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# Feasibility study concerning the use of expert systems for the development of procedures in pharmaceutical analysis

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**Abstract**: The feasibility of using expert systems for the development of analytical procedures is investigated. A system for the computer generation of procedures to determine active drug substances in commercial formulations is proposed. It is shown that in nearly 85% of the cases investigated the present system immediately yields a correct procedure or conclusion. It is concluded that selecting methods and developing procedures with the use of expert systems is difficult but feasible.

**Keywords**: *Expert system; drug analysis; ultraviolet spectrophotometry.*

## Introduction

One of the principle tasks of an analytical chemist is to develop analytical procedures. Particularly in laboratories, confronted with many different analytical problems, an enormous amount of time and energy can be spent on this task. Chemometrics offers many techniques that can be of help in this respect. Indeed, the aims of chemometrics are defined as follows [1]:

"Chemometrics is the chemical discipline that uses mathematical and statistical methods:
(a) to design or select optimal measurement procedures and experiments; and
(b) to provide maximum chemical information by analyzing chemical data."

Until now, item (a) has focused more on the optimization of existing methods (experimental optimization, Simplex) than on the design of new procedures, because no methods were available to permit 'automatic design'. It is the authors' intention to show in this article that a method from artificial intelligence, namely the expert system approach, does allow this. If expert systems must be considered as part of chemometrics, the definition should probably be corrected to read "mathematical, statistical and other methods employing formal logic".

In recent years, analytical chemists have been showing a growing interest in the

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application of expert systems [2–5], pattern recognition [6–9] and other techniques of artificial intelligence. These applications nearly always have to do with data interpretation (item b in the chemometrics definition). However, intelligence is applied by the analytical chemist not only in data interpretation, but also in method selection and development of suitable procedures. It is the authors' intention to investigate the possibilities of expert systems in the latter area.

The laboratory of the authors is engaged in official analysis of drugs, which means that the conformity of the drug content specifications as given by the manufacturers on the label must be validated. To speed up method development, particularly in the field of HPLC, a strategic approach was elaborated. For instance, a standardized analysis strategy for basic drugs was developed, using ion-pair extraction with one of two possible extracting agents and HPLC on a nitrile column with one of two possible mobile phases [10]. It was shown that this is a good starting point for HPLC of any basic drug. However, the routing of samples towards a particular technique (UV spectrophotometry, fluorimetry, HPLC, GLC, . . .) or subtechnique (e.g. for HPLC, reversed- or normal-phase, UV- or electrochemical-detection, etc.) and the selection of the initial steps (the initial solvent, for instance) still remain largely a matter of specialist experience or reasoning. It is the authors' intention to develop an expert system that would take over this function and provide the analyst with procedures. This article reports on a study carried out to investigate the feasibility of such an approach.

## Expert Systems and Their Application in Pharmaceutical Analysis

*Description of purpose of t e expert system*

*Expert systems and their advantages.* Expert systems are software products that allow a computer to simulate the train of thought of an expert, in this case the scientist or technician who selects the methodology to be applied, and writes down the procedure.

Expert systems applied for this kind of purpose should offer the following advantages:

(a) The automation of routine decision processes, freeing scientific personnel for more demanding tasks;

(b) The minimization of time consuming errors or oversights;

(c) The formalization of knowledge: the need to develop rules for the expert system, obliges even experts to systematize their knowledge. It may reveal gaps for which there are no good rules or solutions, and it also shows that there is an enormous amount of redundant information available (see below under: logical structure of the problem);

(d) Since laboratory robots are becoming available [11–13] one can imagine that it will be possible to connect the expert system to a robot, thus developing a system that will automate the analysis of similar but non-identical samples.

*Logical structure of the problem.* The logical structure can be described as a decision tree or graph. In each node, there are a number of possible connections with the next node. A very simple, hypothetical example of such a decision tree is given in Fig. 1. This points immediately to a major difficulty. While at the first two levels the number of nodes is not too large, at the lowest end the number of possible directions is very high. The number of easily available stationary phases in GLC exceeds 200 and the number of combinations of mobile phase mixtures in HPLC or TLC is, strictly speaking, infinite. The same kind of reasoning can be held in many other fields (for instance, reactions in colorimetry).

