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New Approachs in Drug Quality Control: Matrices and Chemometrics

Sigrid Mennickent, M. de Diego, B. Schulz, M. Vega
and C. G. Godoy

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1. Quality control

Quality control refers to the process of quality evaluation that focuses on the internal measurement of the quality of a process, institution, product, service, or other. Often used interchangeably with *quality management* and *quality assurance* [1-3].

2. Drug quality control

Quality Assurance plays a very important role in making sure that the GMP standards are met and products comply with the international quality standards. The main functions carried out by drug quality control are:

- Approval of raw materials
- Monitoring of manufacturing processes
- Approval of finished products
- Documentation of technical information
- Implementation of cGMP

Manufacturing processes are monitored and controlled by testing of raw materials, in-process parameters. Final active pharmaceutical ingredients and dosage forms are tested for specified parameters before release. Analytical testing is carried out with highly sophisticated instruments: viz. HPLC, GC, IR, UV spectrophotometer mettler titrators, particle size analyzer etc.

All the analytical test procedures and manufacturing procedures are well documented and revision is undertaken as per specified protocol. Analytical methods are validated to give the reproducible results. Stability study as per stability protocol is considered to be very important area of Quality Assurance.

Automated systems are becoming increasingly important tools for appropriate monitoring and controlling of the pharmaceutical packaging process. Solutions for comprehensive quality assurance or production data acquisition and evaluation are just as important as applications that meet the legislative requirements of different countries in terms of serial numbering and the unique marking of products.

Quality control involves many phases, such as sample collection, measuring, analysis of results, and the approval/rejection of the batch. Nonetheless, the most important thing is the continuity and systematization of the quality control.

Effective process validation contributes significantly to assuring drug quality. The basic principle of quality assurance is that a drug should be produced that is fit for its intended use. This principle incorporates the understanding that the following conditions exist: Quality, safety, and efficacy are designed or built into the product.

Quality cannot be adequately assured merely by in-process and finished-product inspection or testing.

Process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and process. Usually, process validation includes three stages:

- **Process Design:** The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.
- **Process Qualification:** During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
- **Process Verification:** Ongoing assurance is gained during routine production that the process remains in a state of control [1-3].

3. New approaches in drug quality control

3.1. Matrices

3.1.1. Residue analysis of pharmaceuticals in the aquatic environment

Residue analysis of pharmaceuticals in the aquatic environment has attracted considerable interest during the last few years.

Traces of such compounds have been detected in surface water samples from all countries where pharmaceuticals are widely in use.

Pharmaceutically active compounds have captured the attention of the scientific community because such pollutants result not primarily from manufacturing but from widespread, continual use in human and veterinary clinical practice. The biological activity of these compounds can lead to adverse effects in aquatic ecosystems and potentially have an impact on drinking-water supplies [4].

In the human body, pharmaceuticals can be transformed to one or more metabolites and excreted as a mixture of parent compound and metabolites, in which the parent compound is often the minor component. However, some drugs are poorly metabolized and are excreted unchanged. The degree of metabolism depends on a number of parameters, including age, gender and ethnicity, the constitution of the patient and the time of administration. Drug-drug interactions caused by enzyme induction or inhibition, as well as enhanced metabolism due to previous exposure, can also influence the pharmacokinetics of drugs [5].

Both the parent compound and the metabolites enter the aquatic environment once they are excreted from the human body. Monitoring studies in the environment have demonstrated the discharge of pharmaceuticals and their metabolites through municipal wastewater-treatment plants (WWTPs). Although unchanged drugs can undergo biochemical transformations during sewage treatment, some studies indicate that the absence of pharmaceutical compounds in treated water does not necessarily imply their complete removal. In most instances, human drugs are metabolized in the body to more polar compounds that are more likely to pass through the WWTP. In some cases, pharmaceuticals and their human metabolites can be microbially degraded in the activated sludge treatment.

Knowledge of the formation of stable metabolites in WWTPs is also important in order to understand the environmental fate of the parent compound. Once in the environment, these compounds can be transported and distributed in rivers, streams, and possibly further biodegraded. For most pharmaceuticals and their biotransformation products, these pathways in the aquatic environment are largely unknown, and investigations into their occurrence in environmental compartments are still rare.

