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Design and utilization of the drug–excipient chemical compatibility automated system

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ABSTRACT

To accelerate clinical formulation development, an excipient compatibility screen should be conducted as early as possible and it must be rapid, robust and resource sparing. This however, does not describe the traditional excipient compatibility testing approach, requiring many tedious and labor intensive manual operations. This study focused on transforming traditional practices into a completely automated screening process to increase sample throughput and realign resources to more urgent areas, while maintaining quality. Using the developed system, a complete on-line performance study was conducted whereby drug–excipient mixtures were weighed, blended and subjected to accelerated stress stability for up to 1 month, followed by sample extraction and HPLC analysis. Compared to off-line traditional study protocols, the system provided similar relative rank order results with equivalent precision and accuracy, while increasing sample throughput. The designed system offers a resource sparing primary screen for drug–excipient chemical compatibility for solid dosage form development. This approach allows risk assessment analysis, based upon formulation complexity, to be conducted prior to the commitment of resources and candidate selection for clinical development.

1. Introduction

The need to accelerate drug development timelines, while managing attrition risk, requires a change in the traditional paradigm of solid dosage form development, with its many tedious rounds of optimization (Kola and Landis, 2004). An excipient chemical compatibility screen can play an integral role in clinical formulation development by reducing excessive formulation optimization and minimizing costly time delays due to unexpected drug product instabilities. A properly designed and executed excipient chemical compatibility screen provides a systematic approach to determine the chemical interaction (stability/instability) between a drug substance and a selection of excipients under accelerated stressed conditions (Serajuddin et al., 1999; Sims et al., 2003; Wyttenbach et al., 2005). These results offer guidance to the formulator in selecting excipients that are likely to confer chemical stability in the final drug product. The screen must be rapid, robust and resource sparing; allowing it to be used during the pre-clinical candidate selection process to mitigate risk and thereby maximize its value.

There have been several approaches proposed that could satisfy the requirements of a drug–excipient chemical compatibility screen. The most resource sparing of these approaches is computational. Where drug–excipient chemical compatibility can be predicted, using a comprehensive database of reactive functional groups, for both drug and excipient, combined with an in-depth knowledge of potential impurities in excipients (Zhou, 2004). This approach provides rapid analysis and requires no bulk substance. However, there are inherit risks to using this computational approach as the sole source of information. While most possible degradant products can be predicted, there can be relatively little certainty placed upon discerning the probable from the possible products, to any known quantitative level. Thermal techniques, such as differential scanning calorimetry, can provide a rapid evaluation of drug–excipient incompatibility; while this too, is rapid and drug-sparing, the data interpretation is complex and often requires follow-up experimentation utilizing traditional approaches to substantiate any findings (Schmitt et al., 2001; Mura et al., 2002; Mcdaid et al., 2003).

As a result of the inconclusive methods mentioned above, the traditional drug–excipient chemical compatibility is still the preferred approach, where a set of standard excipients in binary or multi-component mixtures are placed on accelerated stability conditions. These studies are known to be labor intensive, requiring hundreds of individual weighings and tedious post-stability sample preparation and extraction. As such, the focus of this study was to design and develop a robust automation platform capable of executing a drug–excipient chemical compatibility screen

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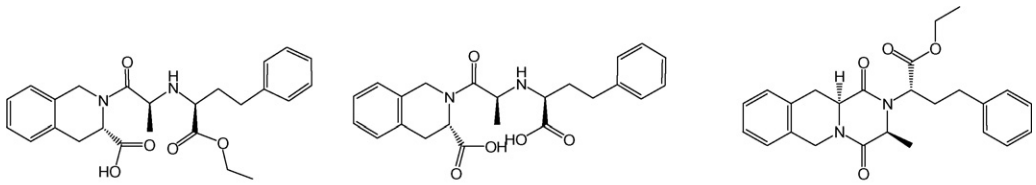

Fig. 1. Quinapril and related degradants. Chemical structures for quinapril and its two degradation products, quinaprilat and cyclic impurity.

that is both active pharmaceutical ingredient (API) and resource sparing, allowing the screen to be conducted prior to clinical candidate selection. As designed, the drug–excipient chemical compatibility automated system (DECCAS) is capable of weighing and blending drug–excipient mixtures, accelerated stress stability, sample extraction and HPLC analysis. DECCAS capabilities are described using the model compound quinapril, an angiotensin-converting enzyme (ACE) inhibitor used for the treatment of high blood pressure, heart failure and kidney failure prevention due to hypertension and diabetes. Quinapril was selected for its well-documented degradation profile, whereby it degrades into two major components; quinaprilat via hydrolysis of the ester group and a cyclic impurity by way of an intramolecular cyclization (Fig. 1) (Freed et al., 2005).

