3

Stability Indicating Methods

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1. Introduction

1.1 How define a SIM?

According to FDA guideline (Guidance for Industry, Analytical Procedures and Methods Validation, FDA, 2000), a Stability Indicating Method (SIM) is defined as a validated analytical procedure that accurate and precisely measure active ingredients (drug substance or drug product) free from process impurities, excipients and degradation products. The FDA recommends that all assay procedures for stability should be stability indicating. The main objective of a stability indicating method is to monitor results during stability studies in order to guarantee safety, efficacy and quality. It represents also a powerful tool when investigating out-of-trend (OOT) (Swartz et al., 2004) or out-of-specification (OOS) results (CDER, 2006) in quality control processes.

1.2 How develop a SIM?

There are basically 3 steps necessary for developing a SIM:

1.2.1 Step 1: generation of degraded samples for testing selectivity of the method

Here lies one of the main concerns related to a development of a SIM, since the available guidance documents do not state the extent to which stress tests should be carried out – that is, how much stress should be applied or how much degradation should be aimed for.

In fact, there is not a "gold rule" that attends this issue and therefore, it is important to keep in mind that experimental conditions of stress tests, should be realistic and lead to "purposeful degradation" (Ngwa, G., 2010).

Stress tests should generate representative samples to assess drug substance and drug product stability, provide information about possible degradation pathway and demonstrate the stability indicating power of the analytical procedures applied.

1.2.1.1 Determination of Limit of Quantification (LoQ)

In close relation to the determination of the amount of degradation is the evaluation of Limit of Detection (LoD) and Limit of Quantification (LoQ) of the method. These limits should be closely related to the Reporting, Identification and Qualification of degradation products, as stated in ICH Q3B (R2) (EMEA, 2006). These thresholds are determined either as percentage of drug substance or total daily intake (TDI) of degradation product.

The analytical methods are usually expected to be validated for the ability to quantify potential degradation products and drug impurities with a LoD and LoQ at least as sensitive as the ICH threshold (see Figure 1).

Attachment 1: Thresholds for Degradation Products in New Drug Products

Reporting Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
≤ 1 g	0.1%
> 1 g	0.05%

Identification Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
< 1 mg	1.0% or 5 µg TDI, whichever is lower
1 mg - 10 mg	0.5% or 20 µg TDI, whichever is lower
>10 mg - 2 g	0.2% or 2 mg TDI, whichever is lower
> 2 g	0.10%

Qualification Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
< 10 mg	1.0% or 50 µg TDI, whichever is lower
10 mg - 100 mg	0.5% or 200 µg TDI, whichever is lower
>100 mg - 2 g	0.2% or 3 mg TDI, whichever is lower
> 2 g	0.15%

Notes on Attachment 1

1 The amount of drug substance administered per day

2 Thresholds for degradation products are expressed either as a percentage of the drug substance or as total daily intake (TDI) of the degradation product. Lower thresholds can be appropriate if the degradation product is unusually toxic.

3 Higher thresholds should be scientifically justified.

Fig. 1. ICH thresholds for degradation products in New Drug Application (ICH Q3B)

The identification threshold (IT) varies from 0.1 to 1.0% of the labeled amount of active ingredient in the dosage form, or from 5 µg to 2 mg TDI, depending on the maximum daily dosage in the product´s professional labeling. The identification threshold may be lowered for degradation products that may be exceptionally toxic.

The Reporting Threshold (RT) is either 0.1% or 0.05% depending on the maxim daily dosage. For very low dose drug products, where this type of sensitivity is not attainable, even after exhaustive tentative, justification may be provided describing the failed reports.

Process-related drug substance impurities that are also degradation products should have the same limits as for ICH Q3B.