Studies have been carried out to investigate their fate not only in surface waters, but also in sediment and soil environments. By nature, most pharmaceuticals are designed to be at least moderately water-soluble and to possess half-lives in the human body in the range of hours. Because human and microbial degradates will generally coexist with their parent compounds in the environment, indicators that summarize all the information on parent substances and degradates would be important instruments for decision-making and assessment [6].

Progress in instrumental analytical chemistry has resulted in the availability of methods that allow a monitoring of these pollutants at ng levels.

Improvements in detection limits over the past years have mainly been due to sophisticated mass spectrometric detection techniques. Furthermore, robust sample preparation and pre-concentration protocols have contributed significantly to the achievements observed so far.

Nowadays it is a well-established fact that pharmaceutical drugs used during medical treatment may partly be excreted in an un-metabolized form, enter municipal sewage systems, and can even survive the passage through the sewage treatment plant. Therefore, sewage treatment plant effluents are the major source for introduction of pharmaceuticals into the aquatic environment. Furthermore, pharmaceuticals employed in veterinary medicine may be introduced into soil (and eventually into water) via manure, or may find a direct way into the aquatic system when used in fish farms.

Unfortunately, the consequences of continuous presence of low concentrations of pharmaceuticals for the ecosystem are still not fully known.

In many cases, the analytical procedures for residue analysis of pharmaceutical drugs nowadays available includes a pre-concentration and clean-up step by solid-phase extraction or related techniques, followed by chromatography in combination with mass spectrometry (MS) as detector.

Although GC–MS may still be the perfect technique for certain classes of pharmaceuticals, high-performance liquid chromatography (HPLC) hyphenated with atmospheric pressure ionization-MS has established itself as the better choice for simultaneous determination of pharmaceuticals of widely differing structures.

The concentration levels of pharmaceuticals found in environmental water samples are generally too low to allow a direct injection into a chromatographic system. Therefore, efficient pre-concentration steps are necessary which should also result in some sample clean-up. One of the most widely used sample treatment technique for residue analysis of pharmaceuticals in water is the extraction of the analytes by means of a solid sorbent.

This extraction procedure can be based on multiple equilibria between the liquid phase and the sorbent filled into a small cartridge (solid-phase extraction, SPE), or on a single equilibrium (sorption extraction) [7-23].

3.1.1.1. Solid-phase extraction

Pharmaceuticals of adequate hydrophobicity can easily be pre-concentrated using any reversed-phase material such as alkyl-modified silica or polymer-based materials. Deprotonation of acidic compounds and protonation of basic compounds should be suppressed to ensure sufficient hydrophobicity of the analytes. Therefore, acidic pharmaceuticals should be pre-concentrated under acidic conditions, whereas basic analytes should be pre-concentrated at an alkaline pH. Alternatively, mixed-mode SPE materials can be used which exhibit both reversed-phase and cation-exchange properties due to the presence of sulfonic acid groups on the hydrophobic surface of the particles. Using acidified sample solutions, acidic and neutral analytes would be extracted by hydrophobic interactions, whereas protonated basic analytes would interact via ion exchange mechanisms.

A recent review has summarized new SPE materials that can improve the recoveries for polar analytes. These materials are mainly polymeric sorbents that improve the retention of polar compounds either by novel functional groups in the polymeric structure (resulting in a

hydrophilic–hydrophobic balance material) or by considerably increased surface area. Some of these new materials have turned out to be well suited for multi-class analysis of pharmaceuticals in water samples. Nowadays, one of the most widely used sorbent is a copolymer of divinylbenzene and vinylpyrrolidone [7-23].

3.1.1.2. Sorptive extraction

Sorptive extraction based on a single partitioning equilibrium of analytes between the aqueous sample and a solid sorbent includes solid-phase microextraction (SPME), stir-bar sorptive extraction (SBSE), and several related variants. Originally, these techniques were based on polydimethylsiloxane (PDMS) as material for trapping trace analytes from a water sample due to partitioning between the aqueous matrix and the PDMS phase. Besides PDMS, some alternative sorptive materials have become commercially available recently, such as polyacrylates, copolymers of PDMS with divinylbenzene, copolymers of polyethylene glycol with divinylbenzene, and mixtures of carboxen (an inorganic adsorbent) with PDMS or divinylbenzene [7-23].