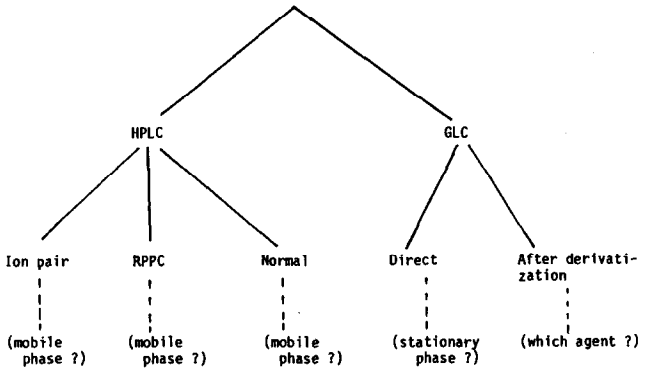



**Figure 1**
Example of a tree structure of an analytical decision problem. The broken lines indicate that at that node many different decisions can be taken.

Long before one began to think about expert systems, the problem of too many alternatives was a topic for research and discussion in several fields of analytical chemistry. It is, for instance, well known that a much smaller number of stationary phases in GLC is sufficient to carry out virtually all possible separations needed and formal methods have been developed to select these few phases [14–15]. In HPLC, recent work in the authors' laboratory [16] has shown that a very large number of all possible separations of non-macromolecular compounds can be carried out with one single stationary phase (the nitrile column) for both reversed-phase and normal-phase, with only six different solvents. The elimination of redundant possibilities is an absolute necessity if one wants to keep expert systems within feasible dimensions.

Lennat [17], one of the leading specialists in artificial intelligence, states: "Most problems can be cast in the same form: as the search for a path from some initial state to a desired final state. Most interesting problems also share the characteristic that they are too complex to be solved by random search, because the number of choices increases exponentially as one proceeds from the first intersection, or decision point . . . Therein . . . lies the essence of intelligence: finding ways to solve otherwise intractable problems by limiting the search for solutions".

At each node, the expert system must decide in which direction it will move. To do this it needs rules. In many cases these rules are based on the contents of lists. For instance, to decide whether a substance is basic or acidic, the system looks at the presence of certain functional groups and these groups are gathered in lists of basic and acidic functions. It must also be possible to add or delete new information and new rules. Thus the expert system must consist essentially of a set of rules that manipulates a knowledge base consisting of lists, with the additional characteristic that rules and lists must be readily updatable.

*The analytical problem.* One of the important areas of pharmaceutical analysis is verification of the label claim of manufactured drug formulations. The main object is the assay of the active drug component(s). Since it would be too ambitious for a feasibility study to attempt a general expert system for all active components in all kinds of drug formulations, the present study was restricted to:

(i) analysis by UV spectrophotometry, which in this domain, is the method of choice;

(ii) tablets and other solid forms for oral ingestion (i.e. about 50% of all drugs used in Belgium);

(iii) drug formulations with a single active component. Because there is a trend to abandon multicomponent formulations, this amounts to the majority of all drug formulations.

(iv) synthetic or semi-synthetic drugs belonging to a large variety of chemical and pharmacological classes. The main families excluded for the time being are the antibiotics and the steroids.

*Development of rules*

People who construct expert systems know that one of the main difficulties is to make the experts explain in a logical way how they make decisions. Very often, the expert uses rules based on experience in an implicit way. To construct expert systems one does need, however, explicit and formal rules. Moreover, there is usually a communication problem. The expert has developed his own language and often does not realize this. This difficulty was encountered in this case. It was solved by setting up a 'rule committee', consisting of 'teachers' (the experts) and 'pupils' (mathematicians, specialists in informatics and other people with not too much knowledge about the chemical problem). The 'teachers' constructed rules in a stepwise fashion, checking communication problems by asking the 'pupils' to apply them for solving exercises. This led to a 'rule book', the purpose of which is to make decisions on how the determination of a given active substance in a given formulation should be carried out. Based on these decisions a recipe is then developed. The software is described under the heading PROGRAMS.