Ideally, the same analytical methodology should be used for Quality Control and Stability Studies. The determination of Out-of-Specification or Out-of-Trend results should be more reliable, when using a SIM, since LoD and LoQ used allows detection of impurities and/or degradation products adequately. In the situation in which a new peak arises during stability study and one may expect that it should not exist and hence it would constitute a type of OOT, the use of a well studied and well determined LoQ in a SIM, will help the applicator to decide if additional action are needed to investigate a new substance or a OOT.
It should be mentioned that these thresholds are established for new drug products or New Drug Application (NDA). For Abbreviated New Drug Application (ANDA) or generic drugs, there are not specific regulations about this topic and even less, the companies dealing with these products, have background information as those obtained in the development of NDA. Such application is expected to contain a "full description of the drug substance including its physical and chemical characteristics and stability as well; such specifications and analytical methods are necessary to assure the identity, strength, quality, purity and bioavailability of drug product and stability data with proposed expiration date". As already cited, for ANDA, there are not specific regulations and the same ICH recommendation has been used. However, precisely because of the lack of information derived from the new drug development, the complexity and responsibility in developing/validating a SIM for an ANDA is high.
Information like aqueous solubility, pH versus solubility profile, excipients compatibility studies, etc, all information that enable fully assume the knowledge of the product ,will help to ensure that best (more appropriate) condition were chosen for developing a SIM, like those related to the forced degradation design.

1.2.1.2 Overstressing/Understressing

Care should be taken in order to avoid overstressing or understressing samples, with may lead to non representative or non-purposeful degradation. So, the use of a properly designed and executed forced degradation study will generate representative samples that will help to ensure that resulting method reflects adequately long-term stability (EMEA, 2003).
About the forced degradation (or stress test, both terms will be used in the text) design, it is recommended (Klick S., et al, 2005) to include alkaline and acidic hydrolysis, photolysis, oxidation, humidity and temperature stress. An compilation of data from literature (Klick S., et al, 2005; Alsante et al. 2007, Reynolds, et al. 2002, Reynolds, D.W, 2004; Kats M., 2005; Reynolds, D.W, 2002) is shown at Table 1 and compiles the more often used conditions to perform forced degradation studies.
These conditions can be used as a starting point in the development of a SIM. Changing conditions to harsher or softer levels, can be applied, when too little or too much degradation are obtained. For example, in cases in which too little degradation was obtained in the hydrolyses stress, it is recommended to increase concentrations to 1 Mol L^{-1} or higher; for oxidation stress, increase peroxide concentration to 10% or 20% (v/v) and/or time of reaction, as well as temperature. If co-solvents are necessary to increase solubility, it is recommended the use of acetonitrile that does not work as a sensitizer in photostability stress. Data needs to be evaluated as unusual degradants may form with co-solvents. If even not all conditions may cause degradation, document efforts and severity of conditions and should be include in final report.
By the other side, if too much degradation is detected, the severity of conditions may be decreased, by diluting acid/bases, neutralizing, reducing exposure time.

Solid State			
Stress		**Condition**	**Period of time**
Heat		60° C	Up to 1 month
Humidity		75% RH	Up to 1 month
Photostability		3 mm (powder) Exposed and non-exposed samples ("control")	Follow ICH requirements (Q1B)
Solution State			
Stress		**Condition**	**Period of time**
Hydrolysis	**Acid**	0.1 – 1 Mol L^{-1} HCl	Up to weeks and 60° C
	alkaline	0.1 – 1 Mol L^{-1} NaOH	Up to weeks and 60° C
Oxidation		H_2O_2 3% (v/v)	Up to 24 hours
Photostability		Exposed and non-exposed samples ("control")	Follow ICH requirements (Q1B)
Heat		60° C	Up to 1 month

Table 1. "More often" used conditions for forced degradation studies

Also, need to be clarified, that synthesis impurities when are not also degradation products do not need to be described in Stability Studies, but SIM may assure that these impurities do not interfere on degradation products determination.