Comparing DECCAS to a more traditional study protocol (manually prepared) in a performance study provided similar relative rank order of excipient acceptability for solid dosage form development. The successful design and implementation of this system not only allows for a realignment of resources to other areas of preformulation development but also an opportunity to assess formulation complexity prior to clinical candidate selection.

2. Materials and methods

2.1. Materials

Quinapril and all excipients were obtained from Pfizer Global Research and Development materials management. Symmetry C8 column (5 μm, 3.9 mm × 150 mm) was purchased from Waters Corp. (Milford, MA). HPLC solvents were of an analytical grade or better and purchased from Mallinckrodt Baker Inc. (Phillipsburg, NJ). Polypropylene 96-deep-well block (2 ml Whatman Uniplate™), polystyrene lids, 4-ml glass scintillation vials with screw cap and 200 μl disposable pipette tips (Eppendorf) were purchased from VWR International (Buffalo Grove, IL).

2.2. System hardware and plate flow

The DECCAS is a 96-well block plate-based system comprised of three automated stations fully integrated into a single 8 in. × 14 in. platform as depicted in Fig. 2. Station 1 handles the weighing of all dry components (drug and excipient) using the Many-to-Many Powdernium (Symyx Technologies, Santa Clara, CA), equipped with a Sartorius BP211D balance. Station 2 handles all sample mixing, addition of liquid excipients or accelerants, stress stability, and post-stress stability sample extraction and preparation. Station 2 is comprised of a Sciclone ALH high volume liquid handler equipped with a 96 cannula main array, Z-8, four bulk-dispense units, microplate shaker, and a plate seal piercing head (Caliper Life Sciences, Hopkington, MA); a PlateLoc thermal plate sealer and VSpin microplate centrifuge (Velocity 11, Palo Alto, CA); sonicator (L&R Ultrasonics, Kearny, NJ) maintained at 22 °C with a closed-looped circulating water bath (Polyscience, Niles, IL); orbital action plate shaker (H&P, Oberschleissheim, DE); two StoreX40 variable temperature/humidity chambers (Liconic, Nendein, LI). Station 3 handles all sample analyses and post-stress stability storage and comprised of a Micro215 liquid handler, equipped with an 841 micro-injector module (Gilson, Middleton, WI), and model 1100 HPLC system, equipped with vacuum degasser, quaternary pump, automatic injector with column oven and photodiode array detector (Agilent Technologies, Palo Alto, CA). The three stations platform design allows each station to actively handle one block plate at any given time, allowing three plates to be processed simultaneously.

Sample plates and consumables are handled within and across the individual stations by three TwisterII microplate handlers (Caliper Life Sciences, Hopkington, MA) and one centrally located MoveMaster RV-E2 6-axis robotic arm (Mitsubishi, Nagoya, JP). Barcode readers (MicroScan, Renton, WA) are strategically positioned in each station to track plate progress across the system. Plate transfer stations equipped with photoelectric sensors are located between stations and serve as a staging area for plates to be moved from one station to the next, providing a cross-check to prevent

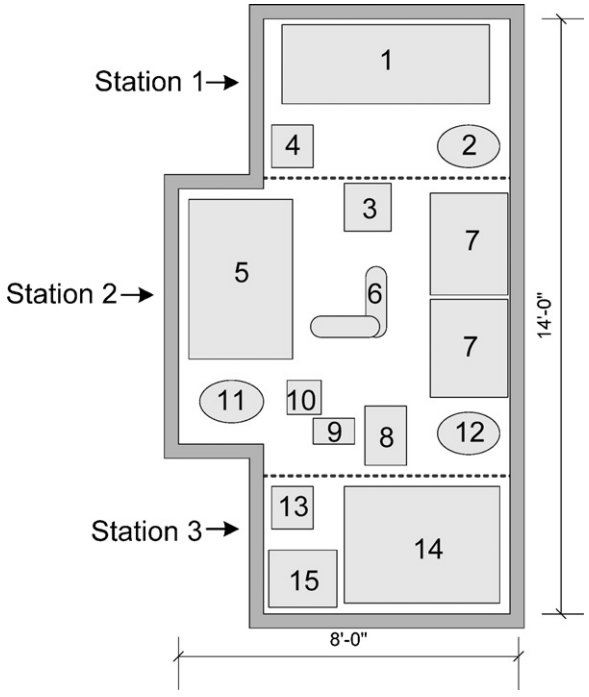

Fig. 2. DECCAS layout. Station 1 is comprised of Many-to-Many Powdernium (1) and TwisterII plate handler (2). Station 2 is comprised of PlateLoc plate sealer (3), Sciclone liquid handler (5), Mitsubishi robotic arm (6), two StoreX40 variable temperature/humidity chambers (7), VSpin centrifuge (8), sonicator bath (9), orbital action shaker (10), and TwisterII plate handler (11). Station 3 is comprised of TwisterII plate handler (12), Micro215 liquid handler (14), and Agilent 1100 HPLC (15). The system is controlled by five computers where computer terminals 1–4 (4) and terminal 5 (13) are depicted. For simplicity, plate transfer stations and barcode readers are not shown.

two work processes from occurring within one station at the same time.