*The rule book*

The solubilization of the drug is the first instance where one encounters the need for a reduction of the number of nodes in the decision tree, since the number of possible solvents is very large. The authors decided to standardize on three solvents; namely, 0.1 M HCl, 0.1 M NaOH and methanol. In principle, the first two are used to dissolve salts and acidic or basic substances, while the latter is used to dissolve neutral compounds and also as an all-round and second-choice solvent. The rules for selection are the following:

(i) One first investigates whether the substance is a salt. Most common salts of organic acids and bases are water-soluble. However, to ensure more rapid and complete dissolution it is preferable to make use of aqueous acid or alkaline solutions depending on the salt-type. Basic salts (such as, for instance, sodium sulfadimidine and calcium cyclobarbital) are dissolved in 0.1 M NaOH and acidic salts (such as papaverine.HCl or codeine phosphate) in 0.1 M HCl. A salt is called basic or acidic when its active component is an acidic or a basic compound, respectively. The computer program recognizes them as such by looking up whether the inactive counterion belongs to one of the first two lists given in Table 1. In a few instances, this rule leads to problems, because the inactive component is not soluble in the selected acidic or basic aqueous medium. For instance, the salicylate ion of eserine salicylate is partly soluble in HCl. In that case, one decides to dissolve the substance in methanol. A third list contains those counterions. Finally, if an ion does not figure in these lists, the substance must be dissolved in methanol (except when the expert decides that one of the lists must be updated by addition of the ion concerned).

**Table 1**
Extract of lists of counterions. List A and B contain counterions that require drugs containing them to be dissolved in respectively 0.1 N HCl and 0.1 N NaOH. List C gives counterions that require drugs containing these counterions to be dissolved in methanol

| A. | B. | C. |
|---|---|---|
| Chloride | Sodium | Benzoate |
| Nitrate | Calcium | Salicylate |
| Sulphate | Ethanolamine | Nicotinate |
| Phosphate | | Gallate |
| Acetate | | Gentisate |
| Lactate | | Pamoate |
| Tartrate | | |
| Citrate | | |
| Gluconate | | |

(ii) When the active substance is not a salt, one first investigates whether it can be ionized (i.e. exhibits acidic or basic properties). This means that the expert system must be able to identify acidic and basic functional groups in a molecule and also to define them as 'weak' or 'strong'. The terms weak and strong do not have the usual meaning of partial or complete dissociation in water, since in this sense all organic acids and bases of pharmaceutical importance are weak, but they give a gradation in acid (or base) strength. Some of the 23 functional groups recognized by the program are given in Table 2. The following rules are then applied successively:

(a) if there is any strong function present, neglect all weak functions;

(b) if there are only acidic functions, dissolve in 0.1 M NaOH;

(c) if there are only basic functions, dissolve in HCl 0.1 M;

(d) if there are both strong acidic and strong basic functions, dissolve in HCl 0.1 N;

(e) if there are only weak functions of both acidic and basic nature present, dissolve in methanol;

(f) if there are no functions, dissolve in methanol.

When rules (b), (c) or (d) apply, one must still check for some special situations. For example, acids that contain also an ester function such as acetylsalicylic acid are classified by these rules as acids and therefore they would be dissolved in NaOH. However, the product is not stable in these circumstances and the solvent is then changed to methanol. For this reason, a list of exceptions and the corresponding solutions must be incorporated.

(iii) In the next stage, one must decide whether the drug substance can be measured by UV spectrophotometry or not. Therefore the following three decision criteria were introduced:

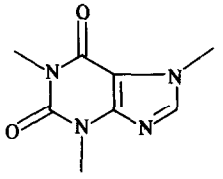
(a) when the UV spectrum in the solvent selected does not include an absorbance maximum above 229 nm another analytical method must be chosen. When a maximum does occur above 229 nm, the $\lambda_{max}$ value with highest absorbance above this cut-off is selected and the $E^{1\%}_{1cm}$ value at this wavelength is obtained from the literature [18–19] or, when no literature data are available, experimentally.