3.1.1.3. Sample pre-concentration procedures for sediment and sludge samples

Extraction of pharmaceuticals from sediment and sludge is generally done by blending the sample with an organic solvent or with mixtures of aqueous buffers and organic solvents.

Ultrasonication is frequently applied to assist the extraction process.

Additional clean-up steps for the extract may be necessary employing SPE or liquid–liquid extraction. Somewhat more advanced procedures are based on pressurized liquid extraction (accelerated solvent extraction) which may need less time and less solvent consumption [7-23].

3.1.1.4. Derivatization of the compounds

Various groups of pharmaceuticals can be derivatized to make them suited for GC analysis. Typical derivatization reagents for acidic pharmaceuticals include pentafluorobenzylbromide, methyl chloromethanoate, methanol/BF₃, or tetrabutylammonium salts (for derivatization during injection). Phenazone-type drugs have been derivatized by silylation using *N*-*tert*-butyldimethylsilyl-*N*-methyltrifluoroacetamide (MTBSTFA). Silylation procedures are also commonly used for synthetic estrogens [7-23].

3.2.1. Some latest researches in this area

3.2.1.1. Pharmaceuticals in the aquatic environment: a critical review of the evidence for health effects in fish

The authors review the current data on the presence and reported biological effects in fish of some of the most commonly detected pharmaceuticals in the aquatic environment; namely nonsteroidal anti-inflammatory drugs (NSAIDs), fibrates, beta-blockers, selective serotonin

reuptake inhibitors (SSRIs), azoles, and antibiotics. Reported biological effects in fish in the laboratory have often been shown to be in accordance with known effects of pharmaceuticals in mammals. Water concentrations at which such effects have been reported, however, are generally, between $\mu\text{g L}^{-1}$ and mg L^{-1} , typically at least 1 order of magnitude higher than concentrations normally found in surface waters (ng L^{-1}). There are exceptions to this, however, as for the case of synthetic oestrogens, which can induce biological effects in the low ng L^{-1} range. Although generally effect levels for pharmaceuticals are higher than those found in the environment, the risks to wild fish populations have not been thoroughly characterised, and there has been a lack of consideration given to the likely chronic nature of the exposures, or the potential for mixture effects. As global consumption of pharmaceuticals rises, an inevitable consequence is an increased level of contamination of surface and ground waters with these biologically active drugs, and thus in turn a greater potential for adverse effects in aquatic wildlife [24].

3.1.1.2. Human Pharmaceuticals, Hormones and Fragrances: The Challenge of Micropollutants in Urban Water Management

The observed concentrations of pharmaceuticals and personal care products (PPCPs) in raw wastewater confirm that municipal wastewater represents the main disposal pathway for the PPCPs consumed in households, hospitals and industry. In sewage treatment plant effluents most PPCPs are still present, since many of these polar and persistent compounds are being removed only partially or, in some cases, not at all. Treated wastewater therefore represents an important point source for PPCPs into the environment. After passing a sewage treatment plant the treated wastewater is mostly discharged into rivers and streams or sometimes used to irrigate fields. If drinking water is produced using resources containing a substantial proportion of treated wastewater (e.g. from river water downstream of communities) the water cycle is closed and indirect potable reuse occurs. Human Pharmaceuticals, Hormones and Fragrances provides an overview of the occurrence, analytics, removal and environmental risk of pharmaceuticals and personal care products in wastewater, surface water and drinking water. [25].

3.2.1.2. Factors affecting the concentrations of pharmaceuticals released to the aquatic environment

Although recent research has demonstrated that pharmaceuticals are widely distributed in the aquatic environment, it is difficult to assess the threat that they

pose to drinking water supplies or their rate of attenuation in natural systems without an adequate understanding of the sources of contamination. To identify pharmaceutical compounds of significance to water supplies in the United States, the authors have reviewed available data on the use of prescription drugs. Results of our analysis indicate that approximately 40 compounds could be present in municipal wastewater effluent at concentrations above $1,000 \text{ ng/L}$ and at least 120 compounds could be present at concentrations above 1 ng/L . Important classes of prescription drugs include analgesics, beta-blockers, and antibiotics. Analysis of a group of the most commonly used pharmaceuticals in the United States indicates that they are ubiquitous in wastewater effluents. Authors have detected concentra-

