Reuse of Pharmaceutical Experience on Patient-individual Formulations

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Abstract

This paper presents on a novel knowledge and experience management approach for the development of patient-individual formulations in pharmacies applying case-based reasoning to solve problems with formulations that are under construction. A detailed analysis of the tasks and problems of formulating mixtures is given. A sophisticated domain model, a case base for problem solving and some first services are described that support pharmacists in their daily formulation tasks. The evaluation results from a first field test are presented. A brief discussion of related work and an outlook conclude the paper.

1. Introduction

Pharmacies are not only dispensing medications that have been fabricated by the pharmaceutical industry. They are also compounding medications for individual patients. The development of a formulation for an efficient, safe, and stable mixture requires plenty of task-oriented, pharmaceutical knowledge. A huge amount of this knowledge is documented in heterogeneous information sources like pharmaceutical textbooks and electronic publications[1]. It is a difficult and time-consuming task to check all relevant properties of a new mixture. Even experienced pharmacists have to review the literature carefully for relevant information, as there is such a wide variety of prescriptions and prefabricated substances. In current pharmacy practice, a profitable creation of patient-individual formulations is hardly possible. Task-oriented, electronic assistance is urgently needed.

This paper presents a knowledge and experience management approach [Bergmann, 2002] that supports pharmacists in formulating drugs for individual patients by means of a pharmaceutical domain model and case-based reasoning. It focuses on *modeling* pharmaceutical knowledge on substances, properties, and relationships of them, *using* the properties and relationships as check criteria in order to examine formulations for efficacy, safety, and stability, and for providing drug information, and employing case-based reasoning for *reusing* cases that record solutions of hurt check criteria.

The paper is organized as follows: In Section 2, we introduce the tasks and problems of patient-individual formulation. Section 3 addresses our knowledge and experience management approach in order to support the formulation tasks. Section 4 presents first evaluation results from a field test. Section 5 concludes the paper with a discussion and an outlook.

2. Development of a patient-individual formulation

A pharmacist develops a patient-individual formulation usually on the basis of a medical *prescription*. The prescription form contains a list of quantified substances called *prescription positions*. Figure 1 shows a sample prescription with a prefabricated salve 'Volon A' in the first position and a basic skin cream 'Basiscreme DAC'[2] in the second position. The 'aut idem' label on the left hand side means that the substance may be substituted by a generic drug.

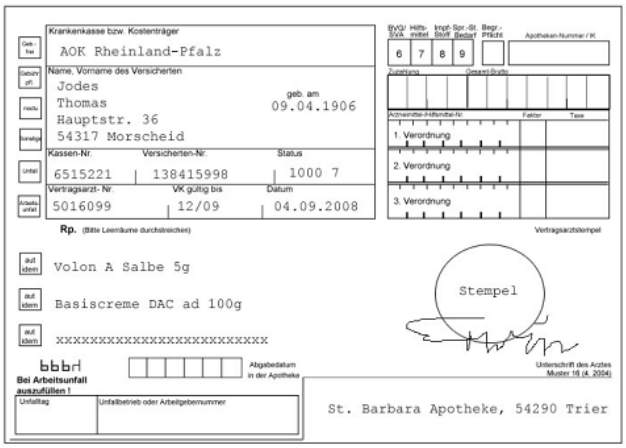

Fig. 1: Sample prescription form handed in at a pharmacy.

The pharmacist extracts the relevant information from the prescription in order to acquire an *initial formulation*. The initial formulation has to be checked carefully and to be adapted if necessary. With the availability of the *final formulation*, the expiration date and further drug information can be determined.

[1] A prominent German sample for an electronic source of over 500 formulation-related references is the formularium NRF ('Neues Rezeptur-Formularium') of the ABDA ('Bundesvereinigung Deutscher Apothekerverbände'), online available at http://www.pharmazeutische-zeitung.de/index.php?id=2264, Retrieved October 24, 2008.

[2] DAC stands for the German drug codex '**D**eutscher **A**rzneimittel **C**odex', which specifies the components of some basic pharmaceutical substances. The DAC is part of ABDA's NRF (see previous footnote).