2.3. System software, instrument control and data flow

The DECCAS utilizes a mini-network to operate the entire system. The system provides an interface to the HPLC with analysis being performed with Empower Pro (Waters Corp., MA).

The DECCAS has four levels of operational control that are fully integrated as depicted in Fig. 3. The operating system is based in an SQL server 2000 (Microsoft, ver. 8.00) framework with Visual Basic (Microsoft, ver. 6) generated graphical user interfaces (GUI). Excel (Microsoft, 2000) provides data logging outputs and some inputs. The master control system (MCS) is the main interface that serves as a message hub and command dispatcher across the three stations. Each station has its own station control system (SCS) that receives and executes commands from the MCS, followed by relaying back run-time status. The SCS is also the portal for error management/recovery, method linking across individual components and data output. iLink method editor (Caliper Life Sciences, Hopkington, MA) is used to define the environment for each station and method development. Station environments are composed of a series of individual control programs (ICP) that translate commands and messages to and from the SCS and individual component software. In addition, each component within the system can be controlled independently through the original manufacturer GUI.

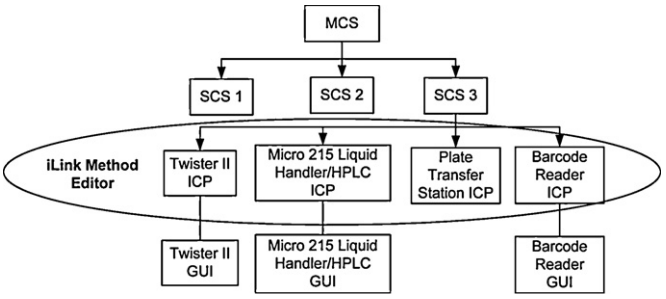

Fig. 3. DECCAS control/communication overview. The four levels of operational control are fully integrated with the MSC providing the main interface sending commands to each of the three SCS. SCS serve as a portal for error management/recovery, method linking across ICPs and Data output (SCS 3 is fully shown with the expanded control stream). iLink method editor defines each ICP environment within each SCS and is used for method development. Station environments are comprised of several ICPs, which translate communications to and from the SCS and individual component software. Highly functional components also have a GUI, which can be used to control the component independent of the DECCAS.

2.4. System sample handling

General sample handling and routine execution follows the process map depicted in Fig. 4. A barcode labeled block plate (motherplate—MP) enters Station 1 and all dry components (API and excipients) are individually weighed into the MP. MP is trans-