1.2.1.3 Photostability studies

Photostability tests should follow ICH requirements (EMEA, 1998) , i.e., should be done in a sequential manner, starting with the fully exposed product and proceeding, if necessary to the immediate pack and then to the market pack, until studies demonstrate the drug product is adequately protected from exposure to light. Besides this, design of forced degradation test should consider the previous knowledge of the substance or product being tested, since photoreactivity is wavelength dependent and degradation pathways can be different for UV and visible ranges (case by case basis). It is recommended to use artificial sources of irradiation, like ID65 and specific filters to guarantee the exposure above 320 nm (indoor daylight standard). Also, forced degradation may be conducted on quartz glassware that does not filter radiation from the light sources and specific filters arrangement.
It can be found in literature (ICH Q1B) that exposition to an overall irradiation of not less than 1.2 million lux.hours and an integrated near ultraviolet energy of not less than 200 W h. m^{-2} may give reasonable degradation for photosensible active ingredients. Tests may only be valid when chemical actinometers are exposed simultaneously (preferably) to the samples and shows a pattern of degradation. Control samples (samples in the same condition of that exposed, except for the irradiation, i.e., protected from the light by aluminum foils for example) should also be analyzed, in order to guarantee that the degradation is really only due to the light and not to other factors like temperature (irradiation chamber should have rigorous temperature control) (Christensen, K. et. al 2000). In some cases, the ANDA holder justifies not performing photostability studies for the drug product based on the fact that the drug substance did not show photodegradation during forced degradation studies. However, this not must be acceptable, since in some cases, excipients or impurities may catalyze photodegradation of the main active in the drug product.

1.2.2 Step 2: method development (manipulating and evaluating selectivity/specificity)

Liquid chromatography is the most appropriate technique for developing/validating a SIM. The use of diode-array-detector and additionally mass spectrometers, gives best performances for people working with SIM development.

The goal is to manipulate selectivity by changing mobile phase composition, wavelength of detection and pH. Related to mobile phase pH, it can be said, that the advances in LC column technology have made possible the use of pH as a true selectivity tool for the separation of ionizable compounds (Neue, et. al, 1999; Cheng et. al, 2010). Columns mechanically strong, with high efficiency and that are operate over an extended pH range, should be preferred. Acidic compounds are more retained at low pH; while basic compounds are more retained at higher pH (neutral compounds are unaffected). At traditionally used pH values (pH 4 - 8), a slight change in pH would result in a significant shift in retention.

Type of chromatography used (e. g. HPLC or GC) and arrangements/detectors (GC/FID, GC/MS, LC/DAD or LC/MS) are certainly useful tools. For HPLC, different modes of chromatography can be used (normal or reversed phase, ion par or HILIC). Other powerful tool is the use of Light Scattering Detector (LSD) coupled to HPLC to monitor compounds without light absorption in uv/Vis region. Gas chromatography may only be used when no additional thermal degradation of the sample is produced (sample inlet works on high temperatures).

The use of HLPC coupled to diode-array detectors (DAD) in the achievement of peak purity usually give reasonable results, mainly related to reliable determination of the main active ingredient. It is possible to guarantee no co-elution with degradation peaks and other impurities. Indeed, the main feature of DAD detectors is that it is possible to collect spectra across a range of wavelengths at each data point collected across a peak, and through software manipulations involving multidimensional vector algebra, to compare each of the spectra to determine peak purity (Swartz & Krull, 2005; Gilliard & Ritter, 1997). In this manner, DAD detectors can distinguish spectral and chromatographic differences not readily observable by simple overlay comparisons (Gorenstein et al 1994; Young et al 1994, Warren et al 1995). DAD detectors can be limited on occasion the more similar the spectra, and the lower the relative absorbance, the more difficult it can be to distinguish co-eluted compounds. MS detection overcomes many of these limitations. MS can provide unequivocal peak purity information, exact mass, structural and quantitative information depending upon the type of instrument used. MS is also a very useful tool to track peaks to selectivity manipulations in method development. As disadvantage, MS detectors cannot handle non-volatile buffers, which are frequently used as mobile phase in drug analysis. The combination of both DAD and MS on a single instrument and software platform provides the type of valuable orthogonal information required when evaluating specificity on SIM development.

After determination of peak purity, in fact, the identification of degradation products and also mass balance determination usually are more complexes steps of analytical development, as in most of cases, commercial reference standards of degradation products are not available.

Calculations using area-percent-normalization (area %) are not precise, since it is necessary to take into consideration the response factors (area relative to amount). Degradation products may have not the same ultra-violet spectra of that of the parent drug and even if the UV spectra are similar, the absorptivity coefficient (Turro 2008) may have different values.