2.1 Creating an initial formulation from a prescription

The first step of drug formulation is to create the initial formulation from the prescription. Several prescription-related challenges have to be addressed concerning the substances to be processed:

1. Synonymous names for substances,
2. Heterogeneous units of measurement,
3. Prefabricated substances.

ad 1: Substances can be named by a variety of synonymous names. For instance, the common dermatological agent 'urea' is often prescribed by its Latin form 'carbamidum', or by 'carbamide', 'carbonyl diamide', or 'carbonyl diamine'. Sometimes, also trade marks like 'Aspirin' instead of 'acetylsalicyl acid' are taken. A pharmacist is hardly able to know all the names for substances that may be used by the physicians. In practice, she successively learns the preferences of particular physicians only in addition to her own pharmaceutical language use. Novel names have to be looked up when they occur.

ad 2: The second difficulty is the variety of measurements in which the substances can be denoted. Mass values can be seen alongside volume and proportion specifications.3 A missing unit means that the value is interpreted in gram. The supplementary 'ad' stands for filling up the whole mixture with this substance until the specified amount. For instance, the 'ad 100 g' in the above sample prescription specifies that the pharmacist should add an amount of 95 g of this basic cream. Frequently, the prescription positions are given in different units. That means that the units of measurement have to be transformed into unified, explicit specifications.

ad 3: Positions with an explicated unit of measurement may still suffer from incomplete knowledge concerning the content. This is to be found if a compound substance is denoted as it is frequently the case with prefabricated substances. Sometimes, detailed information on the particular ingredients is missing. 'Volon A', for instance, contains 0.01 g Triamcinolon per gram, i.e. 0.05 g in the whole sample mixture above. Furthermore, the vendor's specification of 'Volon A' says only that it contains Polyethylen and Paraffin. The proportion of these two auxiliary substances is not published by the vendor. The pharmacists have to estimate the amounts of subcomponents if necessary. The estimation can be feasible over multiple assembly levels.

When the pharmacist has solved the prescription-related problems that we described above, the initial formulation is available. Before the mixture is actually made, the initial formulation has to be reviewed for efficacy, safety, and stability.

2.2 Validating a formulation and solving problems

The review of an initial formulation requires pharmaceutical knowledge on the basic and prefabricated substances, their properties and relationships, as well as on the particular patient, and use. Obviously, the concentration of active components is very important, but also potential problems with particular substances and mixtures have to be considered. The check criteria for validating a formulation can be assigned to the following three areas:

I. Physical, chemical, and galenic characteristics of a certain substance or a group of substances,
II. Physical, chemical, and galenic characteristics of a combination of certain components,
III. Microbiological quality of a mixture.

ad I: First, the pharmacist confirms that the particular substances are medically unobjectionable for a certain patient and use. Phenol, for instance, is not any more recommended to be applied on the skin. Furthermore, she checks whether the concentrations of the active components of the drug, i.e. of the medical and preservative agents, are within the mandatory range. Further characteristics to be validated are, for instance, the range of pH-values in which a substance should be formulated best or which impact a type of wrapping has on the stability of a particular substance.

ad II: Second, the pharmacist clarifies that there are not any serious incompatibilities of components of the formulation. This concerns, for instance, the physical stability of two components in a mixture. The pharmacist knows whether an agent is soluble sufficiently in an auxiliary substance like olive oil or whether problems like sedimentation or caking are to be expected.

ad III: The microbiological quality of a mixture is not only depending on the use of preservative substances. It also plays a role to avoid the generation of a nutrient medium within the mixture by a certain combination or treatment of substances. Sometimes, the decisions of the pharmacist rely on incomplete knowledge for the reason of incomplete specifications of substances that we have described above or for other reasons.

If the pharmacist detects a problem during the validation of a formulation it can be solved in different ways. Sometimes the pharmacist is able to mend the potential problem without changing the formulation, for instance with a soon expiration date or with adding the instruction that the drug has to be refrigerated. If a major adaptation of the formulation, not such as the addition of a preservative agent, becomes necessary the prescribing physician has to be contacted in order to develop a solution conjointly. A sample adaptation that requires the approval of the physician is depicted in Figure 2. Sometimes, the physician decides not to adapt the formulation, for instance for the reason of tradition or for intentionally prescribing a placebo that is effective psychologically only.

[3] The ratio '% (m/m)' stands for 'mass per mass', for instance '% (g/g)' for 'gram per gram'. '% (m/V)' is for 'mass per volume' like '% (g/ml)'. '% (V/V)' units for 'volume per volume' are quite common as well as mass proportions with respect to drops, pieces, or international units.

Uncommittedly composed formulation

Acid. salicyl. plv.	5.0
Triamcinolonacetonid	0.1
Ol. oliv.	ad 100.0

Problem

- solubility of Salicyl acid in olive oil 2.5 % only; consequence: sedimentation, growth of crystals
- Triamcinolonacetonid not solvable in olive oil, consequence: sedimentation, caking
- restricted temperature exposure for vegetable oils
- solubility by shaking the drug is not sufficient

Alternative

Salicyl acid	5.0
Triamcinolonacetonid	0.1
2-Propanol	10.0
Octyldodecanol	ad 100.0

Directions: solve Salicyl acid in Octyldodecanol while heating and separately Triamcinolonacetonid in 2-Propanol. Let both solutions cool down and mix them at room temperature.