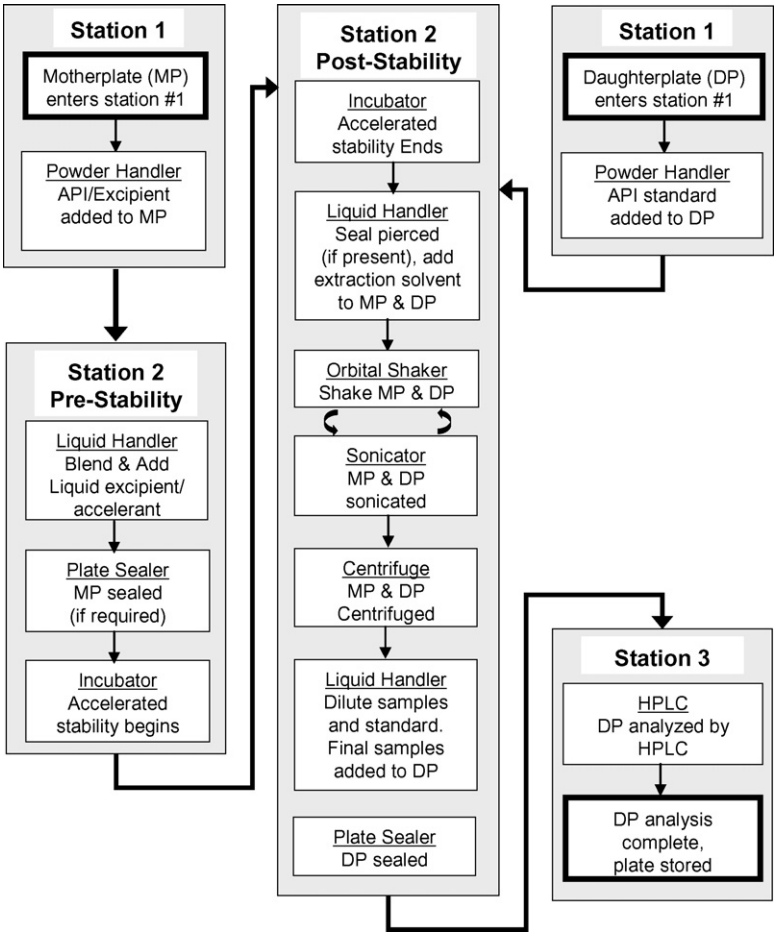

Fig. 4. General workflow and routine execution across the DECCAS. (Top left—Station 1) Powder handler individually weighs API and excipients into a bar-coded block plate (MP). MP enters Station 2 where the dry components are blended, addition of liquid components, if needed, followed by sealing and placement on accelerated stability. MP called from incubator at predetermined time. (Top right—Station 1) simultaneously, API standard is added to DP and transferred to Station 2. Samples (MP and DP) are extracted and/or diluted to target concentration. Final samples are transferred to DP, which is sealed and transferred to Station 3. DP is analyzed by HPLC and stored.

Table 1
Summary of multi-component blend and binary composition

Component	Blend # (value in mg)										Binary ratio (quinapril 5 mg:excipient)
	1	2	3	4	5	6	7	8	9	10	
Quinapril	5	5	5	5	5	5	5	5	5	5	
Microcrystalline cellulose	95					95					1:19
Lactose, monohydrate		95					95				1:19
Dicalcium phosphate, anhydrous			95					95			1:19
Mannitol				95					95		1:19
Corn starch					95					95	1:19
Croscarmellose sodium	5	5	5	5	5						1:1
Sodium starch glycolate						5	5	5	5	5	1:1
Magnesium stearate	1		1		1		1		1		1:0.2

Quinapril extraction qualification was conducted using the following blends with the manual addition of API. All blends and binary components were individually dispensed by the DECCAS into MP for the performance study.

ferred to Station 2 where the dry components are blended and liquid components, if specified, are added followed by foil heat induction sealing, if required. Completed plates are stored in one of the two incubators. At the predetermined time, plates are automatically removed from storage and sent to the liquid handler for extraction, dilution and transfer to the daughterplate (DP), which is sealed and transferred to Station 3. DP is analyzed by HPLC and all plates are transferred to a storage rack.

2.5. System qualification

Four aspects of the DECCAS were qualified prior to use, API-excipient weighing, blending, post-stability solvent addition and API extraction. The BP211D balance has a manufacturer stated standard deviation of less than or equal to ±0.1 mg. Verification was performed using ASTM class 1 weights (Troemner, Thorofare, NJ) across the range of 1–200 mg, in the presence of a 96-deep-well plate (tarred).

Blending (content uniformity) qualification was performed by adding quinapril (5 mg) and lactose (95 mg) into the four corner wells and one center well of the 96-well plate, mixtures were then allowed to vortex on the microplate shaker for 2 min at ~1500 rpm, while changing direction of rotation every 30 s. Individual blends were fractioned into thirds and placed into 4-ml screw cap scintillation vials and prepared for HPLC analysis as stated for the manual compatibility studies, described below.

Calibration curves were developed for each of the three solvent delivery methods available on the liquid handler. Qualification range for each delivery method were as follows: Z-8, 2–100 μl; main array, 5–200 μl; bulk dispense, 50–2500 μl. Volume dispensed ($n = 5$) was determined by weighing the solvent and converting to volume with experimentally derived density values for each solvent mixture used.

Quinapril extraction was qualified by the manual addition of quinapril (5 mg) and a subset of the excipient blends (Table 1) to a 96-well plate and then allow the DECCAS to extract the API, while optimizing the number of cycles and duration and/or agitation speed of the orbital shaking and bath sonication. HPLC analysis was performed on-line.

2.6. DECCAS performance study design

The DECCAS performed the drug–excipient chemical compatibility study design outlined in Table 1, following the work flow depicted in Fig. 4. Drug–excipient mixtures were blended for 2 min at ~1500 rpm, while changing direction of rotation every 30 s, on the microplate shaker, sealed if necessary, and placed under accelerated stability at 40 °C/75% relative humidity for 1–4 weeks. At the specified times, plates were automatically removed from storage and extracted with 1 ml of acetonitrile:water (20:80, v/v) through three cycles of shaking (orbital shaker, ~600 rpm for 5 min) and sonicating (5 min), followed by removal of insoluble excipients through centrifugation (2000 rpm for 10 min). Samples were transferred to the DP and diluted to 0.1 mg/ml in 0.025 M $NH_4H_2PO_4$ (pH 6.5):acetonitrile (60:40, v/v) for HPLC analysis.