(b) The analysis sample is obtained by pooling ten formulation units. It is preferable to use for the analysis an amount of this pooled sample that does not exceed the weight of three dosage units (three tablets, three capsules, . . .), since part of the same sample must be used for other purposes (identification of excipients, etc.) or kept to carry out

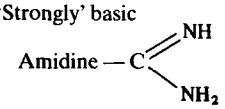
**Table 2**
Extract of lists of 'strong' and 'weak' acidic and basic functions

'Strongly' acidic
Sulphonic acid — $SO_3H$
Carboxylic acid — COOH
Sulfonamide — $SO_2NH$ —

'Weakly' acidic
Imide — CO — NH — CO —
Phenol Ar — OH
Hydroxamic acid — CO — NHOH
Xanthine



'Strongly' basic



Amidine — C(=NH)(NH$_2$)

Aliphatic amines N $R_1R_2R_3$
(primary, secondary, tertiary)

'Weakly' basic
Pyridine

Aromatic amines Ar — N

additional determinations when problems are encountered. After dissolution of an appropriate amount of sample material, not exceeding three dosage units, in 50 ml of the selected solvent and after adequate dilution, a concentration must be attained which permits an absorbance of 0.5 measured at the $\lambda_{max}$ in a 1 cm cell, because this is considered an absorbance value at which accurate measurements can be made. The criterion is then

$$m = 250/(E^{1\%}_{1\,cm}.D) < 3,$$

where $m$ is the number of formulation units needed to obtain an absorbance of 0.5 in a 1 cm cell after dissolution in 50 ml of solvent and $D$ is the quantity in mg of active substance in one formulation unit. If $m > 3$ but $< 15$, the measurement will be carried out in a 5 cm cell, after dividing $m$ by 5.

Criterion (b) has to do with the way in which the samples are presented to the authors by the governmental agency. It is therefore not necessarily a good criterion for other laboratories carrying out the same kind of work. However, some limit on the number of formulation units to be used is always necessary, e.g. to avoid solubility problems.

(c) To avoid non-linearity of the calibration graph at higher concentrations, the molar concentration CM of the drug substance may not exceed $10^{-3}$ M. By introducing in

$$CM = (m.D)/(50.MW)$$

the value of $m$ obtained in (b) the criterion becomes:

$$CM = 5/(E^{1\%}_{1cm}.MW) < 10^{-3}$$

where MW is the molecular weight of the drug compound. If CM $>10^{-3}$ M but $<5 \times 10^{-3}$ M, the measurement can again be carried out in a 5-cm cell after dividing $m$ by 5.

When one of the three criteria is not met, one concludes that UV spectrophotometry cannot be carried out and another analytical method must be chosen.

*Procedures*

When the conditions for determination by UV spectrophotometry are found to be favorable according to the above criteria and when the experimental conditions (solvent, $\lambda_{max}$, number of formulation units) have been determined, the computer must develop a procedure. The main problem is to integrate the experimental conditions selected with adequate dilution schemes in a standard procedure. For this reason, the program contains a list of dilution factors that allow the concentration of the active substance in the sample and the reference solution to be brought to a comparable level, yielding an optical absorbance value of about 0.5. This is done in such a way that the volumes of pipettes, etc. usually available are taken into account. An example of a resulting procedure is shown in Fig. 2.

*Programs*

In this initial phase of the project two separate programs were developed. The first, written in FORTRAN-77, for use on a PDP 11/70 is used to complete what in expert system terminology is called the frame (i.e. the data structure holding the information about a certain object). It searches for the presence in a molecule of the functional groups of Table 2 and stores the information obtained in the frame. It has been written in such a way that one can easily add or delete without difficulty functional groups to be recognized. The second program, written in BASIC for an Apple 2, has the frame as input, i.e. the list of functional groups recognized by the first program together with data about the formulation and substance to be analysed. It asks for information as it goes along and yields the kind of procedure shown in Fig. 2.

There is no particular reason for the choice of languages and computers for these two programs, other than the convenience of the programmers and the availability of hardware. However, an analysis of the logical structure of the problem (see above) shows that one should use a language that manipulates lists and that permits easy updating of rules and lists. This points to an artificial intelligence language such as PROLOG or LISP. The authors are now investigating whether PROLOG is suitable in this particular case.