Fig. 2: Sample adaptation of a formulation [RLH03, own translation].

3. Knowledge and experience management approach

The analysis of the development of patient-individual formulations in Section 2 has shown that it would be worthwhile to have an assistant system for the management of the required pharmaceutical knowledge and experience. In the following, we will describe the modeling and reuse of pharmaceutical knowledge in a knowledge and experience management system. The system supports the following tasks of formulation:

- Acquisition of initial formulation,
- Retrieval of relevant check criteria,
- Review of check criteria,
- Mending of hurt criteria (deactivate criterion, adapt formulation: re-calibrate, change list of positions),
- Generation of additional instructions for how to prepare and use a mixture.

The degree of automatic support that is provided by the system varies from task to task: The acquisition of an initial formulation from a prescription form is done mainly automatically but requires user interaction for the acquisition of missing information on ingredients and amounts within prefabricated substances (compare Section 2.1). The retrieval and review of the check criteria is performed automatically. It addresses the validation areas I – III that have been introduced in Section 2.2. The mending of hurt criteria is supported by a case-based approach. The generation of instructions has still to be done by the pharmacist.

In order to realize the support capabilities mentioned above, the assistant system provides a set of services using an underlying domain model. Section 3.1 will introduce this domain model. Section 3.2 will briefly sketch the services.

3.1 Domain model

The domain model represents knowledge on patient-individual formulations in a task-oriented way. That means that it does not aim to describe general knowledge on substances like all chemical, physical and galenic properties of substances. Instead, it focuses only on those characteristics that are relevant for the tasks of formulation. The model consists of four main parts:

- *substances*: a task-oriented taxonomy of substances, their properties, and relationships,
- *formulations*: data on prescriptions and formulations including the routes of application and the wrappings,
- *master data* of patients, health professionals, and health insurances, including administrative as well as medical information like history data on a patient's prescriptions,
- *system administration data* like user roles.

In the following, we will present some details on the substances as this part of the model has the most important impact on providing assistance for the formulation tasks.

The core of the substances model is a taxonomy of substances, groups of substances, and prefabricated substances. Figure 3 depicts the section of this taxonomy for the prefabricated substance 'Volon A'. It consists of three ingredients: the medical agent Triamcinolon with 0.01 % (g/g), Polyethylen, and Paraffin, which belongs to the group of Alkanes.

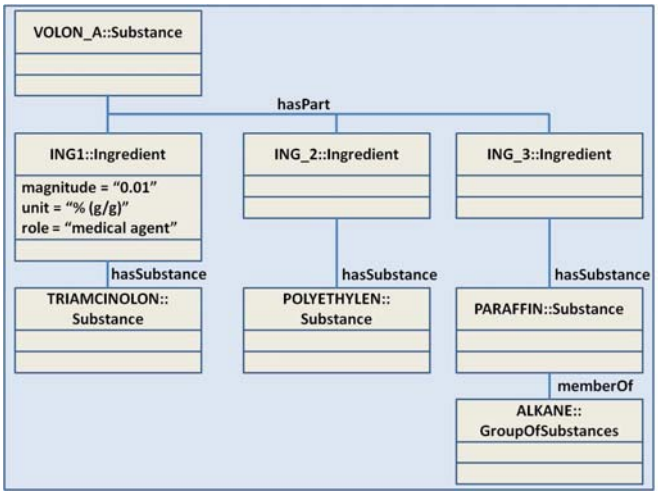

Fig. 3: Sample section of the substances model describing Volon A.

Synonym names are not depicted in Figure 3 due to space limitations. They are integrated as objects of the class Synonym that are related to the abstract term, for instance 'Volon A::Synonym' and 'VolonA::Synonym' related to 'VOLON_A::Substance'.

Check criteria are represented by objects of the class 'CheckCriterion' encapsulating terms in predicate logics. For instance, the term `Phenolic(x) ∧ (Cyclohexene(y) ∨ Benzol (y))` stands for the following sentence describing an incompatibility: "Phenolic substances might react with Benzol or Cyclohexenes producing unwanted phenolic by-products". Atomic formulas with the arity one (one predicate about one term) stand for

check criteria on properties of single substances within a mixture like '`AppropriateConcentration(x)`'.