Using traditional manual methods the drug–excipient chemical compatibility study design outlined in Table 1 was conducted in parallel to the studies outlined above and served as a validation control. Briefly, components of the blends and binary mixtures were individually weighed on a MT 5 microbalance (Mettler-Toledo, Columbus, OH) and transferred into pre-labeled 4 ml clear glass scintillation vials with screw cap and mix by vortex. An individual sample, along with API control, was prepared for each time point. Vials were placed under accelerated stability, as indicated above. At the designated time point, samples were extracted via multiple rinses/vortex cycles using 0.025 M $NH_4H_2PO_4$ (pH 6.5):acetonitrile (60:40, v/v) to quantitatively transfer the vial contents to a 50-ml volumetric flask. Transferred samples where brought to volume with 0.025 M $NH_4H_2PO_4$ (pH 6.5):acetonitrile (60:40, v/v), sonicated (5 min) and mixed by inversion. Samples were syringe filtered (nylon, 0.45 μm) prior to HPLC analysis.

2.7. HPLC and results analysis

The HPLC analytical method is a validated method for quinapril (PfizerInc., 1998). Method parameters are outlined in Table 2 and a representative chromatograph highlighting the respective retention times for quinapril and the primary degradants is also provided (Fig. 5). Data analysis for both approaches, DECCAS and manual,

Table 2
Validated HPLC method parameters for quinapril and associated degradants

Column	Symmetry C8, 5 μm, 3.9 mm × 150 mm
Flow rate (ml/min)	1.4
Run time (min)	10
Injection volume (μl)[a]	10
Column temperature (°C)	30 ± 2
Detection	214 nm; bw, 8 nm; 450 nm; bw 50 nm (reference)
Mobile phase	0.02 M SDS pH 2.2 (phosphoric acid):acetonitrile (50:50)
Target sample concentration	0.1 mg/ml in 0.025 M $NH_4H_2PO_4$ pH 6.5 (NaOH):ACN (60:40)
Retention time (min)	Quinapril—5.9 Cyclic impurity—2.3 Quinaprilat—3.5

[a] Needle and needle set are washed twice, respectively, between injections to prevent any potential sample carry over.

Table 3
Binary tabulated results

Binary excipient	Area% quinapril remaining					Linear regression slope	Relative rank order
	Initial	1 week	2 week	3 week	4 week		
Quinapril control	100	102	98	99	101	0.0	
	100	101	99	100	99	−0.3	
Diluent							
Lactose, monohydrate	101	98	97	95	96	−1.3	1
	99	100	96	92	94	−1.7	1
Corn starch	101	97	98	95	92	−2.0	2
	102	95	95	93	94	−1.8	2
Microcrystalline cellulose	99	100	101	96	89	−2.5	3
	101	101	102	97	92	−2.3	3
Mannitol	100	103	98	93	91	−2.9	4
	99	102	99	84	87	−4.2	4
Dicalcium phosphate, anhydrous	100	0	0	0	0	−19	5
	102	0	0	1	0	−20	5
Disintegrant							
Croscarmellose sodium	101	82	77	70	72	−7.0	1
	98	78	73	72	70	−6.2	1
Sodium starch glycolate	103	72	75	73	62	−8.0	2
	99	75	71	67	64	−7.9	2
Lubricate							
Magnesium stearate	103	92	86	83	72	−7.1	1
	102	87	82	80	76	−5.8	1

DECCAS and manual generated results are reported in the shaded and non-shaded region, respectively. DECCAS results are equivalent to the manual approach, when evaluating relative rank order of excipient acceptability based on linear regression analysis over the 4-week testing period.

were performed using Empower Pro. Parent remaining is reported as an area% relative to the initial peak area ($t = 0$ h).

DECCAS and manual excipient chemical compatibility stability results were compared by relative rank order using the slope of the linear regression line through all available data points (time = initial to 4 weeks).

3. Results

3.1. Qualification of components

In establishing a system capable of conducting a primary screening for drug–excipient chemical compatibility, the arbitrary value of ±5% was selected as acceptable total system error. Of the many routines conducted by the DECCAS there were four in need of qualification: API-excipient weighing, blending, post-stability solvent addition and API extraction. Balance qualification was deemed fit for purpose and verified to be within the manufactured tolerance limits of ±0.1 mg. As a result, less than ±2% S.D. could be reasonably assured by setting the minimum weighing limit of quinapril to 5 mg. The blending routine content uniformity was established for the block plate by blending lactose and quinapril. The four corner wells and one center well were selected to be representative of the entire plate. Sampling the sub-fractions of each test well ($n = 3$) resulted in an average potency of 98.6 ± 3.7% R.S.D. This result was well within the established internal acceptance limits of 90–110% potency with 5% R.S.D. Post-stress solvent handling calibration curves (aspirate and dispense) were generated for each of the three solvent delivery methods available on the liquid handler. All three delivery methods were within 1.2% of the stated value (data not shown). API extraction was conducted by manually spiking a 96-well placebo block plate (excipient blends describe in Table 1) with a known amount of quinapril (5 mg). The DECCAS then extracted and analyzed the plate. The results are highlighted in Tables 3 and 4, as indicated by the initial time point. Values ranged from 97% to 103% with an average of 100 ± 1.4%.