*Validation*

To check whether the analytical procedures obtained as described above, really do allow one to obtain acceptable results, procedures were developed for the assay of 65 randomly chosen commercial formulations. They were carried out and the results were examined (see Table 3). In 46 cases the analytical procedure yielded a correct result in the first round. After adding, among others, a special rule for the phenothiazines (to avoid instability in aqueous solutions), the expert system was found to yield correct conclusions in 55 cases: 52 led to correct determinations and in three cases the system

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RECIPE

PREPARATION OF STANDARD

DISSOLVE APPROXIMATELY 47.16 MG IN 100 ML NaOH 0.1 N .
RECORD THE EXACT WEIGHT IN MG.  CALL THIS C.
SHAKE UNTIL A CLEAR SOLUTION IS OBTAINED.
IF AFTER 30 MINUTES, NO CLEAR SOLUTION IS OBTAINED, STOP AND
CONSULT THE EXPERT RESPONSIBLE.
DILUTE 50 TIMES WITH THE SOLVENT

WEIGH 10 FORMULATION UNITS.  THE WEIGHT PER FORMULATION UNITIS
CALLED GEX.
RECORD GEX.
CRUSH THE TABLETS IN A MORTAR
BRING AN EXACTLY WEIGHED QUANTITY PR = 149.81 MG +- 10% POWDER
IN A CENTRIFUGATION TUBE.  RECORD PR.
ADD 50.0 ML NaOH 0.1 N
SHAKE DURING 30 MINUTES.
CENTRIFUGE.
DILUTE 200 TIMES WITH NaOH 0.1 N
USE A 1 CM CELL
MEASURE AT 287 NM
RECORD THE RESULT, EX
MEASURE THE STANDARD AT THE SAME λMAX.  RECORD THE RESULT, ES

COMPUTATIONS
COMPUTE THE DOSIS AS DOSIS=(EX/ES)*C*(GEX/PR)*2
EX= ABSORPTION OF SAMPLE
ES= ABSORPTION OF STANDARD
C = MG STANDARD
GEX= MG WEIGHT OF FORMULATION UNIT
PR = MG WEIGHT OF SAMPLE
COMPUTE Y%=(100/D)*DOSIS
D= THEORETICAL DOSE IN MG PER FORMULATION UNIT
DOSIS= DOSE FOUND

CONCLUSIONS
CONCLUDE THAT THE DRUG IS CONFORM TO LABEL CLAIM WHEN
  95<=Y%<=105%
  NOT CONFORM WHEN
  Y%<90  OR Y%>110
FOR OTHER  VALUES, CONSULT THE EXPERT RESPONSIBLE
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**Figure 2**
Example of analytical procedure obtained with the expert system. The drug was a specialty containing 200 mg of flufenaminic acid.

correctly decided that UV spectrophotometric determination was not possible. In two cases (phenothiazines) the results were slightly too low and in two cases measurement in the 5-cm cell led to problems. In one other case wrong results were obtained. These are unexplained and may be due to non-conformity of the drug. Closer examination of the results showed that:

(i) in many cases the procedure followed was appreciably simpler than the one given by the registration dossier, but yielded results of comparable precision and accuracy;

(ii) some difficulties were not foreseen (and could not have been foreseen) in the rule book. One of these difficulties was the occurrence of errors in the UV data collections used. The other had to do with some substances (five cases) not dissolving in the solvent

**Table 3**
Results of the validation study (the weights given are the doses of active component in one formulation unit)