tions ranging from approximately 10- 3,000 ng/L for high use pharmaceuticals such as beta-blockers (e.g., metoprolol, propranolol) and acidic drugs (e.g., gemfibrozil, ibuprofen). The concentration of pharmaceuticals in effluent from conventional wastewater treatment plants is similar. Advanced wastewater treatment plants equipped with reverse osmosis systems reduce concentrations of pharmaceuticals below detection limits. In addition to removal during biological wastewater treatment, pharmaceuticals also are attenuated in engineered natural systems (i.e., treatment wetlands, ground water infiltration basins). Preliminary evidence suggests limited removal of pharmaceuticals in engineered treatment wetlands and nearly complete removal of pharmaceuticals during ground water infiltration [26].

3.2.1.3. *A preliminary ecotoxicity study of pharmaceuticals in the marine environment*

Environmental fates and effects of pharmaceuticals in the aquatic environment have been the focus of recent research in environmental ecotoxicology. Worldwide studies of common over-the-counter pharmaceuticals have reported detectable levels in the aquatic environment, but there are few studies examining impacts on marine habitats. These drugs can affect the functions of various vertebrates and invertebrates. The stability of two pharmaceuticals, cyclizine (CYC) and prochlorperazine (PCZ), in seawater was examined under light and dark conditions, as well as the toxicity of these compounds to larvae of the barnacle *Balanus amphitrite*, which is a cosmopolitan marine organism found in most of the world's oceans. CYC was very stable under all the tested conditions. On the other hand, PCZ degraded in light but not in the dark, and was more stable in seawater than fresh water. For the barnacle larvae, the LC50 of prochlorperazine was 0.93 microg/mL and the LC50 for CYC was approximately 0.04 microg/mL [27].

3.2.1.4. *Estrogenic activity of pharmaceuticals in the aquatic environment*

In the last years pharmaceuticals have aroused great interest as environmental pollutants for their toxic effects towards non target organisms. This study wants to draw attention to a further adverse effect of drugs, the endocrine interference. The most representative drugs of the widespread classes in environment were investigated. The YES-test and the E-screen assay were performed to detect the capability of these substances to bind the human estrogenic receptor alpha (hER alpha) in comparison with 17beta-estradiol. Out of 14 tested pharmaceuticals, 9 were positive to YES-assay and 11 were positive to E-screen assay; in particular, Furosemide and the fibrates (Bezafibrate, Fenofibrate and Gemfibrozil) gave the maximal estrogenic response. Tamoxifen showed its dual activity as agonist and antagonist of hER alpha [28].

3.2.1.5. *Colloids as a sink for certain pharmaceuticals in the aquatic environment*

The occurrence and fate of pharmaceuticals in the aquatic environment is recognized as one of the emerging issues in environmental chemistry and as a matter of public concern. Existing data tend to focus on the concentrations of pharmaceuticals in the aqueous phase, with limited studies on their concentrations in particulate phase such as sediments. Furthermore, current water quality monitoring does not differentiate between soluble and colloidal phas-

es in water samples, hindering our understanding of the bioavailability and bioaccumulation of pharmaceuticals in aquatic organisms. In this study, an investigation was conducted into the concentrations and phase association (soluble, colloidal, suspended particulate matter or SPM) of selected pharmaceuticals (propranolol, sulfamethoxazole, mebeverine, thioridazine, carbamazepine, tamoxifen, indomethacine, diclofenac, and meclofenamic acid) in river water, effluents from sewage treatment works (STW), and groundwater in the UK. Colloids were isolated by cross-flow ultrafiltration (CFUF). Water samples were extracted by solid-phase extraction (SPE), while SPM was extracted by microwave. All sample extracts were analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) in the multiple reaction monitoring.