1.2.2.1 Case studies

Case study 1: Consider the analysis of a 100 mg tablet used in medical prescriptions as 3-dose per day and coming from a long term stability study (Figure 1).

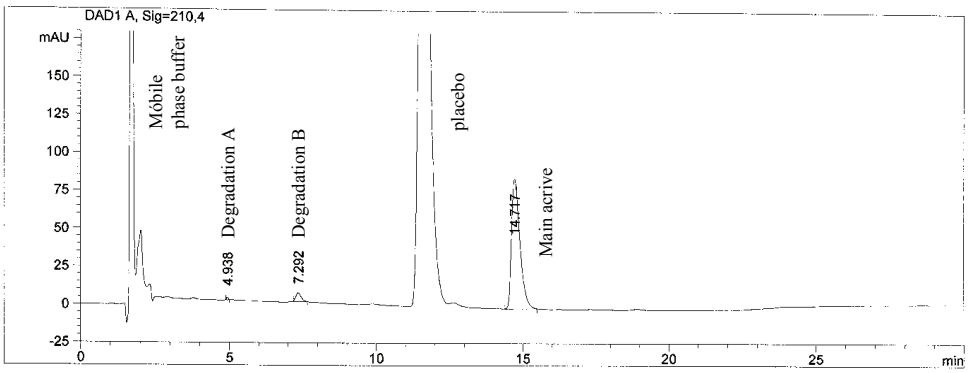
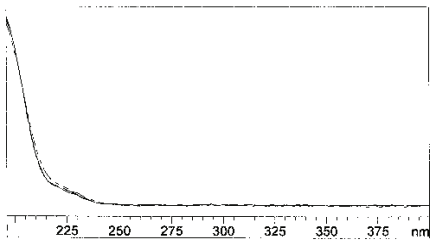
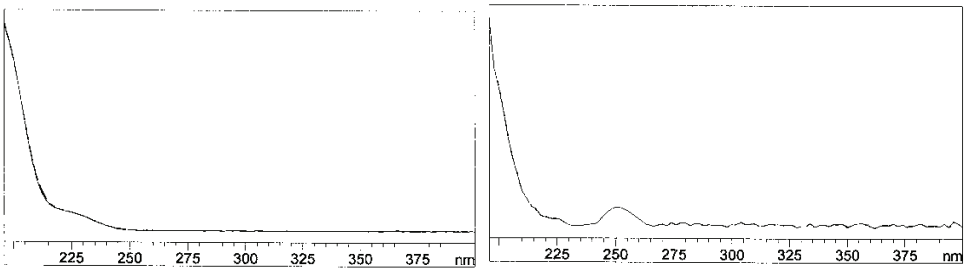


Fig. 1. Representative SIM chromatogram of long-term stability sample

The quantification of degradation product by %area results in 0.2% area for degradation A and 12% area for degradation B, related to the main active. It is confirmed that the degradation products are deriving from the main active, as a SIM was used. Information about UV spectra of both degradation products and main active are shown in Figure 2.



Main active



Degradation A Degradation B

Fig. 2. Representative uv spectra of degradation products A and B

By simple comparison of spectra of main active and degradation A, it can be assumed that mass balance would be probably reached, due to high similarity between it; for degradation B mass balance may give unsatisfactory results, mainly if wavelength of detection and quantification is in the 250-275 nm region of the spectra. Other concern is related to the ICH threshold for the degradation products. In this case, the diary dose is 300 mg and degradation products A (0.2%) and B (12%) fall within the range of identification and qualification, which would means to define toxicity and mutagenicity potential of these two degradation products, and ultimately also redesign the drug product.

Case study 2:

In this second example (representative chromatogram showed on Figure 3), one may consider that when the sample is submitted to light stress the main active degrades to seven different products (see Table 2) and besides these seven common degradation more new two degradation can be detected in acidic stress (Table 3).