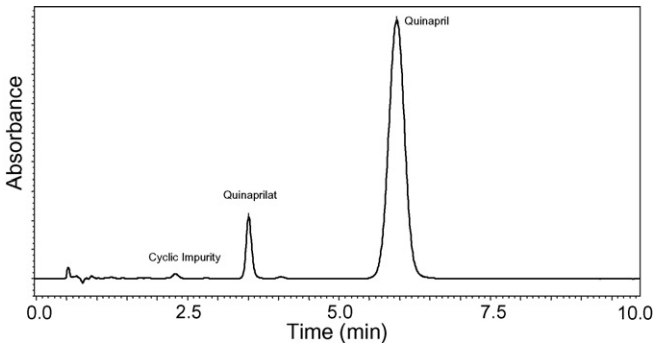

Fig. 5. Representative HPLC chromatogram of quinapril and main degradation products.

3.2. DECCAS performance

Results of system performance study comparing the DECCAS to a traditional manual drug–excipient chemical compatibility screen are shown in Tables 3 and 4 for binary and multi-component blends, respectively. For the purpose of developing an initial screening system, results are evaluated by comparing the slopes of the linear regression line, as chemical degradation is assumed to be zero order or pseudo-zero order. In practice, if the regression line represents a non-linear fit then a higher order can be applied. Overall, the DECCAS results trend well with the data obtained from the manual study. Since there were two primary degradant products formed, quinaprilat and cyclic impurity, there was a good mass balance in samples with degradation of less than approximately 80%. Degradation beyond this point yielded secondary degradants, making it

Table 4
Blend tabulated results

Multi-component blends	% Quinapril remaining					Linear regression slope	Relative rank order
	Initial	1 week	2 week	3 week	4 week		
Control	100	102	98	99	101	0.0	
	100	101	99	100	99	−0.3	
Blend 6	99	77	81	80	75	−4.6	1
	101	84	78	79	81	−4.7	1
Blend 2	101	83	78	72	75	−6.3	2
	100	79	75	n.d.	n.d.	−8.5[a]	4[b]
Blend 8	97	78	81	77	66	−6.3	3
	98	83	78	70	73	−6.4	3
Blend 10	99	94	89	74	71	−7.5	4
	98	81	83	66	67	−7.7	4
Blend 1	99	75	66	63	56	−9.9	5
	99	83	68	67	59	−9.5	5
Blend 7	102	97	85	62	58	−12	6
	99	76	68	65	49	−11	6
Blend 5	101	58	57	53	39	−13	7
	102	51	41	33	31	−16	7
Blend 3	100	75	58	39	17	−20	8
	100	63	41	25	n.d.	−20[a]	8[b]
Blend 9	98	51	28	0	0	−24	9
	101	24	0	0	0	−22	9
Blend 4	99	96	0	1	0	−29	10
	101	102	1	0	0	−30	10

DECCAS and manually generated results are reported in the shaded and non-shaded region, respectively. DECCAS compares favorably with the manual approach, when evaluating relative rank order of blend acceptability based on linear regression analysis over the four week testing period, n.d. = not determined.

[a] Slope value extrapolated from available data.

[b] Represents relative ranking based upon incomplete data set from the DECCAS.

necessary, for ease of comparison, to report the results as potency remaining.

In the binary results, quinapril was found to be relatively stable in the presence of all the diluents except dicalcium phosphate, resulting in rapid degradation of quinapril within the first week. This incompatibility is no surprise given the surface acidity of dicalcium phosphate and the instability of quinapril outside a narrow pH range (5.5–6.5) (Freed et al., 2005). The DECCAS and manual sample set provided equivalent results for the diluents when comparing the slope of the linear regression line. The binary compatibility for the diluents provided the following relative rank order with respect to chemical stability: lactose > corn starch > microcrystalline cellulose > mannitol > dicalcium phosphate. From these findings, lactose, corn starch and microcrystalline cellulose would be considered an acceptable diluent as the remaining potency of quinapril indicated no significant interaction. The potential interaction with mannitol is difficult to ascertain with this moderate level of instability. Mannitol has a saturated suspension pH of approximately 4 (data not shown), an unstable region for quinapril. However mannitol is also deemed non-hygroscopic, which may counterbalance the effects of this potential acidic environment (Rowe et al., 2003).