| | |
|---|---|
| Drugs for which a correct analytical procedure was obtained: | |
| Acefylline piperazine coated tablets | 250 mg |
| Amitriptyline.HCl capsules | 50 mg |
| Benzthiazide tablets | 50 mg |
| Bibenzonium bromide coated tablets | 30 mg |
| Bufexamac coated tablets | 250 mg |
| Chlordiazepoxide tablets | 25 mg |
| Chloroquine.$H_2SO_4$ tablets | 136 mg |
| Chlorpromazine.HCl tablets | 27 mg |
| Chlortalidone tablets | 100 mg |
| Clopenthixol.2HCl coated tablets | 10 mg |
| Cyclobarbital.Ca tablets | 200 mg |
| Diazepam tablets | 5 mg |
| Diethylpropion.HCl tablets | 25 mg |
| Diflunisal tablets | 250 mg |
| Doxepine.HCl capsules | 25 mg |
| Fenfluramine.HCl tablets | 20 mg |
| Flufenaminic acid capsules | 200 mg |
| Flunarizine.HCl tablets | 5 mg |
| Furosemide tablets | 40 mg |
| Ibuprofen tablets | 200 mg |
| Methyldopa coated tablets | 250 mg |
| Nortriptyline.HCl coated tablets | 25 mg |
| Orciprenaline.$H_2SO_4$ tablets | 20 mg |
| Oxazepam tablets | 15 mg |
| Oxolinic acid coated tablets | 750 mg |
| Oxomemazine.HCl tablets | 10 mg |
| Oxomethacine capsules | 100 mg |
| Papaverine.HCl tablets | 300 mg |
| Pentobarbital.Na capsules | 100 mg |
| Perazine dimaleate coated tablets | 25 mg |
| Perfenazine coated tablets | 2 mg |
| Periciazine capsules | 5 mg |
| Phenobarbital tablets | 100 mg |
| Phenylbutazone coated tablets | 200 mg |
| Pipamperon.2HCl tablets | 250 mg |
| Probenecid coated tablets | 500 mg |
| Procainamide.HCl capsules | 300 mg |
| Procyclidine.HCl tablets | 5 mg |
| Promazine.HCl coated tablets | 25 mg |
| Propranolol.HCl tablets | 40 mg |
| Secobarbital.Na capsules | 100 mg |
| Spironolacton coated tablets | 100 mg |
| Sulfaguanidine tablets | 500 mg |
| Sulindac tablets | 100 mg |
| Sulpiride coated tablets | 200 mg |
| Theofylline capsules | 150 mg |
| Thiamine.HCl tablets | 300 mg |
| Thiethylperazone dimaleate coated tablets | 6.5 mg |
| Thioridazine.HCl coated tablets | 25 mg |
| Thioridazine.HCl coated tablets | 100 mg |
| Triflupromazine.HCl coated tablets | 25 mg |
| Trimipramine maleate coated tablets | 25 mg |
| Drugs for which the correct conclusion was obtained that UV spectrophotometry is not possible within the constraints given: | |
| Biperidene.HCl tablets | 2 mg |
| Guanethidine sulphate tablets | 25 mg |
| Dibenzepine.HCl coated tablets | 80 mg |

**Table 3**
(continued)

| | |
|---|---|
| Phenothiazines for which a too low result was obtained: | |
| Levomepromazine maleate coated tablets | 25 mg |
| Thiopropazate.HCl tablets | 5 mg |
| Drugs measured in a 5-cm cell for which problems were encountered: | |
| Guanfacine.HCl tablets | 2 mg |
| Oxyfenonium bromide tablets | 5 mg |
| Drug for which the procedure yielded a wrong result for unexplained reasons: | |
| Bromazepam tablets | 6 mg |
| Drugs that proved to be insoluble in the solvent selected: | |
| Amiloride.HCl tablets | 5 mg |
| Penfluridol tablets | 20 mg |
| Pyrvinium pamoate coated tablets | 50 mg |
| Suloctidil capsules | 100 mg |
| Triamterene capsules | 50 mg |

described by the rule book. This points to the necessity of adding lists of known exceptions to the system to obtain maximal results.

One notes that in nearly 85% of the cases investigated the procedure obtained, or the conclusion that no procedure should be given since UV spectrophotometry is impossible, was correct. One should also be aware that expert systems can be made to remember their errors. For instance, a new application for one of the five substances found to be insoluble in the solvent selected would immediately generate a message to flag that this problem occurs and, if a solution had been found meantime, a correct procedure would also be given. The general conclusion of this study is that it is indeed feasible to develop expert systems for the selection of analytical methods and procedures. The present system is small but it is now being developed for liquid dosage forms, multicomponent formulations and for chromatographic analysis. The amount of effort to be put in is, however, large and it is to be predicted that really powerful systems will not be inexpensive and will take a long time to be developed.

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