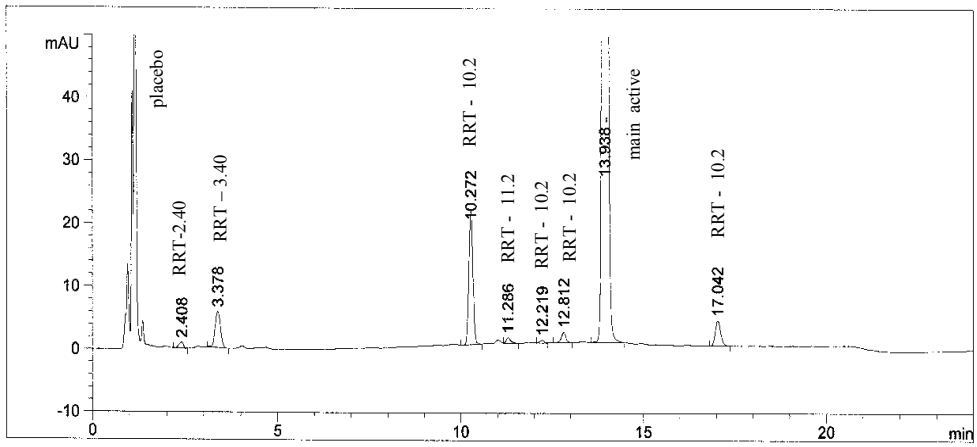


Fig. 3. SIM chromatogram of light stressed sample - 48 hours

Calculation of mass balance by considering % area of degradation product peaks, identified by Relative Retention Time (RRT) is also presented in tables 2 and 3.

% peak area												
RRT / $\lambda_{detector}$	0.17	0.24	0.55	0.69	0.74	0.81	0.88	0.92	1.22	Sub-Total	Main Active*	Total
210 nm	0.2	1.3	nd	nd	3.6	0.2	0.1	0.3	0.9	6.6	74.1%	80.7
245 nm	0.3	2.4	nd	nd	0.5	0.15	<LoQ	<LoQ	1.0	4.75		78.9
360 nm	<LoQ	<LoQ	nd	nd	<LoQ	<LoQ	<LoQ	0.17	1.0	1.17		75.3

*this value represents % of main active on drug product, determined by external calibration with main active analytical standard; nd = non detected

Table 2. Peak % area degradation products after 48- hours of light stress

% peak area												
RRT / $\lambda_{detector}$	0.17	0.24	0.55	0.69	0.74	0.81	0.88	0.92	1.22	Sub-Total	Main Active*	Total
210 nm	0.3	0.2	0.2	0.2	2.3	1.85	<LQ	<LQ	<LQ	5.05	75.4%	80.45
245 nm	<LQ	<LQ	0.2	<LQ	0.3	1.4	<LQ	<LQ	<LQ	1.9		77.3
360 nm	<LQ	<LQ	<LQ	<LQ	<LQ	<LQ	<LQ	<LQ	<LQ	<LQ		<LQ

*this value represents % of main active on drug product, determined by external calibration with main active analytical standard.

Table 3. Peak % area degradation products after 120-hours of acidic stress

In the light stress (Table 2), the concentration of the main active after 48 hours is around 74.1%, and for an acceptable mass balance determination (values in % area or concentration around target concentration value), degradation products must account for 25.9% area. As can be seen at Figure 4, the UV spectra given from the DAD of these nine degradation products, there are significative differences in the profiles, i.e., different absorption intensities in different wavelength and this should be an indicative of difficulties on reaching satisfactory mass balance using % area.

When monitoring at 210 nm, mass balance reached 80.7%, since the sum of total % area of degradation products reached 6.6% area.

When doing the same calculation for 245 nm, mass balance was lower, reaching 78.9% and even lower at 360 nm, giving 75.3%. Degradation products identified at RRT-0.55 and RRT-0.69 were not detected at these three wavelengths, but were detected on acidic stress (Table 3) sample, when monitoring at 210 nm and 245 nm. Any degradation product was detected at 360 nm, in the acidic stress. Usually greater values are obtained in lower wavelengths.