3.2 Services

The domain model that we described in the previous subsection is used by four services at the moment: a service *build data model*, a *formulation service*, a service *maintain system administration and master data*, and a service *maintain substances*. In the following, we will have a closer look at the formulation service, which is called when a new formulation is to be developed. First, the acquisition of the initial formulation has to be done, and then the validation and adaptation of the formulation takes place.

The acquisition starts with building a formulation object and performing a depth first search on the positions of the prescription object to create new position objects for the formulation object. The already existing position objects of the prescription are copied and not overwritten for reasons of documentation. The result is a tree of all substances that are involved in the formulation. Then, the specification of quantities is completed and unified. After the choice of either mass or volume specification, a breadth first search through the tree of substances is executed in order to unify the units of measurement and to complete the missing units. If quantities cannot be derived automatically, the pharmacist is involved for interactively estimating quantity values. The order of dealing with the quantity values is important: In each node of the tree, the mass and volume specifications are handled before expanding the proportion specifications. A special treatment is required if an 'ad' occurs. First, the overall quantity of the mixture is determined from the 'ad' position, second, the quantities of the other positions is computed according to the order mentioned above, and last, the quantity of the 'ad' position is derived.

The validation consists of the retrieval and review of relevant check criteria. It begins with computing the concentration of all substances and storing them in a list. Then, the relevant check criteria are retrieved and tested automatically. In the prototypical implementation, a linear search is employed as retrieval method. This impacts a high computational complexity, which is to be optimized in future.

The adaptation of the formulation when a hurt criterion has been detected is supported by case-based reasoning [Richter, 1998]. A *case* consists of a hurt criterion in any formulation (the problem part) and an alternative set of substances or additional preparation directions (the solution part). In Figure 2, the uncommitted composed formulation together with the four problem items form the problem part of a case while the alternative positions and the directions describe the solution part. A *case base* consists of a set of such cases recording pharmaceutical experience. If a *new problem* occurs that requires the adaptation of a formulation, the best matching case is retrieved from the case base in order to reuse its solution. The retrieval is based on a standard similarity function [Bergmann, 2002] computing a weighted sum of local similarity values based on an internal, structural representation of the problem part of the cases. When building the internal representation of the cases, the domain model is applied to create attribute-value pairs from the initial formulation positions. The representation is created by the same preprocessing algorithm that is applied during the processing of a new recipe for the acquisition of an initial formulation. The user decides after the retrieval of the best matching case whether the solution is applicable to the new problem and transfers it to the new formulation where appropriate.

4. State of implementation and evaluation

The acquisition of initial formulation, the retrieval, and the review of check criteria is fully implemented. The mending of the hurt criteria by means of case-based reasoning is ongoing work.

A field test has been conducted with three German pharmacies to evaluate the already implemented parts of the approach. As all German pharmacies underlie the same accounting mechanism with the health insurance companies and the major part of them makes use of the electronic sources described in Section 2, the evaluation results can be considered representative for Germany. The field test investigated two research questions: The first question is whether the domain model including the check criteria is appropriate for the pharmaceutical knowledge that is required for the task of creating patient-individual formulations. The second question is whether the implementation is usable. The first question has been investigated by an expert review of the domain model. The second question has been investigated by one of the pharmacists involved by means of working with the implemented modeling tool. The results for the first question are quite promising: The model review has shown that it covers the pharmaceutical knowledge including the check criteria to a great extend. Only the potentially heterogeneous granularity of check criteria was considered to cause problems in future. The modeling activities concerning the second research question led to 61 substances and groups of substances, 18 check criteria derived from 11 genuine recipes. It turned out that the tool worked in principle well but that the computational performance of the tool should be improved in future.

5. Discussion of related work and outlook

In this paper, we have presented a knowledge and experience management approach that supports pharmacists in elaborating patient-individual formulations. A domain model of substances including their properties and relationships is used to check potentially problematic properties and relationships for a certain mixture. A case-based approach provides assistance for the adaptation of formulations when check criteria have been hurt.

The literature reports a case-based approach using decision trees to guide tablet formulation [CWR98]. In contrast to our work, this approach addresses the formulation for the industrial production of drugs. In our patient-individual approach, aspects like tablet weight and yield pressure do not play any role. Furthermore, there is a wider variety of prescriptions in pharmacies than in an industrial tablet production. We think that considering particular check criteria is more feasible for this application area than using complex decision trees also with respect to maintenance issues.

In our future work, we aim at finishing the implementation and evaluating the case-based support for the validation and adaptation process.

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