Five compounds propranolol, sulfamethoxazole, carbamazepine, indomethacine, and diclofenac were detected in all samples, with carbamazepine showing the highest concentrations in all phases. The highest concentrations of these compounds were detected in STW effluents, confirming STW as a key source of these compounds in the aquatic environments. The calculation of partition coefficients of pharmaceuticals between SPM and filtrate, between SPM and soluble phase, and between colloids and soluble phase showed that intrinsic partition coefficients are between 25% and 96%, and between 18% and 82% higher than relevant observed partition coefficients values, and are much less variable. Secondly, K_{coc} values are 3–4 orders of magnitude greater than K_{ocint} values, indicating that aquatic colloids are substantially more powerful sorbents for accumulating pharmaceuticals than sediments. Furthermore, mass balance calculations of pharmaceutical concentrations demonstrate that between 23% and 70% of propranolol, 17–62% of sulfamethoxazole, 7–58% of carbamazepine, 19–84% of indomethacine, and 9–74% of diclofenac are present in the colloidal phase.

The results provide direct evidence that sorption to colloids provides an important sink for the pharmaceuticals in the aquatic environment. Such strong pharmaceutical/colloid interactions may provide a long-term storage of pharmaceuticals, hence, increasing their persistence while reducing their bioavailability in the environment.

Recommendations and perspectives from this study:

Pharmaceutical compounds have been detected not only in the aqueous phase but also in suspended particles; it is important, therefore, to have a holistic approach in future environmental fate investigation of pharmaceuticals. For example, more research is needed to assess the storage and long-term record of pharmaceutical residues in aquatic sediments by which benthic organisms will be most affected. Aquatic colloids have been shown to account for the accumulation of major fractions of total pharmaceutical concentrations in the aquatic environment, demonstrating unequivocally the importance of aquatic colloids as a sink for such residues in the aquatic systems. As aquatic colloids are abundant, ubiquitous, and highly powerful sorbents, they are expected to influence the bioavailability and bioaccumulation of such chemicals by aquatic organisms. It is therefore critical for colloids to be incorporated into water quality models for prediction and risk assessment purposes [29].

4. Chemometrics

Chemometrics is the science of extracting information from chemical systems by data-driven means. It is a highly interfacial discipline, using methods frequently employed in core data-analytic disciplines such as multivariate statistics, applied mathematics, and computer science, in order to address problems in chemistry, biochemistry, medicine, biology and chemical engineering.

Chemometrics is applied to solve both descriptive and predictive problems in experimental life sciences, especially in chemistry. In descriptive applications, properties of chemical systems are modeled with the intent of learning the underlying relationships and structure of the system (i.e., model understanding and identification). In predictive applications, properties of chemical systems are modeled with the intent of predicting new properties or behavior of interest. In both cases, the datasets can be small but are often very large and highly complex, involving hundreds to thousands of variables, and hundreds to thousands of cases or observations.

Chemometric techniques are particularly heavily used in analytical chemistry and metabolomics, and the development of improved chemometric methods of analysis also continues to advance the state of the art in analytical instrumentation and methodology. It is an application driven discipline, and thus while the standard chemometric methodologies are very widely used industrially, academic groups are dedicated to the continued development of chemometric theory, method and application development [30-33].

Author details

Sigrid Mennickent^{1*}, M. de Diego¹, B. Schulz¹, M. Vega² and C. G. Godoy¹

*Address all correspondence to: smennick@udec.cl

1 Department of Pharmacy, Faculty of Pharmacy, University of Concepción, Concepción,, Chile

2 Department of Bromatology, Nutrition and Dietetic, Faculty of Pharmacy, University of Concepción, Concepción,, Chile

References

- [1] USP (1999). The United States Pharmacopeia/ The National Formulary (USP 24/NF 19), United States Pharmacopeial Convection, Inc., Rockville
- [2] ICH. (2003). *The Sixth ICH International Conference on Armonization of Technical Requirements for Registration of Pharmaceuticals for Human Use*, Osaka,.