Most frequently giving acceptable mass balance values, but not less complex, is the method in which chromatographic peaks of each degradation product is collected and identified (for example, by infrared spectroscopy, nuclear magnetic resonance as well as mass spectrometry analysis) and then used as analytical standards in a external calibration procedure. The method in which, response factor of each degradation product is achieved (also experimentally hard and complex), can give acceptable mass balance values. The determination of each degradation product is a critical work mainly when ICH thresholds are reached. This may trigger additional investigations about the drug product, so it is recommended to dedicate all analytical tools and expertise available in this step of method development.

1.2.3 Step 3: Method validation

Validation is not a efficient way to do method development so efforts should be dedicated in Specificity step of the method, working with the stressed samples. The validation routine may start with a protocol based on pharmacopeia and/or ICH guidelines (Q2B). For assay procedures, that are intended do measure the analyte present in a given sample, typical validation items should be considered: Accuracy, Precision (repeatability and intermediate precision), Specificity, Detection and Quantitation Limits, Robustness, Linearity and Range.

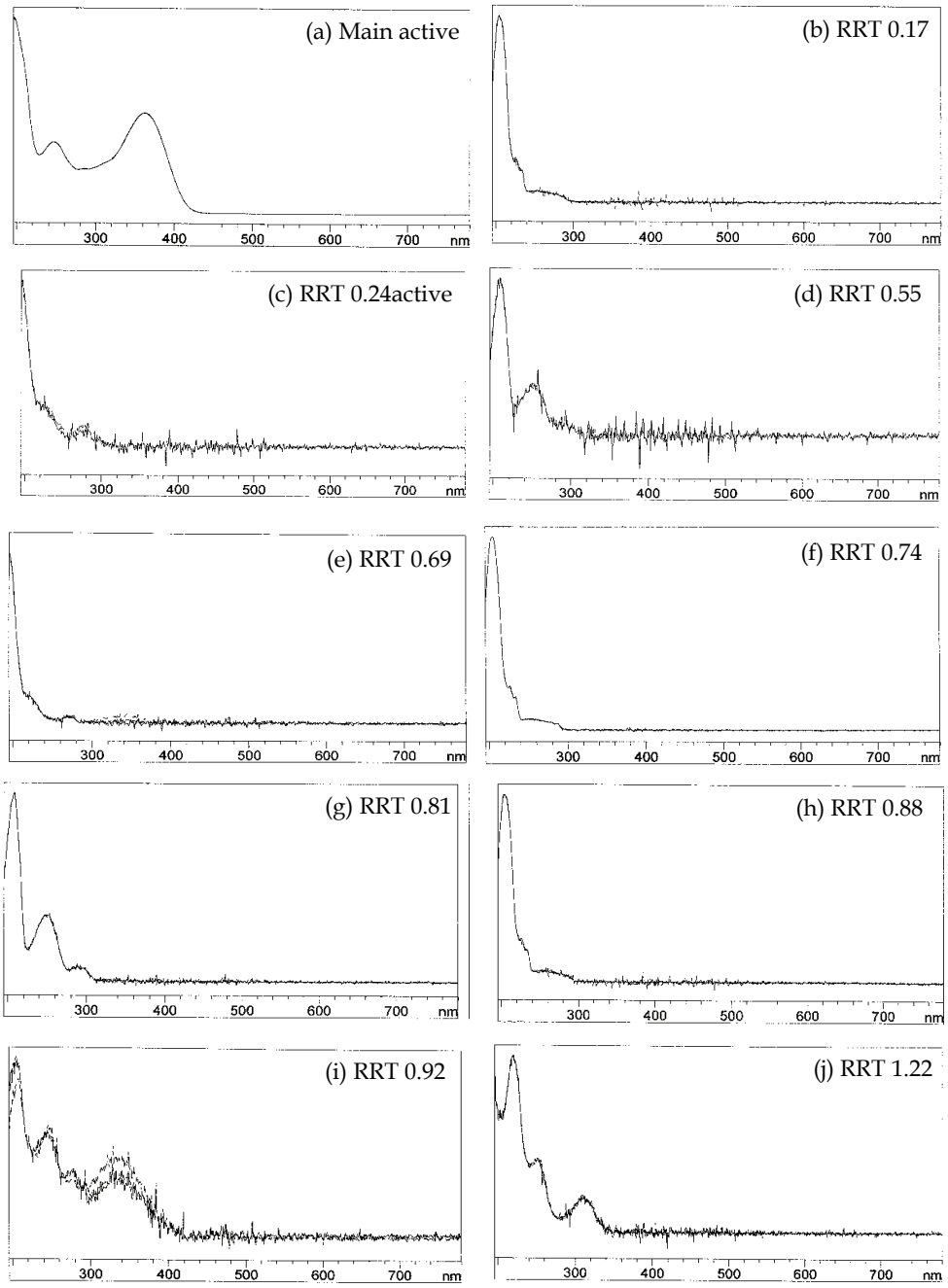


Fig. 4. UV-vis spectra of degradation products observed on light stressed samples (b, c, f to j) and acidic stressed samples (b to g).

2. Conclusion

Stress tests for developing a stability indicating method should always be designed and evaluated with common sense and chemical knowledge, keeping in mind the manufacturing process and the nature of the final drug product. The stability profile needs do be established for drug product to assure safety, efficacy and quality. The results coming from these studies can support formulation and packaging. The know-how coming from stress tests are useful to reduce time and money, related to the drug and final product development, giving the possibility of forecasting analytical problems.

A generic approach can be used as a starting point to set up a stress testing study, but a case-by-case approach for stress testing is essential to allow flexibility. This is also recognized by the regulatory agencies because very detailed instructions about how to perform stress testing are not given in the available guidance documents. In first instance, a SIM should be applied to quantification of the main active in a precise and accurately, even in the presence of interferences (degradation products, impurities, and placebo). In this manner, some