In the presence of the disintegrants tested, quinapril was shown to readily degrade over a 4-week period. Similar results were obtained from both methods with regard to a relative rank order of chemical stability, with croscarmellose sodium being slightly more stable than sodium starch glycolate. The apparent difference may stem from the amount of moisture uptake for these two excipients, as both are considered hygroscopic (Rowe et al., 2003).

A similar degradation profile was shown for both the manual and DECCAS methods in the presence of magnesium stearate, the only lubricant evaluated, when comparing the linear regression slope with a value of −7.1 and −5.8, respectively. Incompatibility with magnesium stearate can be expected due to the basicity of this excipient and the rate of this degradation is mediated by the availability of moisture.

Reviewing the multi-component blend results, regression analysis provided similar relative rank ordering of the blend data for all the blends tested (Table 4). However, one should note that not all blends could be properly ranked. In the case of both blends 2 and 3, a complete data set was not obtained and therefore was only ranked based on the manual results. The DECCAS results for blends 2 and 3 could be extrapolated with the collected data, resulting in a relative ranking of 4 and 8, respectively. Upon extrapolation, blend 2 appears inconsistent in the relative ranking of DECCAS versus the manual approach. However, caution should be exercised in not over interpreting this particular result, as the 4-week time point for the manual study does not align well with the rest of the manual sample set, resulting in a slight skew towards higher trending.

Upon closer inspection, the multi-component blends have a greater apparent instability compared to the binary samples (Table 3). One possible explanation would be that all blends contain a disintegrant, which promotes the uptake of moisture and accelerates the rate of quinapril degradation. The four most stable blends (2, 6, 8, and 10) have one commonality with the absence of magnesium stearate. This data would indicate that during formulation development an alternate lubricate may be needed or minimize the level of magnesium stearate with a preference toward extragranular use. The two least stable blends contained mannitol (blends 4 and 9) and when compared to the mannitol binary sample a significant increase in degradation was evident. The addition of a hygroscopic disintegrant proved deleterious when combined with the acidic environment of mannitol.

4. Discussion

The purpose of this work was to develop a robust automated platform capable of carrying out all of the necessary functions to execute a drug–excipient chemical compatibility with equivalent quality to that of a manual approach. One of the key drivers to developing an automated system was to recover valuable analyst resources being spent on tedious, routine tasks such as, repetitive weighing and sample preparation. The automation of such activities would allow redirection of these resources into more value added activities such as data interpretation. A typical drug–excipient chemical compatibility evaluation may include 8–10 excipients as binaries and in multi-component blends under two conditions at three time points, yielding approximately 350 individual weighings. This approach would require an analyst to spend 3–5 days, preparing the samples for stability then at each time point; the analyst would spend another full day preparing the samples for HPLC analysis. Consequently, one study would require, on average, 6–8 full days of an analyst time for each excipient compatibility study performed. In developing the automated platform the intent was to have the system carry out the same activities, weighing, blending, sample extraction, while requiring little to no analyst involvement. Prior to conducting a study the DECCAS only requires a validation of solvent delivery system (if a new solvent is being used) and sample extraction, controlled by the number and length of orbital mixing and sonication cycles. All of which can be conducted in much less than a day.

The first step in designing the system was to decide to use a block plate format due to the commercial availability of automation equipment using this design as well as the overall desire to reduce API consumption. Next, all the manual operations had to be divided into discrete routines (Fig. 4) that could be automated and design a layout that would provide a small footprint, while affording an efficient work flow, with the final result being the DECCAS (Fig. 2). The overall throughput is increased by the three stations platform design, which allows each station to actively handle one plate at any one time, effectively allowing three plates to be processed simultaneously by DECCAS.

Achieving a higher sample throughput was only a minor consideration due to the desire to conform to the departmental excipient chemical compatibility methods that are based on ICH guidelines (ICH, 2001). The rate-limiting steps in the established methods are the stress stability incubation times (2–12 weeks) and the use of a fit for purpose HPLC method. Working within these constraints provided the opportunity for complete flexibility in the area of experimental design, allowing formulators to vary drug:excipient ratios, blends versus binaries, addition of plasterizer (hydroalcoholic solutions with polymer) or accelerant (dilute solutions of acid, base, or peroxides). The resulting DECAAS is considered as a medium-throughput system with an average throughput of approximately 70 drug–excipient chemical compatibilities per year. The value of this throughput and minimal resource burn allows the system to be integrated into the pre-clinical candidate selection stage, by qualifying clinical formulation complexity and allowing development timeline comparison between candidates within the same series.