- [3] Buchberger, W. W. (2007). *Analytica Chimica Acta*, 593, 129-139.
- [4] Jones, O., Lester, J. N., & Voulvoulis, N. (2005). *Trends in Biotechnonology*, 23(4), 163-167.
- [5] Lemmer, B. (1996). *Chronopharmacology- Cellular and Biochemical Interactions*. Birkhäuser,, New York, USA.
- [6] Boxall, A., Fenner, K., Kolpin, D. W., & Maund, S. (2004). *Environ. Sci. Technol.*, 38, 369A.
- [7] Moldovan, Z. (2006). *Chemosphere*, 64, 1808.
- [8] Cunningham, V. L., Buzby, M., Hutchinson, T., Mastrocco, F., Parke, N., & Roden, N. (2006). *Env. Sci. Technol*, 40, 3457.
- [9] Fent, K., Weston, A. A., & Caminada, D. (2006). *Aquatic Toxicol*, 76, 122.
- [10] Crane, M., Watts, C., & Boucard, T. (2006). *Sci. Tot. Environ*, 367, 23.
- [11] Hernando, M. D., Mezcuca, M., Fernandez-Alba, A. R., & Barcelo, D. (2006). *Talanta*, 69, 334.
- [12] Benito-Peña, E., Partal-Rodera, A. I., Leon-Gonzalez, M. E., & Moreno-Bondi, M. C. (2006). *Anal. Chim. Acta*, 556, 415.
- [13] Fontanals, N., Marce, R. M., & Borrull, F. (2005). *Trends Anal. Chem .*, 24, 394.
- [14] Gomez, M. J., Petrovic, M., Fernandez-Alba, A. R., & Barcelo, D. (2006). *J. Chromatogr. A*, 1114, 224.
- [15] Gros, M., Petrovic, M., & Barcelo, D. (2006). *Talanta*, 70, 678.
- [16] Petrovic, M., Gros, M., & Barcelo, D. (2006). *J. Chromatogr. A*, 1124, 68.
- [17] Trenholm, R. A., Vanderford, B. J., Holady, J. C., Rexing, D. J., & Snyder, S. A. (2006). *Chemosphere*, 65, 1990.
- [18] Roberts, P. H., & Bersuder, P. (2006). *J. Chromatogr. A*, 1134, 143.
- [19] Himmelsbach, M., Buchberger, W., & Klampfl, C. (2006). *Electrophoresis*, 27, 1220.
- [20] Seitz, W., Weber, W. H., Jiang, J. Q., Lloyd, B. J., Maier, M., Maier, D., & Schulz, W. (2006). *Chemosphere*, 64, 1318.
- [21] Pozo, O. J., Guerrero, C., Sancho, J. V., Ibañez, M., Pitarch, E., Hogendoorn, E., & Hernandez, F. (2006). *J. Chromatogr. A*, 1103, 83.
- [22] Rodriguez-Mozaz, S., Lopez de Alda, D., & Barcelo, D. (2007). *J. Chromatogr. A*, 1152, 97.
- [23] Quintana, J. B., Miro, M., Estela, J. M., & Cerda, V. (2006). *Anal. Chem.*, 78, 2832.
- [24] Corcoran, J., Winter, M. J., & Tyler, C. R. (2010). *Crit, Rev. Toxicol*, 40(4), 287-304.

- [25] Ternes, T. (2006). *Human Pharmaceuticals, Hormones and Fragrances: The Challenge of Micropollutants in Urban Water Management*. Iwa Publishing.
- [26] Sedlak, D., & Pinkston, K. (2011). *Factors affecting the concentrations of pharmaceuticals released to the aquatic environment*, University of California.
- [27] Choong, A. M., Teo, S. L., Leow, J. L., & Ho, P. C. (2006). *J. Toxicol. Environ. Health A*, 69(21), 1959-1970.
- [28] Isidori, M., Bellota, M., Cangiano, M., & Parrella, A. (2009). *Environ. Int*, 35(5), 826-829.
- [29] Maskaoui, K., & Zhou, J. (2010). *Environmental Science and Pollution Research*, 17(4), 898-907.
- [30] Verenitch, S. S., Lowe, C. J., & Mazumder, A. (2006). *J. Chromatogr. A*, 1116.
- [31] Gemperline, P. J. (2006). *Practical guide to chemometrics*. 2nd Edition, CRC Press 10.1201/9781420018301
- [32] Mark, H., & Workman, J. (2007). *Chemometrics in spectroscopy*. Academic Press-Elsevier.
- [33] Maeder, M., & Neuhold, Y. M. (2007). *Practical Data Analysis in Chemistry*. Elsevier.