evaluation of mass balance can be done, but the applicant must have in mind, the limitation about the obtained values, since %area is a useful but not precise/accurate tool to determine concentrations. If during long-term stability studies or quality control determinations, the main active concentration decreases, mass balance investigations may start, evaluating %peak, DAD spectra and in parallel, different/contributing analytical techniques.

3. References

Alsante K. M., Ando A., Brown R., Ensing J., Hatajik T. D., Wei K.& Tsuda, Y. (2007) The Role of Degradant Profiling in Active Pharmaceutical Ingredients and Drug Products. *Adv. Drug Delivery Rev.*, Vol. 59, No. 1, ISSN: 0169-409X.

Baertschi, S. W (Ed). (2005). Pharmaceutical Stress Testing: Predicting Drug Degradation. ISBN 0824740211.

Center for Drug Evaluation and Research (CDER). (2006). *Guidance for Industry Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*. Accessed on April, 2011. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070287.pdf>

Cheng, Y. –F, Walter, T. H., Lu, Z, Iraneta, P., Gendreau, C., Neue, V. D., Grassi, J. M., Carmody, J. L., O´Gara, J. E. & Fisk, R., P. (2000). Hybrid Organic–Inorganic Particle Technology: Breaking Through Traditional Barriers of HPLC Separations. *LCGC*, Vol. 18, No. 11, 1162 – 1172, ISSN: 1527-5949.

Christensen, K., Christensen, J. O., Frokjaer, S., Langballe, P., Hansen, L. L., Influence of temperature and storage time after light exposure on the quinine monohydrochloride actinometric system. (2000). *Eur. J. Pharm. Sci.*, Vol 9, No. 3, 317-321. ISSN: 0928-0987

European Medicines Agency ICH Topic Q1B. (1998). *Photostability Testing of New Active Substances and Medicinal Products.* Accessed on April, 2011. Available from: <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002647.pdf>

European Medicines Agency. (1996). *Guidance for Industry Q2B Validation of Analytical Procedures: Methodology.* Accessed on April, 2011. Available from: <http://www.fda.gov/downloads/Regulator%20yInformation/Guidances/UCM128049.pdf>

European Medicines Agency. (2003). *ICH Topic Q 1 A (R2) - Stability Testing of new Drug Substances and Product.* Accessed on April, 2011. Available from: <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002651.pdf>

European Medicines Agency. (2006). *ICH Topic Q 3 B (R2) Impurities in New Drug Products.* Accessed on April, 2011. Available from: <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002676.pdf>

Gilliard, J. A., Ritter, C. Use of simulated chromatography-diode array detection data for the definition of a guide curve in purity assessment by spectral comparison. (1997). *J. Chrom. A*. Vol. 786, No. 1, 1-11. ISSN0021-9673.