The two critical routines that required the most attention were API-excipient blending and API extraction. In handling dry powders the first consideration was dispensing into the 96-well plate. The Many-to-Many Powdernium was capable of dispensing excipients and API with a wide range of bulk properties, as a result of the system's mechanical dispensing head design and algorithm software. As a result, no special preparation of the excipients or API is required. The controlling factors in dry powder blending within a 96-well plate were well design, powder volume and ability to fluidize the powder bed. Several block plates were evaluated for proper well design that varied the volume from 0.4 to 2 ml (with various aspect ratios), wall and well format both having options of round, flat or v-shaped. Of those tested the 2 ml Whatman Uniplate™ with flat walls and round bottom provided the best blending. The combination of rounded bottom appeared to reduce potential dead mass during mixing with the flat walls acting as baffles to provide turbulent flow and prevent segregation. In addition, the powder volume and ability to fluidize this volume where closely linked in that the bulk volume of the powder should be less than approximately 0.3 ml, which is the volume of the rounded bottom. This plate design combined with an alternating high rate of short radial orbital mixing provided uniform blending. Post-stress stability sample extraction, required an approach where the complete sample was consumed, alleviating any concerns of content uniformity. In addition, several cycles of orbital mixing and sonication ensured complete solubilization of the quinapril. This was followed by the removal of insoluble excipients from the sample matrix. The two most readily available approaches were filtration and centrifugation. Centrifugation was selected, as it reduced the number of handling steps, thereby eliminating the need to perform an on-line filter binding assay and it provided a lower consumable cost when compared to using filter plates.

5. Conclusions

The overall design of the DECCAS is a fully integrated automated platform capable of accurate powder dispensing, accelerated stress stability, sample extraction and HPLC data generation, all in a 96-well block plate format. The system has been shown to provide a robust and reliable screen for drug–excipient chemical compatibility allowing flexibility of experimental design and a moderate increase in throughput, while requiring a minimum amount of API. The quinapril performance study demonstrated that the DECCAS provides similar relative rank ordering of excipient acceptability for solid dosage form development with equivalent precision and accuracy to that of manual operations. In summary, this paper provides an automated approach to drug–excipient chemical compatibility, allowing the assessment solid dosage form complexity for pre-clinical drug candidates prior to the full commitment of development resources.

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References

Freed, A.L., Silbering, S.B., Kolodsick, K.J., Rossi, D.T., Mahjour, M., Kingsmill, C.A., 2005. The development and stability assessment of extemporaneous pediatric formulations of accupril. Int. J. Pharm. 304, 135–144.

ICH, 2001. Guidance for Industry—Stability Testing of New Drug Substances and Products.

Kola, I., Landis, J., 2004. Can the pharmaceutical industry reduce attrition rates? Nat. Rev. Drug Discov. 3, 711–715.

Mcdaid, F.M., Barker, S.A., Fitzpatrick, S., Petts, C.R., Craig, D.Q.M., 2003. Further investigations into the use of high sensitivity differential scanning calorimetry as a means of predicting drug–excipient interactions. Int. J. Pharm. 252, 235–240.

Mura, P., Gratteri, P., Faucci, M.T., 2002. Compatibility studies of multicomponent tablet formulations. DSC and experimental mixture design. J. Therm. Anal. Cal. 68, 541–551.

PfizerInc., 1998. HPLC Assay and Impurity Profile for Quinapril API.

Rowe, R.C., Sheskey, P.J., Weller, P.J. (Eds.), 2003. Handbook of Pharmaceutical Excipients. Pharmaceutical Press, London.

Schmitt, E.A., Peck, K., Sun, Y., Geoffroy, J.M., 2001. Rapid, practical and predictive excipient compatibility screening using isothermal microcalorimetry. Thermochim. Acta 380, 175–184.

Serajuddin, A.T., Thakur, A.B., Ghoshal, R.N., Fakes, M.G., Ranadive, S.A., Morris, K.R., Varia, S.A., 1999. Selection of solid dosage form composition through drug–excipient compatibility testing. J. Pharm. Sci. 88, 696–704.

Sims, J.L., Carreira, J.A., Carrier, D.J., Crabtree, S.R., Easton, L., Hancock, S.A., Simcox, C.E., 2003. A new approach to accelerated drug–excipient compatibility testing. Pharm. Dev. Technol. 8, 119–126.

Wyttenbach, N., Birringer, C., Alsenz, J., Kuentz, M., 2005. Drug–excipient compatibility testing using a high-throughput approach and statistical design. Pharm. Dev. Technol. 10, 499–505.

Zhou, P., 2004. IIR Conference on Drug–Excipient Compatibility.