribution studies in pharmaceutical development. *J. Assoc. Lab. Automat.* 7, 83–88
47 Chandler, W. *et al.* (2005) The extended core module robot: a flexible, modular platform for high-throughput development workflows. *J. Assoc. Lab. Automat.* 10, 418–422
48 Fermier, A.M. *et al.* [Ortho McNeil Pharm Inc.] Apparatus for the automation of chemical reaction kinetics studies. *WO02077614*
49 Di, L. *et al.* (2006) Development and application of an automated solution stability assay for drug discovery. *J. Biomol. Screen.* 11, 40–47
50 Sims, J.L. *et al.* (2003) A new approach to accelerated drug-excipient compatibility testing. *Pharm. Dev. Technol.* 8, 119–126
51 Wyttenbach, N. *et al.* (2005) Drug-excipient compatibility testing using a high-throughput approach and statistical design. *Pharm. Dev. Technol.* 10, 499–505
52 Hilfiker, R. *et al.* (2003) Polymorphism – integrated approach from high-throughput screening to crystallization optimization. *J. Therm. Anal. Calorim.* 73, 429–440