Gorenstein, M. V., Li, J. B., Van Antwerp, J & Chapman, D. (1994). Detecting coeluted impurities by spectral comparison. *LCGC*, Vol.12, No. 10, 768-772, ISSN 0888-9090.

Kats, M. (2005). *Pharm International Forced Degradation Studies: Regulatory Considerations and Implementation.* Accessed on April, 2011. Available from: <http://biopharminternational.findpharma.com/biopharm/article/articleDetail.jsp?id=170505>

Klick S., Muijselaar P. G., Waterval. J., Eichinger T., Korn C., Gerding T. K. ; Debets A. J. ; Sanger-Van de Griend C., Van den Beld, C. ; Somsen G. W. ; De Jong G. J. (2005). Toward a Generic Approach for Stress Testing of Drug Substances and Drug Products. *Pharm. Technol.,* Vol. 29, No. 2, 48-57, ISSN: 1543-2521.

Neue, D, Walter, T. H., Alder, B. A., Jiang, Z., Fish, R. P., Cook, J. T., Glose, K. H., Carmody, J. L., Grassi, J. M., Cheng, Y. –F, Lu, Z & Crowley, R., J., (1999), Use of high performance LC packings from pH1 to pH 12. *Am. Lab*, 31-36. ISSN: 0044-7749.

Ngwa, G. (2010). Forced Degradation Studies. *Drug Delivery Technol.*, vol. 10 No. 3, June, ISSN 0976-1225.

Reynolds, D. W. (2004). Forced Degradation of Pharmaceuticals. *Am. Pharm. Rev,* May/June, 56-61, ISSN : 1099-8012.

Reynolds, D. W.; Facchine, K. L., Mullaney, F. F., Alsante, K. M., Hatajik, T., D. & Motto, M. (2002). Available Guidance and Best Practices for Conducting Forced Degradation Studies. *Pharm. Technol.*, Vol. 26, No. 2, 48-54, ISSN : 0147-8087.

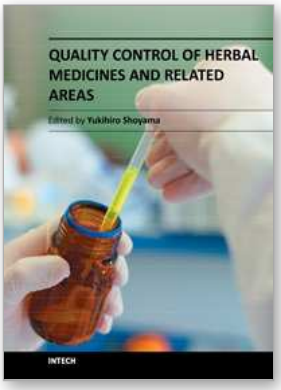
Swartz, M., Krull, I., (2004). Investigating Out-Of-Specifications Results. *LCGC*, Vol. 22, No 2, 132-136, ISSN : 1527-5949.

Swartz, M., Krull, I., (2005). Developing and Validating Stability-Indicating Methods. *LCGC*, Vol. 23, No. 6, 586-593, ISSN : 1527-5949.

Turro, N. J., Ramamurthy, V., Scaiano, J. C. *Principles of Molecular Photochemistry: An Introduction*. University Science Book, 2008. ISBN 978-0849384066.

Warren, W., J., Stanick, M. V., Gorenstein, M. V. & Young, P. M.. (1995). HPLC analysis of synthetic oligonucleotides using spectral contrast techniques. *Biotechniques*, Vol 18, No. 2, 282-297, ISSN: 0736-6205.

Young, P. M., Gorenstein, M. V., (1994) Tryptic mapping by reversed-phase HPLC with photodiode-array detection incorporating the spectral-contrast technique. *LCGC*, Vol 12, No. 11, 832-838. ISSN: 0888-9090.



Quality Control of Herbal Medicines and Related Areas

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The authors of this thematic issue provide a comprehensive summary of most recent knowledge and references on quality control in wide fields. Quality control is essential for natural products like natural medicine and related food products. In this issue fifteen chapters have been included, discussing in detail various aspects of quality control. It will certainly prove useful not only for phytochemical researchers, but also many scientists working in numerous fields. Much effort has been invested by the contributors to share current information. Without their efforts and input 'Quality Control of Herbal Medicine and Related Areas' could not exist.

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